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GORDON RESEARCH CONFERENCES

Topics include venom evolution, green chemistry, meiosis, and more p. 808

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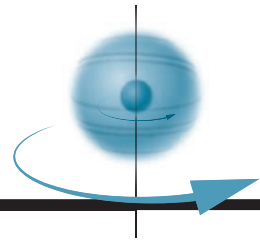

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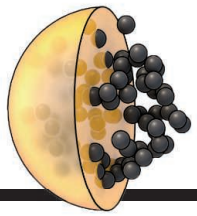

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ON THE COVER

A southern tree funnel-web spider (*Hadronyche cerberea*) with venom droplets on its fangs. When threatened, this spider rears up, and venom slowly flows to the end of its fangs. The venom droplets grow larger as the spider holds its defensive posture. The Gordon Research Conference on Venom Evolution, Function and Biomedical Applications will be held from 5 to 10 August 2018 in West Dover, Vermont. See page 808 for the Gordon Research Conference schedule and preliminary programs. *Photo:* © *Michael Doe*

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EDITORIAL

Exploration before exploitation

The current U.S. administration has proposed to open up 90% of the U.S. continental shelf to oil and gas drilling as part of a new Bureau of Ocean Energy Management (BOEM) Draft Proposed Program. Although there is a clear need to move beyond fossil fuels for America's energy needs and energy security, there are also a number of immediate existential threats posed by an increase in offshore drilling.

The sites that would be opened include vast areas of the ocean floor that remain unexplored, even unmapped. The maps that exist of our oceans, which make up about 70% of the surface of Earth, are at a resolution of about 5 kilometers. If Manhattan were under water, a map of it would be 4 pixels by 1 pixel across—easy enough to miss in a casual survey. Only about 5% of the ocean floor has been mapped in the level of detail equivalent to the high-resolution maps of the Moon and Mars. Of this, only about 0.01% has been seen by humans through photo or video surveys.

Sea corals dwell in the deep Caribbean Sea.

"...vast areas of the ocean floor...remain unexplored, even unmapped."

This is noteworthy because the continental margins are not just featureless, muddy plains that could be drilled at any location with little disturbance. They contain submarine canyons, deep-water coral reefs and mounds, and natural hydrocarbon seep communities. All of these habitats interact with the surface ocean and provide services on which humans rely. As an example, many small fish that feed the larger fish that we rely on for food, migrate every day to the deep sea and interact with the unusual habitats there. The pharmaceutical industry spends untold funds on drug discovery, and many promising finds have come from deep-sea corals and sponges. At a global scale, the ocean absorbs one-third of the carbon that humans emit and more than 90% of the excess heat that has recently entered the atmosphere. Much of this ends up in the deep sea.

The BOEM has a long-running Environmental Studies Program that has made substantial contributions to the predictive capacity that underlies its management strategy in the Gulf of Mexico. These predictive models allow the designation of "mitigation areas" where drilling is excluded to avoid impact on the high-density and potentially sensitive communities that exist there. However, even in this relatively well-explored area, major impacts to four different deep-sea coral habitats were documented after the *Deepwater Horizon* oil spill—none of which had been observed before the spill.

The probability of an offshore drilling accident increases with the depth of the industrial activity, and a single isolated incident may require decades to centuries for recovery because of the slow growth and longevity of the deep-sea fauna. Even in well-studied areas, long-term observation and monitoring, both pre- and postdrilling, will be necessary to distinguish the impacts of drilling from the effects of climate change, pollutants, fishing, and other human disturbances.

The regions now considered for drilling have not been subject to the decades of deep-sea exploration and research that are essential to make sound decisions for siting of new drilling and the effective management of deep-sea resources. If existing maps are insufficient, or our understanding of the basic life-history traits of the fauna are incomplete, we could be losing the next generation of anticancer drugs or the recycling of nutrients essential to support fisheries while we exploit energy reserves that are best left in the ground. A clear national commitment to science-based management of offshore drilling would demonstrate the leadership of the United States on this issue, which has broad relevance globally as the industrialization of the open ocean proceeds.

–Erik E. Cordes and Lisa A. Levin

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10.1126/science.aat2637

> “Smartphone notifications have turned us all into Pavlov’s dogs.”
>
> **Psychologist David Greenfield of the University of Connecticut in West Hartford** to NPR. Greenfield suspects the alerts trigger the brain to release dopamine, a pleasure signal.

IN BRIEF

Edited by **Kelly Servick**

HUMAN RIGHTS

Turkey sentences NASA scientist

Kubra Golge, holding one of her sons, has fought for the release of her husband, Serkan Golge.

Serkan Golge, a Turkish-American research scientist at NASA in Houston, Texas, was sentenced to 7.5 years in a Turkish prison last week on terrorism charges. A dual citizen who had been studying the effects of radiation on astronauts, Golge was swept up in a crackdown that followed Turkey’s 2016 failed military coup. He was arrested at his parents’ home while visiting southern Turkey weeks after the putsch attempt. According to Golge’s wife, a distant relative who was angered over an inheritance dispute told police Golge was a spy and supporter of Fethullah Gülen, the Islamic cleric whom Turkey accuses of masterminding the coup. Prosecutors said Golge held an account at a bank owned by Gülen supporters and attended a Gülen-linked university. The U.S. government has condemned the verdict. Golge will appeal, his wife says, but he faces a lengthy process in Turkey’s appeals court, where terrorism cases like his take on average 6 months to 1 year. If convicted again, he will be able to take his case to Turkey’s Supreme Court and later to the European Court of Human Rights.

Human eggs mature in lab dish

REPRODUCTIVE BIOLOGY | In an advance that could lead to new fertility treatments, researchers have coaxed immature human egg cells to fully develop in the lab for the first time. Using ovarian tissue from women undergoing elective caesarian sections, the scientists isolated primordial follicles, which surround the immature precursors to egg cells, and induced several to produce mature eggs ready to join with sperm during fertilization, they report online in *Molecular Human Reproduction*. If the resulting eggs prove healthy, the technique could someday allow women infertile from chemotherapy to use eggs from their own preserved ovarian tissue for in vitro fertilization.

Physicist dismissed amid protest

SEXUAL MISCONDUCT | Astrophysicist Christian Ott, who resigned from his tenured job at the California Institute of Technology (Caltech) in Pasadena last year after being accused of sexually harassing two female graduate students, has had his latest position terminated before it began. Ott was offered a 2-year post at the University of Turku’s Tuorla Observatory in Finland last month, but after more than 70 Finnish astronomers and other researchers signed an open letter condemning harassment and discrimination, the offer was withdrawn last week. Kalervo Väänänen, rector of the university, announced the termination, stating: “I came to this conclusion after extensively hearing the science community.” Ott was originally suspended from Caltech in 2015 following an investigation into complaints by the two students in his lab (*Science*, 15 January 2016, p. 216).

Canada revamps impact reviews

ENVIRONMENT | After 14 months of deliberation, the Canadian government has released a revised process for assessing the environmental impacts of development projects such as dams, mines, and pipelines. Prime Minister Justin Trudeau’s Liberal Party had promised to revisit changes made by the

PHOTO: THE NEW YORK TIMES/REDUX

A new plan would change how Canada evaluates the potential impact of proposed development, such as this tar sands mine in the province of Alberta.

previous Conservative Party government, which dramatically reduced the number of projects receiving reviews and was criticized for a lack of transparency in the scientific evidence used in evaluations. The Impact Assessment Act released last week would establish a new government agency to oversee environmental assessments, shorten their timelines, and expand them to include social, economic, and climate impacts. The bill now heads to Parliament for approval, alongside a plan to replace Canada's National Energy Board with a new agency, the Canadian Energy Regulator, and a proposal to reverse changes the previous government had made to fisheries laws.

A new way to measure innovation

TECHNOLOGY | The efficiency with which nations turn scientific discoveries into new businesses can be compared using just two variables, a new Brookings Institution analysis suggests. The new formula calculates a country's new business startups as a percentage of invention disclosures—the initial documentation of a new discovery for a later patent claim. The two variables offer a simple but revealing alternative to established innovation indices that rely on many more factors, including patent licensing and scholarly publications, says author Bart Kolodziejczyk, a nanoscientist and fellow at Stockholm University. The number of invention disclosures is a better indicator of new ideas than the widely used metric of patent licenses, Kolodziejczyk contends. The new measure challenges some other conventional wisdom, as well: Israel ranks higher than the United States and the United Kingdom, but Australia ranks lower.

Startups as a percentage of disclosures

NSF tackles harassment

WORKPLACE | The U.S. National Science Foundation (NSF) will soon become the first federal agency that requires its grantee institutions to report when principal investigators and personnel on projects it funds are found guilty of sexual harassment or are placed on administrative leave because of a harassment investigation. Until now, the agency has had to rely on the media to learn of such cases involving its grantees. In the 8 February announcement, NSF also unveiled a web portal that will include policies and procedures to address harassment. NSF Director France Córdova reminded institutions that they're expected to maintain harassment-free workplaces and that the agency can terminate funding or remove personnel to protect other scientists on a grant. The new requirements will take effect after the agency collects public feedback.

THREE QS

Blockchain, meet genomics

Nebula Genomics, a new company co-founded by Harvard University geneticist George Church, aims to create a vast, decentralized, secure database of genomes through blockchain, the technology created to track the bitcoin digital currency. Church, also founder of the nonprofit Personal Genome Project (PGP), which gathers and publicly shares health data from volunteers, told *Science* about his new venture.

Q: Why are you doing this?
A: I've been trying every possible model to bring something forward that I think is overdue—everybody getting their genome. Some of the barriers have been cost and some have to do with ... security and ways of connecting the information to get higher value. We eventually hit on what we think is a good solution. Everybody owns their data but they can get paid for it by people who want to use the data.

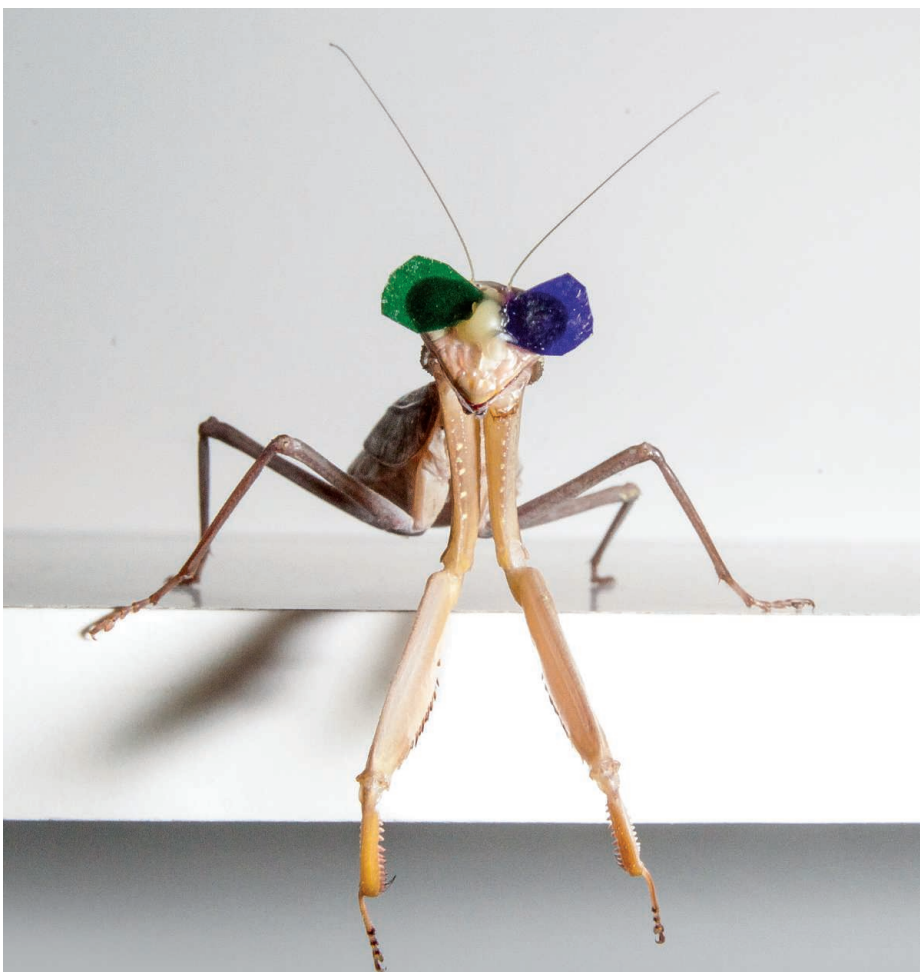
Q: Is Nebula offering to provide free, whole genome sequencing?
A: Not directly. ... If companies want to pay for your particular genome, you can get your information for free and still get some of the benefits like genetic counseling. It's a matter of matching people up.

Q: How does Nebula relate to the PGP?
A: PGP is growing ... but it's not in any danger of impacting 7 billion people. ... This new model will allow you to do it for everybody, even people who don't want to share their data full monty with the world.

CREDITS: (PHOTO) CHRIS KOLACZAN/SHUTTERSTOCK.COM; (GRAPHIC) J. BRAINARD/*SCIENCE*; (DATA) BROOKINGS INSTITUTION ANALYSIS OF NATIONAL INNOVATION AND COMMERCIALIZATION REPORTS

A call to publish peer reviews

PEER REVIEW | Scientific journals should routinely publish peer reviews for each paper they accept, said scientists, academic publishers, and funding organizations at a meeting last week on the quality and transparency of peer review. There was little consensus, though, on whether reviewers should have to publicly sign their critiques, which traditionally are accessible only to editors and authors. The meeting was hosted by the Howard Hughes Medical Institute at its Chevy Chase, Maryland, campus and sponsored by the research charity; ASAPbio, a group that promotes the use of life sciences preprints; and the London-based Wellcome Trust. Speakers said publishing reviews would give early career researchers good models and preserve important insights in the scholarly literature. But other attendees worried that the public might misinterpret critical reviews of papers on controversial topics. Organizers plan to publish a white paper and pursue other follow-up steps.



NEUROSCIENCE

World's tiniest 3D glasses reveal mantis depth perception

Praying mantises excel at detecting prey that comes within striking distance, but—unlike us—they perceive depth only when the prey is moving. Researchers figured that out by gluing 3D glasses on praying mantises (*Sphodromantis lineola*) and showing them a series of 3D movies depicting patches of moving dots—potential "prey items"—camouflaged against a similar background. The insects tried to catch the onscreen prey as long as it appeared to be within 2.5 centimeters of their perch, and they figured out when to strike by looking for movement. Humans see in 3D by comparing the images seen by each eye. But for praying mantises, it's the motion that matters, not the image itself. They only bother matching up places where the picture is changing—a mechanism no other creature is known to use.

Telescope turns to dark energy

ASTRONOMY | The Nicholas U. Mayall Telescope, a 45-year-old 4-meter reflector at Kitt Peak in Arizona, this week embarked on a new career: constructing the largest 3D map of the universe in an effort to understand the mysterious dark energy that is accelerating its expansion. Scientists from Lawrence Berkeley National Laboratory in Berkeley, California, will remove the guts of the telescope and replace them with something called the Dark Energy Spectroscopic Instrument, which can analyze light from 5000 objects simultaneously, allowing it to map the positions of 30 million galaxies and quasars during a 5-year survey. Those positions can reveal whether the rate of acceleration of the universe has changed over the past 10 billion years—and perhaps point to a cause for the acceleration. Transforming the telescope will take 15 months, after which the survey will kick off in early 2020.

Antarctic shelf life, exposed

POLAR SCIENCE | Next week, scientists led by the British Antarctic Survey will begin a voyage to a mysterious ocean seabed that, until recently, was trapped in darkness beneath Antarctica's Larsen Ice Shelf. That darkness vanished last July when an iceberg the size of Delaware, dubbed A-68, calved off the shelf and began drifting north, exposing the sea floor to sunlight for the first time in an estimated 120,000 years. The team of scientists will set off from the Falkland Islands on 21 February for a 3-week expedition aboard the *RRS James Clark Ross* to collect seafloor animals, microbes, plankton, sediments, and water. They hope to document a rare ecosystem before it is reshaped by solar exposure and to test whether it resembles nutrient-poor deep-sea ecosystems. The voyage is not without risks: The ship will have to plow through extensive sea ice in the 5800 square kilometers between A-68 and the shelf. "We need to be bold on this one," says David Vaughan, the survey's science director.

CORRECTION: 9 February 2018
A story on gene therapy in the 9 February issue (p. 621) mistakenly said that an adeno-associated virus caused a death in an early gene therapy trial. An adenovirus was responsible.

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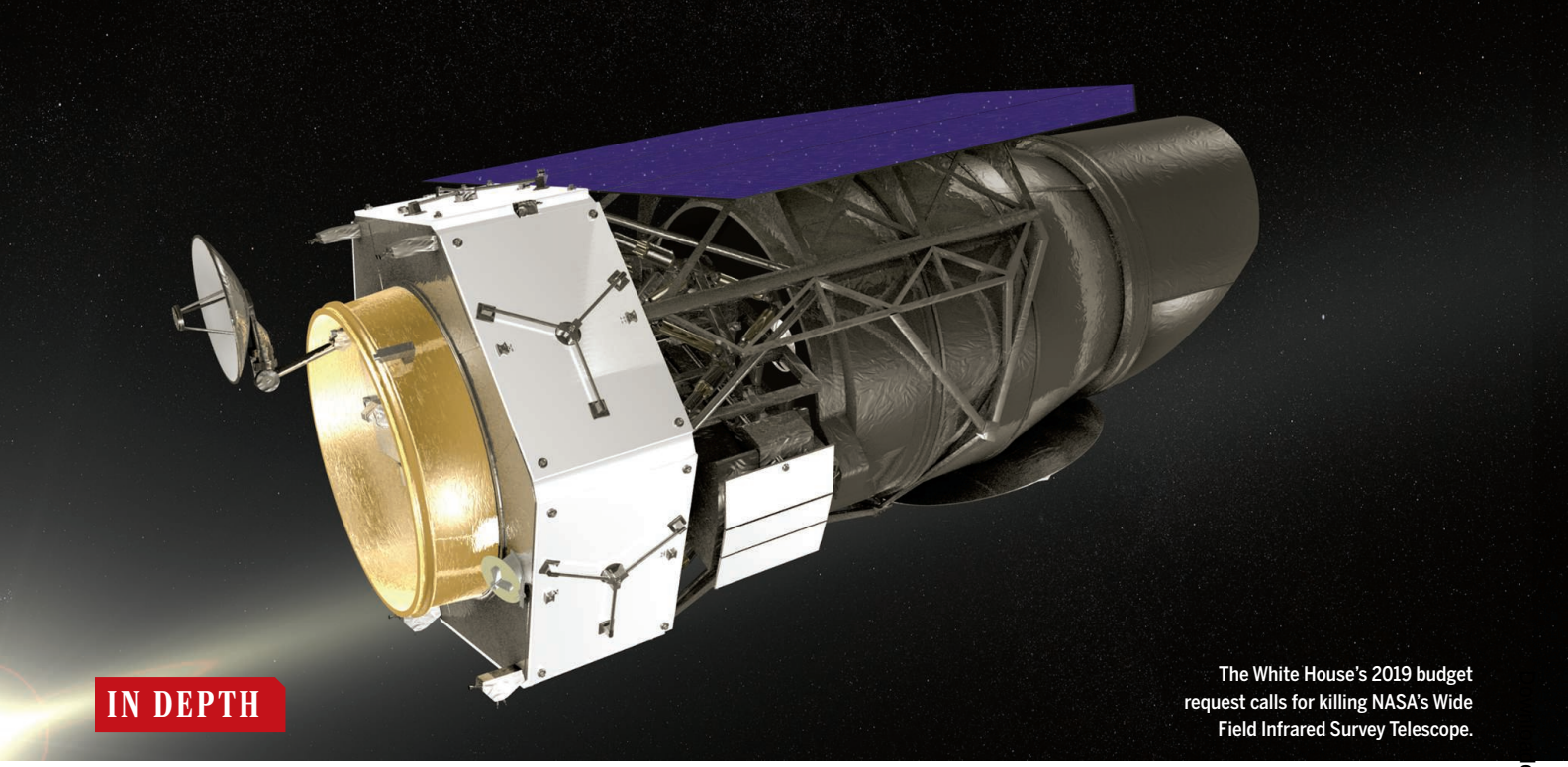
Read more news from *Science* online.

PHOTO: MIKE JRWIN/NEWCASTLE UNIVERSITY



IN DEPTH

The White House's 2019 budget request calls for killing NASA's Wide Field Infrared Survey Telescope.

IMAGE: NASA GODDARD SPACE FLIGHT CENTER CONCEPTUAL IMAGE LAB

U.S. RESEARCH FUNDING

Science gets modest reprieve in Trump budget

Late changes leave major agencies flat, but 2019 request still cuts many research programs

By ***Science*** **News Staff**

Federally funded research got a reprieve last week, but few were celebrating. The latest budget request from U.S. President Donald Trump initially called for double-digit cuts for most research agencies. But at the eleventh hour, following a new congressional deal that will boost federal spending by nearly half-a-trillion dollars this year and next, the administration rescinded many of the planned cuts and instead requested flat funding at major research agencies. What remained, however, was hardly good news: a menu of narrower proposals to cut or kill an array of research programs.

Now, science advocates are placing their faith in Congress to ignore the Trump administration's spending blueprint and to act on its own to bump up agency budgets. And the odds are in the advocates' favor.

The 12 February rollout of Trump's plan for $4.4 trillion in federal spending in the 2019 fiscal year, which begins 1 October, capped a week of high-level political maneuvering that was confusing even for veteran Washington, D.C., hands. It began on 6 February, when Senate leaders struck a deal to avoid a pending government shutdown and also obliterate tight caps on federal spending imposed by a 2011 law designed to reduce the federal deficit. Within a few days Congress had passed the measure, which could open the door to spending increases at some science agencies. Legislators now have until 23 March to finalize agency budgets for the 2018 fiscal year, which began last October.

The White House, meanwhile, had already finished work on the president's impending budget request for 2019. It adhered to the caps and was set to call for boosting military spending by taking a huge bite out of domestic spending, including most research activities. The result would have been a bloodbath for science agencies, White House documents show, proposing a 21% cut to overall federal spending on basic research, a 27% cut at the National Institutes of Health (NIH), a 30% cut to the National Science Foundation (NSF), and a 22% cut to the Department of Energy's (DOE's) Office of Science.

But after Congress approved the higher spending caps, White House budget director Mick Mulvaney scrambled to rejigger the numbers, producing a supplemental request that added billions of dollars for domestic programs. One result: The massive cuts envisioned for NIH, NSF, and DOE disappeared, and were replaced by requests for funding at roughly 2017 levels.

At NIH, the reversal turned a proposed $9.2 billion cut into a small gain for the $35 billion agency. And the administration retreated from its controversial effort to lower administrative costs. Last year, Trump proposed reducing overhead payments on NIH grants by roughly two-thirds and said the savings would allow the agency to make more grants. But lawmakers blocked any changes to the current rules governing these indirect costs, and the 2019 request drops that idea. "I learned a really valuable lesson last year," Mulvaney said. "Not only did Congress not like our proposed NIH cuts … they made them illegal this year."

Science advocates are hoping that lawmakers will also go their own way when it comes to the many research programs targeted for cuts or elimination in the request. The White House wants to cut the Environmental Protection Agency's $762 million Office of Science and Technology by about 40%, for instance, and eliminate several climate science programs. It also wants to kill five NASA earth science missions, eliminate the agency's $100 million education office, and defund DOE's $306 million Advanced Research Projects Agency-Energy. Research programs at the National Oceanic and Atmospheric Administration would drop by nearly 40%, whereas agricultural research and the U.S. Geological Survey would each take about a 20% hit. The Trump administration proposed many of the same cuts in its 2018 request,

however, and Congress has so far rejected most. Advocates are hoping for a replay.

But there will be fresh battles. In a move that shocked astronomers, the administration has proposed killing NASA's Wide Field Infrared Survey Telescope (WFIRST), the agency's next big orbiting observatory, which is designed to investigate the nature of dark energy and study exoplanets. NASA has been studying how to keep down WFIRST's burgeoning costs, now estimated at $3.6 billion, but outright cancellation wasn't expected. One reason: The telescope is the top decadal priority of astrophysics researchers. Killing WFIRST, tweeted David Spergel, an astrophysicist at Princeton University, would see the United States "abandoning its leadership in space astronomy."

Elsewhere prospects were sunnier. Despite the proposed WFIRST cut, NASA again emerged as one of the administration's favorite science agencies, getting tagged for an increase for the second year in a row. Overall, NASA spending would rise by $370 million to $19.9 billion. The agency's science office would grow by about $140 million, or 3%, with most of the additional funds going to planetary science missions.

At NSF, what is now a flat budget request would allow the agency to begin a long-awaited upgrade of its research facilities in the Antarctic, where it is the lead U.S. science agency. And it could launch two cross-cutting research programs from its list of 10 "big ideas"—human-machine interactions in the workplace and the manipulation and analysis of large data sets. The budget would also accommodate construction of two new midsize ocean research vessels (although Congress has told the agency to build three).

Amid concerns about its readiness to conduct the 2020 census, the Census Bureau would receive a $2 billion increase. But advocates cite an earlier cost estimate by Commerce Secretary Wilbur Ross, whose department includes the Census Bureau, to argue that the decennial exercise still needs an additional $262 million next year to stay on track.

The White House also used budget day to unveil its long-awaited infrastructure initiative, which calls for spending $200 billion in federal funds to attract some $1.2 trillion from private and nonfederal sources. To the disappointment of some researchers, however, the plan includes no cyber or scientific infrastructure. Critics were quick to dismiss the plan as mostly for show, like many of the items in the budget request. And they hope neither the infrastructure plan nor the budget request will go far in Congress. ■

With reporting by Jocelyn Kaiser, David Malakoff, Jeffrey Mervis, and Paul Voosen.

ASTROPHYSICS

A weight limit emerges for neutron stars

Merger reveals mass at which the cosmos's densest objects collapse into black holes

By **Adrian Cho**

How heavy can neutron stars get? Astrophysicists have long wondered how massive these stellar corpses could be without collapsing under their own gravity to form a black hole. Last year's blockbuster observations of two neutron stars merging (*Science*, 20 October 2017, p. 282) revealed a collapse as it happened, enabling four different groups to converge on the maximum mass—about 2.2 times that of the sun.

"I'm encouraged that they all agree," says James Lattimer, a nuclear astrophysicist at the State University of New York in Stony Brook. A solid mass limit for neutron stars will help theorists understand these mysterious objects. "Of all the characteristics of a neutron star, the two most important are the maximum mass and the radius," Lattimer says.

A dying star can have one of three afterlives. A lightweight star shrinks into a white dwarf, an Earth-size sphere of carbon. A heavy star explodes when its massive core collapses to an infinitesimal point: a black hole. A star in the middle range—8 to 25 solar masses—also explodes, but leaves behind a fantastically dense sphere of nearly pure neutrons measuring a couple of dozen kilometers across: a neutron star.

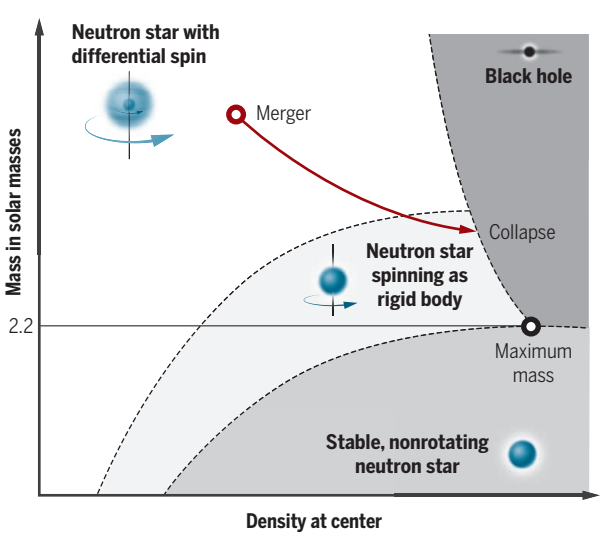
Neutrons in a neutron star repel one another mightily through the strong nuclear force, keeping the neutron star from collapsing. But the strength of that repulsion has been difficult to calculate. Previously, theorists could say only that a neutron star had to weigh less than about 2.5 solar masses. Otherwise, its core would be so dense that, according to basic physics, the speed of sound in it would exceed the speed of light, a violation of Albert Einstein's theory of relativity. On the flip side, astronomers have found a neutron star that weighs 2.01 solar masses orbiting another star in our galaxy.

The new work lowers the mass limit substantially. Ben Margalit and Brian Metzger of Columbia University reported a limit of 2.17 solar masses on 21 November 2017 in *The Astrophysical Journal Letters* (*ApJ Letters*). Masaru Shibata, an astrophysicist at Kyoto University in Japan, and colleagues say 2.15 to 2.25 solar masses in a paper published on 22 December 2017 in *Physical Review D* (*PRD*). Luciano Rezzolla, a theoretical astrophysicist at Goethe University in Frankfurt, Germany, and colleagues set a similar limit on 9 January in *ApJ Letters*, as did Milton Ruiz and colleagues at the University of Illinois in Urbana on 11 January in *PRD*.

All four groups analyzed the merger of two neutron stars spied on 17 September 2017 by dozens of observatories. That approach may seem unpromising, as it might appear that the merging neutron stars would have

Lucky stars

The neutron star created in a merger was traced as it lost its fast-spinning outer layers, spun as a rigid body, then collapsed into a black hole. That allowed researchers to infer the maximum mass of a stable neutron star.



GRAPHIC: L. REZZOLLA *ET AL.*, ARXIV, ARXIV:1711.00314V2. ADAPTED BY C. BICKEL/*SCIENCE*

immediately produced a black hole. However, the researchers argue that the merger evolved along a more complicated—and revealing—path that delayed that collapse.

As the neutron stars spiraled into each other, gravitational-wave detectors in the United States and Italy sensed ripples in space generated by the whirling bodies. The waves allowed physicists to peg their combined mass at 2.73 solar masses. Two seconds after the gravitational waves, orbiting telescopes detected a powerful, short gamma ray burst. Telescopes on Earth spotted the event's afterglow, which faded over several days from bright blue to dimmer red.

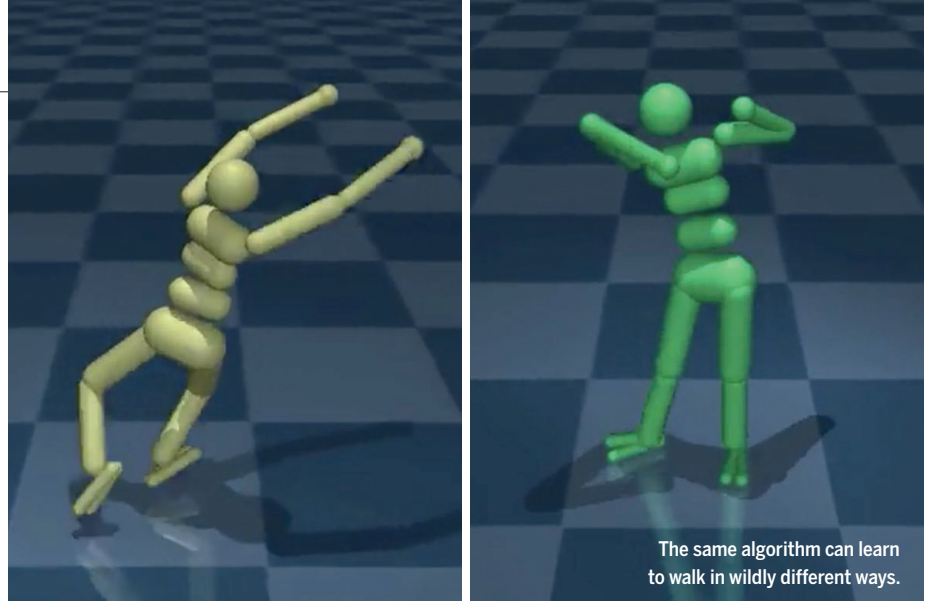
Together, the clues suggest the merger first produced a spinning, overweight neutron star momentarily propped up by centrifugal force. The afterglow shows that the merger spewed between 0.1 and 0.2 solar masses of newly formed radioactive elements into space, more than could have escaped from a black hole. The ejected material's initial blue tint shows that at first, it lacked heavy elements called lanthanides. A flux of particles called neutrinos presumably slowed those elements' formation, and a neutron star radiates copious neutrinos. The short gamma ray burst, the supposed birth cry of a black hole, indicates that the merged neutron star collapsed in seconds.

To derive their mass limits, the teams dove into the details of the spinning neutron star. They generally argue that at first the outer layers of the merged neutron star likely spun faster than its center. Then it flung off material and slowed to form a rigid spinning body whose mass researchers could calculate from the masses of the original neutron stars minus the ejected material. The fact that this spinning neutron star survived only momentarily suggests that its mass was close to the limit for such a spinner.

That last inference is essential, Rezzolla says. Theory suggests that the mass of a rigidly spinning neutron star can exceed that of a stationary one by up to 18%, he says. That scaling allows researchers to infer the maximum mass of a stationary, stable neutron star. The whole argument works because the initial neutron stars weren't so massive that they immediately produced a black hole or so light that they produced a spinning neutron star that lingered longer, Shibata says. "This was a very lucky event," he says.

The analyses are persuasive, Lattimer says, although he quibbles with the precision implied in numbers such as 2.17 solar masses. "If you say 2.2 plus or minus a 10th, I would think it gets the same message across." ■

IMAGES: YUVAL TASSA



The same algorithm can learn to walk in wildly different ways.

COMPUTER SCIENCE

Artificial intelligence faces reproducibility crisis

Unpublished code and sensitivity to training conditions make many claims hard to verify

By **Matthew Hutson**

Last year, computer scientists at the University of Montreal (U of M) in Canada were eager to show off a new speech recognition algorithm, and they wanted to compare it to a benchmark, an algorithm from a well-known scientist. The only problem: The benchmark's source code wasn't published. The researchers had to recreate it from the published description. But they couldn't get their version to match the benchmark's claimed performance, says Nan Rosemary Ke, a Ph.D. student in the U of M lab. "We tried for 2 months and we couldn't get anywhere close."

The booming field of artificial intelligence (AI) is grappling with a replication crisis, much like the ones that have afflicted psychology, medicine, and other fields over the past decade. AI researchers have found it difficult to reproduce many key results, and that is leading to a new conscientiousness about research methods and publication protocols. "I think people outside the field might assume that because we have code, reproducibility is kind of guaranteed," says Nicolas Rougier, a computational neuroscientist at France's National Institute for Research in Computer Science and Automation in Bordeaux. "Far from it." Last week, at a meeting of the Association for the Advancement of Artificial Intelligence (AAAI) in New Orleans, Louisiana, reproducibility was on the agenda, with some teams diagnosing the problem—and one laying out tools to mitigate it.

The most basic problem is that researchers often don't share their source code. At the AAAI meeting, Odd Erik Gundersen, a computer scientist at the Norwegian University of Science and Technology in Trondheim, reported the results of a survey of 400 algorithms presented in papers at two top AI conferences in the past few years. He found that only 6% of the presenters shared the algorithm's code. Only a third shared the data they tested their algorithms on, and just half shared "pseudocode"—a limited summary of an algorithm. (In many cases, code is also absent from AI papers published in journals, including *Science* and *Nature*.)

Researchers say there are many reasons for the missing details: The code might be a work in progress, owned by a company, or held tightly by a researcher eager to stay ahead of the competition. It might be dependent on other code, itself unpublished. Or it might be that the code is simply lost, on a crashed disk or stolen laptop—what Rougier calls the "my dog ate my program" problem.

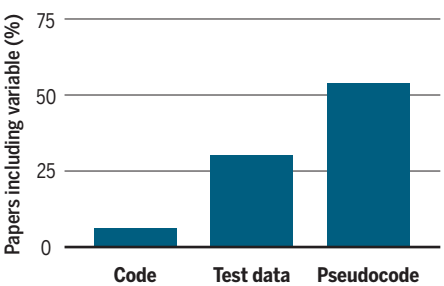
Assuming you can get and run the original code, it still might not do what you expect. In the area of AI called machine learning, in which computers derive expertise from experience, the training data for an algorithm can influence its performance.

Ke suspects that not knowing the training for the speech-recognition benchmark was what tripped up her group. "There's randomness from one run to another," she says. You can get "really, really lucky and have one run with a really good number," she adds. "That's usually what people report."

At the AAAI meeting, Peter Henderson, a computer scientist at McGill University in Montreal, showed that the performance of AIs designed to learn by trial and error is highly sensitive not only to the exact code used, but also to the random numbers generated to kick off training, and to "hyperparameters"—settings that are not core to the algorithm but that affect how quickly it learns. He ran several of these "reinforcement learning" algorithms under different conditions and found wildly different results. For example, a virtual "half-cheetah"—a stick figure used in motion algorithms—could learn to sprint in one test but would flail around on the floor in another. Henderson says researchers should document more of these key details. "We're trying to push the field to have better experimental procedures, better evaluation methods," he says.

Code break

In a survey of 400 artificial intelligence papers presented at major conferences, just 6% included code for the papers' algorithms. Some 30% included test data, whereas 54% included pseudocode, a limited summary of an algorithm.



Henderson's experiment was conducted in a test bed for reinforcement learning algorithms called Gym, created by OpenAI, a nonprofit based in San Francisco, California. John Schulman, a computer scientist at OpenAI who helped create Gym, says that it helps standardize experiments. "Before Gym, a lot of people were working on reinforcement learning, but everyone kind of cooked up their own environments for their experiments, and that made it hard to compare results across papers," he says.

IBM Research presented another tool at the AAAI meeting to aid replication: a system for recreating unpublished source code automatically, saving researchers days or weeks of effort. It's a neural network—a machine learning algorithm made of layers of small computational units, analogous to neurons—that is designed to recreate other neural networks. It scans an AI research paper looking for a chart or diagram describing a neural net, parses those data into layers and connections, and generates the network in new code. The tool has now reproduced hundreds of published neural networks, and IBM is planning to make them available in an open, online repository.

Joaquin Vanschoren, a computer scientist at Eindhoven University of Technology in the Netherlands, has created another repository for would-be replicators: a website called OpenML. It hosts not only algorithms, but also data sets and more than 8 million experimental runs with all their attendant details. "The exact way that you run your experiments is full of undocumented assumptions and decisions," Vanschoren says. "A lot of this detail never makes it into papers."

Psychology has dealt with its reproducibility crisis in part by creating a culture that favors replication, and AI is starting to do the same. In 2015, Rougier helped start *ReScience*, a computer science journal dedicated to replications. The large Neural Information Processing Systems conference has started linking from its website to papers' source code when available. And Ke is helping organize a "reproducibility challenge," in which researchers are invited to try to replicate papers submitted for an upcoming conference. Ke says nearly 100 replications are in progress, mostly by students, who may receive academic credit for their efforts.

Yet AI researchers say the incentives are still not aligned with reproducibility. They don't have time to test algorithms under every condition, or the space in articles to document every hyperparameter they tried. They feel pressure to publish quickly, given that many papers are posted online to arXiv every day without peer review. And many are reluctant to report failed replications. At *ReScience*, for example, all the published replications have so far been positive. Rougier says he's been told of failed attempts, but young researchers often don't want to be seen as criticizing senior researchers. That's one reason why Ke declined to name the researcher behind the speech recognition algorithm she wanted to use as a benchmark.

Gundersen says the culture needs to change. "It's not about shaming," he says. "It's just about being honest." ■

Matthew Hutson is a journalist in New York City.

CITIZEN SCIENCE

U.K. moms are turning parenting into an experiment

Unusual collaboration studies human milk, baby temperature, and schooling

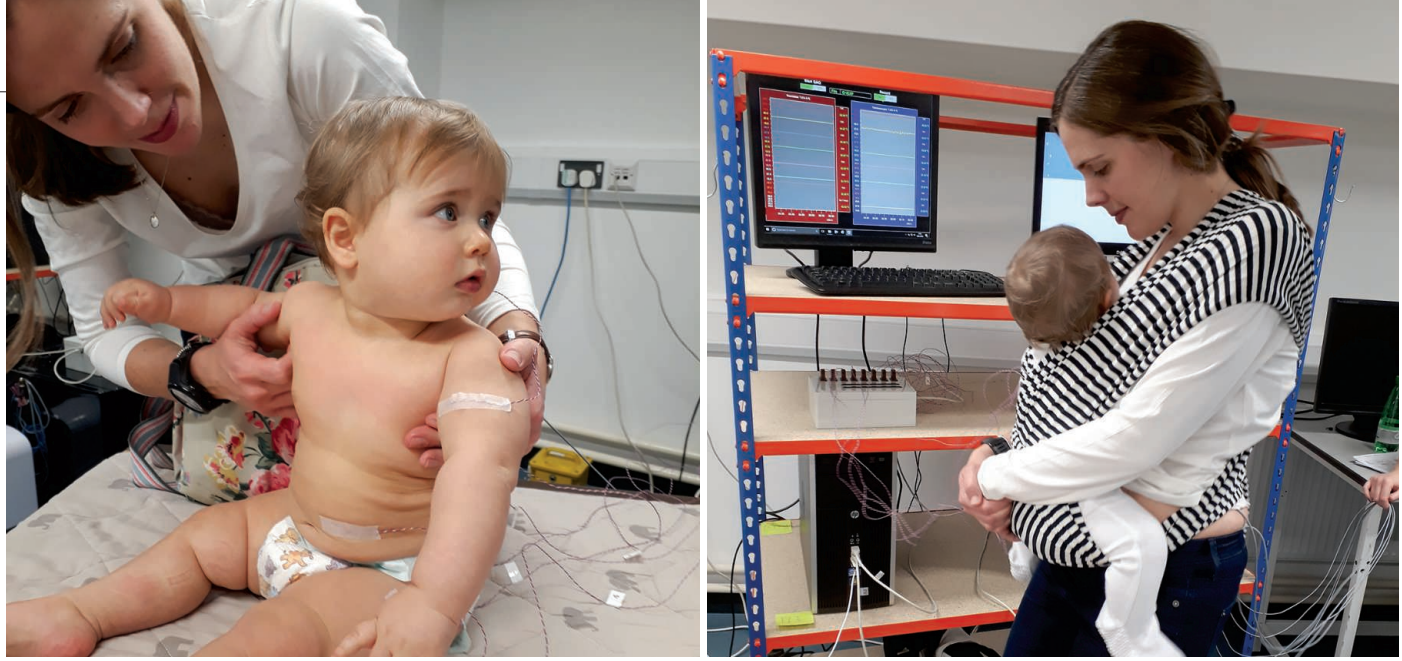
By **Tania Rabesandratana**

On 21 February, about 160 lactating mothers will head to Charing Cross Hospital in London to donate 25 milliliters of milk each for an unusual scientific study. The freshly pumped samples will be analyzed to determine how the composition of human milk changes with the nursling's age, from 3 months to 4 years old.

It's a matter about which surprisingly little is known. But the experiment is equally remarkable for its origin: A group of mothers came up with the idea for the study and designed it together with breast cancer researcher Natalie Shenker and microbial ecologist Simon Cameron, both at Imperial College London. The mothers recruited the milk donors—in just a few days—and they will be involved in the data analysis and possible write-ups.

This unusual collaboration was made possible by the Parenting Science Gang (PSG), a citizen science project in the United Kingdom funded by the Wellcome Trust. It links parents, gathered in Facebook groups around a specific interest, with scientists who help them design and carry out experiments. The project, which has already initiated multiple lines of research into issues such as schooling and gender stereotypes, is an effort to bring evidence to a realm rife with uncertainty and folk wisdom. "I try to raise my children with science in mind," explains Melissa Branzburg, a PSG member and mother of two.

Several blogs and publications have recently sprung up to address the growing hunger for evidence among science-minded parents, and some academics are dispensing advice as well. But PSG allows parents to take matters into their own hands. It was born from a smaller-scale project in which mothers studied which detergents were best to clean cloth diapers, or nap-



In one Parenting Science Gang study, sensors measure temperature variations when a baby is carried by an adult doing light exercise.

pies. ("There are no scientists looking at washable nappies," says PSG Founder and Director Sophia Collins.) The Nappy Science Gang ran from March to November 2015, with funding from the Wellcome Trust and the United Kingdom's Royal Society of Chemistry; it showed there was no evidence that "nonbiological" detergents—which lack dirt-attacking enzymes—help avoid skin irritation. The finding led the United Kingdom's National Health Service to rescind its recommendations to use them.

After the project ended, the trust donated £147,000 to launch PSG, which started in February 2017 and will run for 2 years. Some 2000 parents are involved, the vast majority of them women, despite efforts to include fathers. PSG addresses issues that matter to mothers, whereas funding agency committees "are often made up of middle-aged white men who have a different perspective," Collins says. "As a parent, our point of view is being taken seriously," says PSG member Mitch Wright, a mother of one. "It makes me feel empowered."

> ***"I try to raise my children with science in mind."***
>
> **Melissa Branzburg**, mother of two

The mothers behind the milk study want to know how human milk changes after children reach age 2. Mothers are often told there is no benefit to breastfeeding past a certain age, even though many children around the world wean between 2.5 and 7 years old. The study will also act as a pilot project to plan recruitment for a large study on the links between breast cancer risk and infant feeding, and it could benefit an area that Shenker is interested in as co-founder of the Hearts Milk Bank, based at the University of Hertfordshire in the United Kingdom, which provides donated milk to babies in neonatal units and for research purposes. At the moment, donors are recruited in the first 6 months of their baby's life and can donate until the infant reaches age 1. Yet Shenker says that preliminary evidence from other studies suggests that as a baby goes into toddlerhood, milk becomes higher-calorie and richer in antimicrobials. "Would that be more appropriate for a preterm baby? This could make a big difference. We don't know."

PSG members have plenty of other questions. One subgroup teamed up with environmental physiologist Davide Filingeri, head of the Thermosenselab at Loughborough University in the United Kingdom, to help answer a question that vexes many new parents: How many layers of clothing are needed to keep babies carried in a sling comfortable while avoiding overheating? There is "surprisingly little evidence" behind oft-repeated advice to give a baby "one extra layer of clothing" beyond what an adult would wear, Filingeri says. His role was to help translate the mothers' idea into a robust experimental design to measure babies' temperature variations in different conditions. The study, which is ongoing, will include about 15 mother-baby pairs.

A third PSG study focuses on flexi-schooling, an arrangement in which children are registered at school but attend part-time, for instance because their parents think they need additional support or to accommodate a special interest in art. The mothers will conduct a survey of parents of flexi-schooled children, as well as interviews with teachers, and will use Freedom of Information Act requests to learn the numbers of flexi-schooling requests and refusals in Scotland. Other, more recent PSG subgroups will focus on gender stereotypes, health care experiences around breastfeeding, as well as pregnancy and birth for women with a higher body mass index.

Wright says PSG has so inspired her that she wants to study chemistry or forensic science. But the goal is not to turn every parent into a scientist, Collins says; nor does she expect all participants to become experts at reading scientific literature. "But they might become more critical of what they read; they might seek information from a science magazine [or a clinical body] instead of a celebrity blog."

The studies are also an opportunity for parents to learn more about the process of science. In the milk study, for instance, the mothers had to understand the practical limitations of mass spectrometry, the technique used for analyzing the milk. "They had hoped to analyze a wider range of compounds in milk, such as antibodies," Cameron says. Filingeri says he insisted on keeping the temperature study's scope as specific as possible, explaining to the mothers that "it's more beneficial to focus on one question or one set of small questions." Tara Jones, an education researcher at the University of West Scotland in Paisley who provides guidance to the flexi-schooling group, encouraged the mothers to question their preconceptions and remain objective. "They'd made certain assumptions that flexi-schooling was a good thing," she says.

Carlos González, a pediatrician in Gavá, Spain, who wrote several parenting books peppered with peer-reviewed references, applauds the initiative—and yet he cautions that parenting often isn't about evidence, but about choices. "Science cannot tell us how to raise our children," González says. "Science can offer data that we can use to make decisions, but it cannot decide for us, because we have beliefs, principles, desires, and goals." ■

PHOTOS: DAVIDE FILINGERI

CELL BIOLOGY

'CAMERA' records cell action with new CRISPR tricks

The powerful genome editor shows off its versatility again

By **Jon Cohen**

Airplane flight recorders and body cameras help investigators make sense of complicated events. Biologists studying cells have tried to build their own data recorders, for example by linking the activity of a gene of interest to one making a fluorescent protein. Their goal is to clarify processes such as the emergence of cancer, aging, environmental impacts, and embryonic development. A new cellular recorder that borrows from CRISPR, the revolutionary genome editing tool, now offers what could be a better taping device that captures data on DNA.

In *Science* online this week, chemist David Liu and postdoc Weixin Tang, both of Harvard University, unveil two forms of what they call a CRISPR-mediated analog multievent recording apparatus, or CAMERA. In proof-of-concept experiments, they show in both bacterial and human cells how this tool can record exposure to light, antibiotics, and viral infection or document internal molecular events. "The study highlights the really creative ways people are harnessing discoveries in CRISPR to build these synthetic pathways," says Dave Savage, a protein engineer at the University of California, Berkeley.

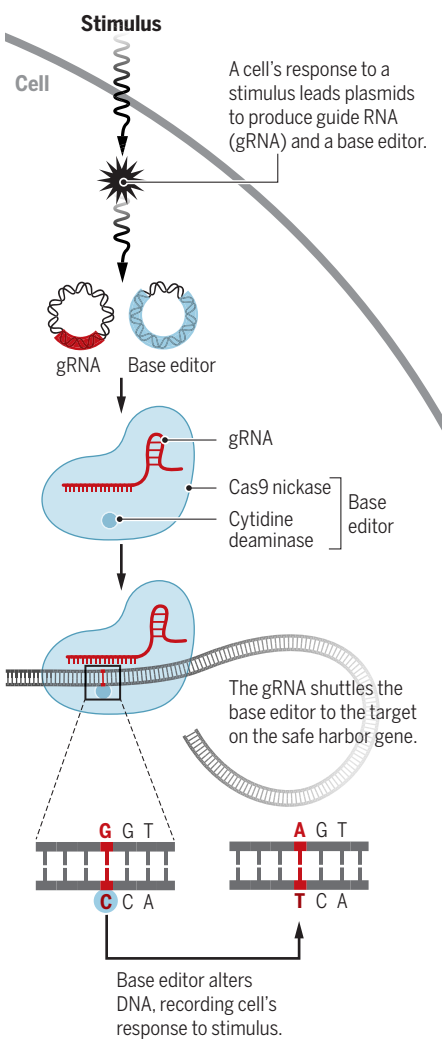
Other investigators have created recording devices with CRISPR components, among them Timothy Lu of the Massachusetts Institute of Technology in Cambridge (*Science*, 9 September 2016, p. 1115). But Lu notes that his system was limited to bacteria, and compared with CAMERA it required "an order of magnitude" more cells to reliably record signals and had a much poorer signal-to-noise ratio. The new work, he says, "is really beautiful stuff" and has "a level of efficiency and precision that goes beyond what we did earlier." (Lu this week plans to release a preprint describing a system similar to one version of CAMERA.)

The original use of CRISPR was to target and cut double-stranded DNA. Cells naturally repair these cuts, but in the process, they can introduce random, or stochastic, errors to a target gene, disabling it. Several groups have used these random errors as markers—or barcodes—to track how cells "differentiate" from one state to another.

Liu sought a cleaner readout. "We wanted to shy away from that stochastic mixture. It's much harder to interpret your findings." His team also aimed to record not just whether a cell experienced a stimulus, but how strong it was and how long it lasted. To better understand cancer, for example, Liu says, "We'd love to be able to see whether cells in certain states listen to or ignore signals to stop growing."

A new lens on cells

One form of a research tool called CAMERA engineers cells to record signals triggered by various stimuli using the DNA of a "safe harbor" gene.



One form of CAMERA takes advantage of a peculiarity of bacteria: the circular "plasmids" of DNA that float in their cytoplasm, copying themselves but tightly regulating their population size. The researchers introduced two "recorder" plasmids, R1 and R2, that settle at a stable ratio. They then fashioned a separate plasmid with genes for CRISPR's components—a "guide" RNA (gRNA) that targets a DNA sequence and the Cas9 enzyme that cuts the double helix. Those genes are designed to kick into action, making the components that target R1 for destruction, when the cell experiences a specific stimulus. In one test, they equipped bacteria with an antibiotic-activated CAMERA. By sequencing the plasmids and documenting how the R1:R2 ratio had changed, they could tell how long the cells had been exposed to the drug.

A second CAMERA makes use of a modified Cas9 that doesn't cut the double helix and is linked to an enzyme that chemically switches cytosine, one of four DNA bases, into another one, thymine (see diagram, left). To record an event, the gRNA shuttles this so-called base editor to a "safe harbor" gene, whose DNA can be altered without harming the cell. Again, the researchers tailor the system to respond to specific signals. As a test, they stimulated human cells to activate the Wnt signaling pathway, which plays a role in the development of embryos and in cancer. CAMERA turned on in the presence of Wnt activity, inscribing a record of those signals in the safe harbor gene.

CAMERA works in samples that contain as few as 10 cells, nearing the goal of recording the actions of a single cell. "If you're doing the activity map of the brain, each cell is a different story," notes Harvard geneticist George Church, whose own lab has developed CRISPR-based recording devices. "Ideally you'd have a nice single molecule ticker tape recording of a DNA sequence that you could read off and it tells you what was happening in each cell over the function of time."

CAMERA has other potentially useful features, including the ability to erase its recorded information, with drugs that "reset" the plasmid ratio to their baseline, for example. CAMERA also can record several different signals at the same time or one after the other. But for CAMERA to prove its worth in the crowded biological recording field, researchers have to show that it can work when engineered into the cells of an animal—not simply in the cell line used in Liu's Wnt experiment. "The real power is what's going to happen next," Savage says. "Right now, the killer app is still to come." ■

GRAPHIC: K. SUTLIFF/*SCIENCE*

NUCLEAR SAFETY

Isotope cloud linked to failed neutrino source

Mishandling of spent fuel in Russia may have caused radioactivity to spread across Europe

By **Edwin Cartlidge**

For 2 weeks in September and October last year, traces of the human-made isotope ruthenium-106 wafted across Europe, triggering detectors from Norway to Greece and Ukraine to Switzerland. The radioactive cloud was too thin to be dangerous, containing no more than a few grams of material, but its origin posed an outsize mystery.

Now, scientists at the French Institute of Radioprotection and Nuclear Security (IRSN) in Paris say the isotope may have been released from the Mayak nuclear facility near Ozyorsk in southern Russia. IRSN argues that the leak could have taken place when Mayak technicians botched the fabrication of a highly radioactive component for a physics experiment at the Gran Sasso National Laboratory in L'Aquila, Italy.

The Russian government and state nuclear operator Rosatom have vehemently denied that an accident took place, however. Meanwhile, an international committee set up by the Russian Academy of Sciences's Nuclear Safety Institute (IBRAE) in Moscow that met on 31 January is divided over the origins of the pollution.

Based on a computer model that used the air-sampling data and weather patterns, IRSN concluded in early October 2017 that the ruthenium most likely originated in the southern Urals; its German counterpart agreed. The French team went on to rule out a number of potential sources, including a mishap at a nuclear reactor. Such an incident would have spewed many other radioactive pollutants besides ruthenium.

The southern Urals are home to the secretive Mayak facility, the scene of one of the world's worst nuclear accidents 60 years ago, and speculation soon turned to a possible accident at its reprocessing plant, which extracts isotopes from spent nuclear fuel. The IRSN report, made public on 6 February, says Mayak's attempt to manufacture a capsule of cerium-144 destined for Gran Sasso "should be investigated" as a possible cause. Scientists at Gran Sasso needed the cerium for a search—now called off—for hypothetical particles called sterile neutrinos.

The estimated amount of radioactive ruthenium released could only have come from processing several tons of spent nuclear fuel, IRSN says. What's more, the ratio of ruthenium-106 to the faster-decaying isotope ruthenium-103, detected in smaller amounts last autumn, reveals that the fuel must have been removed from its reactor only a year or two earlier. Spent fuel is normally cooled for up to a decade before it is reprocessed, so it seems the plant was preparing material for an application requiring high levels of radioactivity, IRSN says.

That fits the description of the sterile neutrino experiment at Gran Sasso, known as SOX and supported by Italy's National Institute for Nuclear Physics (INFN) and the French Alternative Energies and Atomic Energy Commission. It required a source that was both extremely radioactive and very small, says SOX spokesperson Marco Pallavicini, a particle physicist at the University of Genoa in Italy. He says Mayak Production Association, the only company able to supply it, signed a contract in fall 2016 to produce a cerium capsule, expected to arrive in early 2018.

But in December 2017 the company stated it could not reach the desired radioactivity level. ("The Russians said absolutely nothing" about a radiation leak, Pallavicini says.) That meant SOX would lack the required sensitivity, and on 1 February, INFN announced it had axed the experiment, in what Pallavicini described as "a big blow" for scientists.

Jean-Christophe Gariel, IRSN's director of health, says an uncontrolled temperature rise during the separation of cerium from the spent fuel at Mayak might have converted some of the ruthenium in the waste to gaseous ruthenium oxide. That gas would have escaped through the facility's filters and solidified in the cool outside air, he says, turning into small solid oxide particles that could have wafted across Europe.

IBRAE Director Leonid Bolshov calls IRSN's scenario "a good hypothesis," but says it's incorrect. For one thing, he says, the separation process never reached "the hot phase." And in any case, he adds, "major operations" on the spent fuel at Mayak were done in late October 2017, after the ruthenium release. Bolshov says that a "rather rare meteorological event" might have transported the ruthenium from an as-yet-unidentified place to the southern Urals, from which it then appeared to spread.

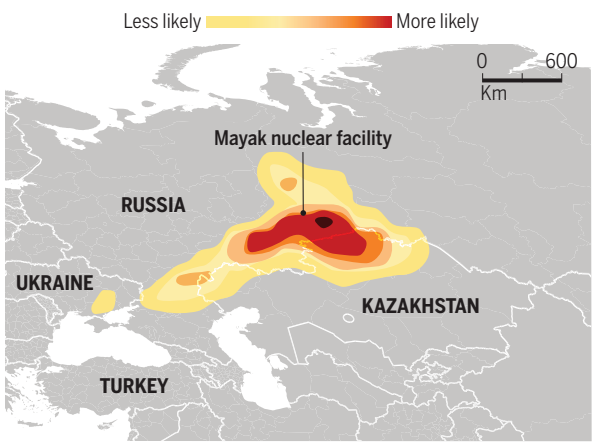
Non-Russian members of IBRAE's international panel, which is due to meet again in April, support IRSN's conclusion that the southern Urals is the likely source of the leak, says IRSN physicist Jean-Luc Lachaume, a panel member, although some argue that the region is too large to pinpoint an exact location. Russian members claim the leak could have arisen "in the eastern part of the Russian federation," Lachaume says. He says a representative of the Russian nuclear regulator Rostechnadzor who inspected Mayak in November 2017 told the panel that he saw no anomalies from a month earlier, but didn't supply data to support that statement.

Princeton University physicist Frank von Hippel, a nonproliferation expert, says he doesn't see "anything wrong with the IRSN analysis." He notes that the amount of ruthenium-106 that the French team estimates was emitted—between 1 gram and 4 grams—matches the 30 grams of cerium-144 required for SOX, given that spent fuel contains the two isotopes in a ratio of about one to 14. And although the cloud over Europe was harmless, an accident at Mayak could mean that people living close by took in "potentially significant lung doses," Von Hippel says. ■

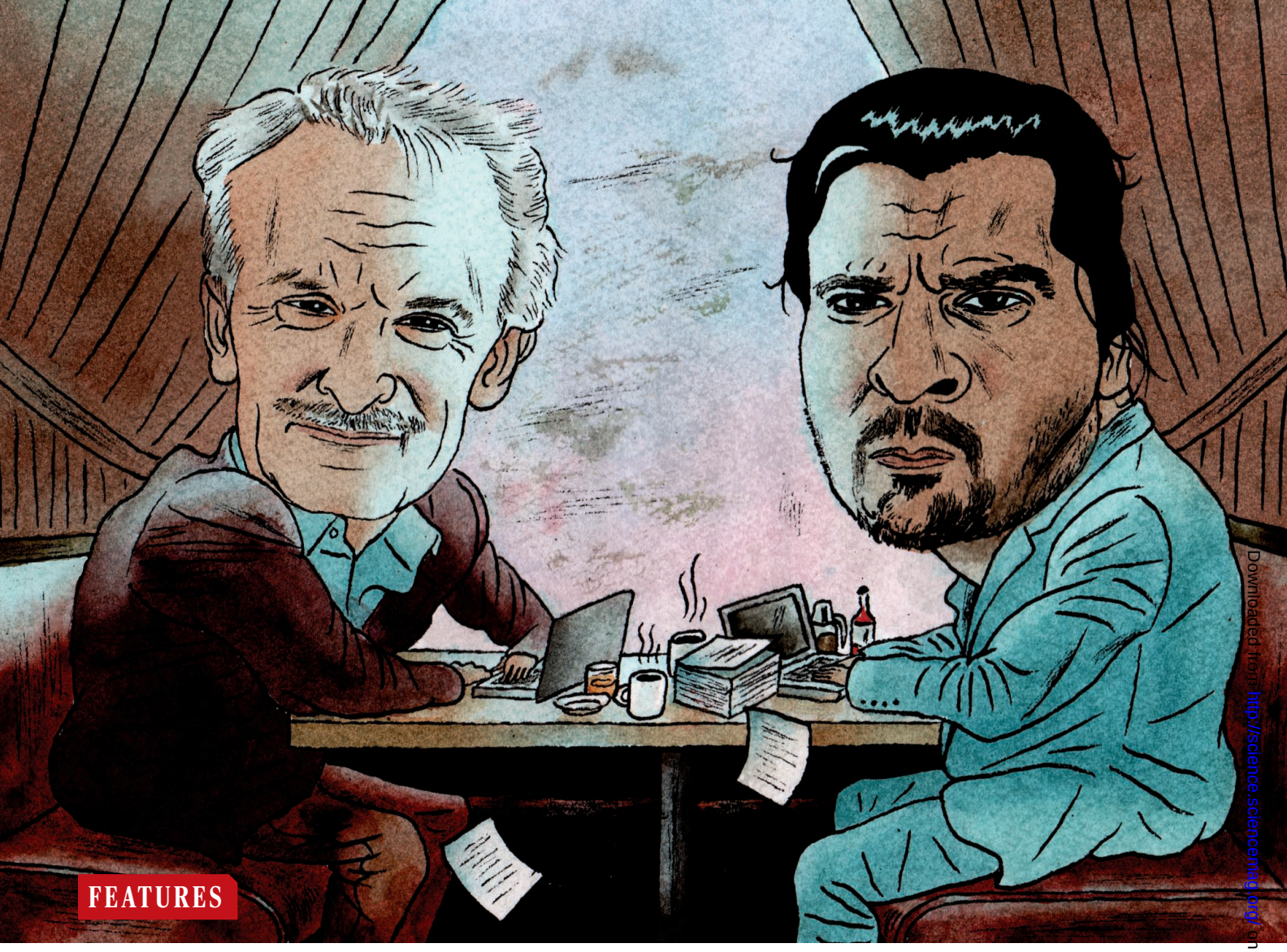
Edwin Cartlidge is a journalist in Rome.

Pinpointing an accident

A simulation by French scientists shows where the ruthenium-106 cloud probably originated; darker colors denote a higher likelihood.



CREDITS: (GRAPHIC) N. DESAI/*SCIENCE*; (DATA) INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE



THE DATA THUGS

Nick Brown and James Heathers have had striking success in catalyzing retractions by publicly calling out questionable data

By **Adam Marcus** *and* **Ivan Oransky**, *Retraction Watch*

In 2015, Nick Brown was skimming Twitter when something caught his eye. A tweet mentioned an article by Nicolas Guéguen, a French psychologist with a penchant for publishing titillating findings about human behavior, for example that women with large breasts get more invitations to dance at nightclubs, or blond waitresses get bigger tips. Now, Guéguen was reporting that men are less likely to assist women who tie up their hair.

Brown, a graduate student in psychology at the University of Groningen in the Netherlands, sent an email about the study to James Heathers, a postdoc in behavioral science at Northeastern University in Boston whom he had met a few years earlier. The description alone triggered a laughing spell in Heathers—not an uncommon reaction to science he finds risible.

Once the chuckling stopped, Brown and Heathers took a deeper look at the findings reported by Guéguen, who works at the University of Southern Brittany in Vannes, France. Many failed the duo's homegrown test for statistical rigor. The pair also found

ILLUSTRATION: ANDY FRIEDMAN

Corrected 15 February 2018. See full text.

Nick Brown (left) and James Heathers (right) act as enforcers when they spot anomalies in the literature.

odd data in nine other articles from Guéguen.

Soon, Brown and Heathers were asking Guéguen and the French Psychological Society about the numbers. The pair says Guéguen failed to adequately address their questions, and the society agreed that their critique seemed well-grounded. So late last year, the men did something that many scientists might find out of bounds: They went public, sharing their concerns with a reporter for Ars Technica, which published a story, and posting their critiques on a blog. (Guéguen declined to discuss the matter with *Science*; the society says a university panel is examining the papers.)

When it comes to correcting scientific literature, styles vary. Some scientists prefer to go through "proper channels," such as private conversations or letters to the editor. Others leave anonymous comments on online forums, such as PubPeer, set up to discuss papers. Then there is the more public approach Brown and Heathers are taking.

The two watchdogs have been remarkably effective at uncovering problematic publications. So far, Brown estimates that the analyses he and Heathers have done, sometimes working independently and often with other collaborators, have led to corrections to dozens of papers and the full retraction of about 10 more. That total includes five papers retracted over the past year or so by Brian Wansink, a high-profile nutrition researcher at Cornell University.

The duo concedes that their assertive style might rub some scientists the wrong way. Heathers, who has called himself "a data thug," notes that in academia "the squeaky wheel gets Tasered." But other researchers laud the pair as the vanguard of a movement to make science more rigorous. "Without people like them actively scouring the literature [it is easy for] misbehavior to go unnoticed," says psychologist Brian Nosek of the University of Virginia in Charlottesville and founder of the Center for Open Science, which promotes replication efforts. "I might see a paper and say, 'I don't believe that,' and put it aside. They're willing to pursue it … wherever it goes."

As a result, Brown and Heathers have become go-to whistleblowers of a sort: Researchers now pepper the pair with tips about suspect papers. "It's like a work tumor we've been infected with," Heathers says. "You talk about these things in public and all of a sudden people start bringing these things to you."

THE PARTNERSHIP is unlikely, an odd-couple pairing made possible only by the sociological blender that is the internet.

Brown, 57, is a demure ex-pat raised in Birmingham, the second largest city in the United Kingdom. He started out as an engineering student at the University of Cambridge, but "my maths weren't good enough," he says, and he wound up working as a computer network manager.

That position led to one of two encounters that Brown says fostered his current pursuits. While attending a human resources conference he met a U.K. psychologist, Richard Wiseman, who in 2010 wrote an influential blog post critiquing the methods of a soon-to-be published study by Cornell psychologist Daryl Bem purporting to demonstrate the existence of extrasensory perception. Brown says the chance meeting "planted the seed" that led him to seek a master's degree in psychology at the University of East London.

That coursework led to his first successful scientific debunking. In 2013, he teamed up with two other academics, one of whom was Alan Sokal of New York University in New York City, a mathematician and physicist who in 1996 perpetrated one of the most famous scientific hoaxes ever by getting a cultural studies journal to publish a gobbledygook paper (*Science*, 1 December 2000, p. 1703). They published a critique of a leading paper on psychological theory, noting that the formulas in the paper relied on irrelevant equations from the field of fluid dynamics. Their article eventually triggered the paper's partial retraction.

> ***"Hey, we found these problems with this article in your journal, you might want to check it out."***
> **Nick Brown**, University of Groningen

The episode showed Brown that well-crafted arguments about flawed research are hard for editors to ignore. In 2014, he waded into another controversy, this one surrounding Diederik Stapel, a notorious fraudster from Tilburg University in the Netherlands who fabricated dozens of studies in the field of behavioral psychology (*Science*, 7 December 2012, p. 1270). This time, Brown jailbroke Stapel's memoir by translating it into English and posting the document on a public website. The memoir offered Stapel's take on the fraud, but was available only in Dutch behind an online paywall.

Brown's second pivotal encounter came that same year with Heathers, through a Facebook group that had been discussing concerns with a paper on heart rate variability, a topic Heathers had once studied.

The two are temperamental opposites. Whereas Brown does not consider himself a crusader and has no trace of the swashbuckler, the Australian-born Heathers, 35, revels in acting like a dinner guest who farts loudly—and unapologetically—during grace. And he appears constitutionally unable to accept authority.

As an undergraduate at The University of Sydney (where he also earned master's and doctorate degrees), Heathers began studying economics, but switched to physiology, "which I didn't like because I got into fights with the lecturers all the time when they said stuff I didn't agree with." So, he shifted again, to psychology. Then his supervisor's mother was murdered; the tragedy removed his mentor from the scene and effectively left Heathers with no one to guide him in the niceties of academia. "I spent most of the next 3 years trying to figure things out by myself," Heathers says. "I had no sense of normal academic parameters or what I should be doing."

Heathers drifted back to physiology, this time with an emphasis on what he loosely calls "data stuff." Simply put, that means critiquing the results of other researchers. "My normal day at work, when I'm not doing metascience, is retrieving measurements from other people" and telling them where they've gone astray, he says. "I'm usually the bearer of bad news."

When the two work together, usually one party is clearly in the lead. "We don't turn up as the dynamic duo," Brown says. "It's usually an 80/20 or 90/10 split. Sometimes I'm doing most of the work and James is just there to put up with my profanity and check I'm not going down a rabbit hole, and vice versa."

THE RUDIMENTS of the duo's mathematical approach began to take shape in 2015, as they began to jointly examine Guéguen's papers.

One technique, which they describe in a May 2016 posting on Heathers's blog, looks at what the researchers call the granularity-related inconsistency of means, or GRIM. The essence of the test is the disarmingly simple fact that the mean value in a collection of N integers must be a fraction whose denominator is N. For example, it might seem plausible if a researcher running a study involving 12 children aged 11 to 17 reports a mean age of 15.7. (After all, it's less than 17 and greater than 11.) But the GRIM test reveals that value is mathematically impossible, because 15.7 is not a number that

Corrected 15 February 2018. See full text.

can be produced by dividing the sum of the ages by 12.

The GRIM test is little more than "glorified adding up," says Heathers, and the two don't see it primarily as a way of detecting misconduct. Rather, "We are looking for mistakes. That's literally it." The GRIM is ideal for spotting errors in psychology and other fields that report results from small samples, its creators note. But they readily acknowledge that it doesn't work for large studies and more complex data sets.

For those, Heathers came up with a somewhat more sophisticated test, which he and Brown call sample parameter reconstruction via iterative techniques, or SPRITE. In essence, SPRITE allows the researchers to do some reverse engineering: deriving statistically possible data sets from the means and standard deviations reported in a study.

SPRITE has figured heavily in the pair's analyses of papers by Cornell's Wansink, who received extensive media coverage for his studies of nutrition and eating habits. The test showed that the data in at least one of his studies—a 2012 article in the journal *Preventive Medicine* looking at carrot consumption among school children—appeared iffy. How so? Running the published data through SPRITE showed that at least one child in the sample would have had to have eaten roughly 60 carrots in a single sitting. That amount, Heathers quips, is more appropriate for a cart horse than a child. (Wansink, who declined to be interviewed for this story, recently published a lengthy correction to the paper, stating it measured "matchstick carrots," four of which are equivalent to one baby carrot.)

Despite the charged nature of their work—after all, careers can be on the line—Brown and Heathers have attracted surprisingly little criticism from their peers in science. In part, that's likely because of their strategy of gently but methodically ratcheting up the pressure on authors and journals. For example, the Wansink analysis, like others the pair has undertaken, began with "some very polite" emails asking for data from the researcher's department, Brown says, as well as from Cornell's Office of Research Integrity and Assurance. "But both of those stopped replying to us once—we assume—our questions became too awkward." (The university has said it is investigating the papers.) At about the same time, Brown and two collaborators—Jordan Anaya and Tim van der Zee, a graduate student at Leiden University in the Netherlands—were working on a preprint that they posted in *PeerJ* titled "Statistical heartburn: An attempt to digest four pizza publications from the Cornell Food and Brand Lab."

"Once we had our preprint online, we moved to blogging about new issues as they arose," Brown recalls. "At one point I wrote three blogs posts in as many weeks and someone commented, 'Ah, I see it's Wansink Wednesday.'" By early 2017, after the media picked up on the affair, Brown says, "We felt we had established enough questions to start writing to the journal editors." But he says even those emails tended to take a sabers-sheathed tone: "'Hey, we found these problems with this article in your journal, you might want to check it out.' I thought that was less provocative than an outright demand for a retraction."

Soon, however, Wansink had begun retracting five papers and correcting more than a dozen. That unusual turn of events prompted Brown to launch a Twitter poll, asking his followers whether he should add the results of his data sleuthing to his resume. The responses were decidedly mixed: Thirty-five percent said it was "cool," whereas 24% chose "WTF." The other options—"OK, I guess," and "Cheesy"—earned 25% and 16% of the votes, respectively.

> ***"In short, peer review misses all the hard stuff, and a worrying amount of the easy stuff."***
>
> **James Heathers**, Northeastern University

SOME EDITORS and publishers are clearly paying attention. The Wansink episode made "clear to us … that online fora for postpublication discussion are a valuable part of the scientific record," says Gearóid Ó Faoleán, the London-based ethics and integrity manager for Frontiers in Lausanne, Switzerland; one of its journals retracted a 2016 paper by Wansink after being alerted to the *PeerJ* preprint and Brown's blog. The preprint also prompted editors at the *Journal of Sensory Studies* to investigate a 2014 Wansink paper they had published, and ask for a correction, which the researcher made last August.

Other would-be data whistleblowers are impressed by the duo's success in getting journals to act. Paul Brookes, of the University of Rochester Medical Center in New York, briefly used his now-defunct blog, sciencefraud.org, to highlight questionable papers anonymously. Brookes, who was outed amid legal threats in 2013 after only 6 months, says he would "routinely write dozens of emails [to journal editors], and it was common to have no response at all."

Elisabeth Bik, now a science editor at uBiome in San Francisco, California, experienced similar silence. When Bik was a researcher at Stanford University in Palo Alto, California, she spearheaded an analysis of 20,000 papers, published in *mBio* in 2016, that concluded that 4%, or 800, contained inappropriately manipulated images. She contacted most of the journals involved more than 2 years ago, but only about one-third have responded.

It's not clear why Brown and Heathers have gotten a better response—it may be that the overall climate has changed—but they say just about anyone with rudimentary math skills and a willingness to go public could replicate what they are doing. So why aren't more scientists following suit?

One big obstacle, they say, is that many are reluctant to rock the boat. "Some people have a block on criticizing others, even to themselves," Brown says. Their reaction to evident problems is to flinch, as if a scientific superego is saying: "Am I allowed to get this professor's article and read it? And will something bad happen to me if I recalculate the mean?"

Another hurdle is an overabundance of trust. "Other people really sort of lack the mindset that this might even be necessary," Heathers says. "There's no guide to spotting errors. There's no text that you can read. What we have done so far has been quite ad hoc."

The pair also admits it enjoys luxuries—time and freedom—that many scientists with pressing grants and academic appointments do not have. "When you have funding, people expect reports on what you've done with their money," Heathers says. "They also don't expect you to investigate them."

Still, Heathers believes the sleuthing efforts the two have developed are the "thin end" of a growing wedge of analytic techniques that, once refined, can be formalized and taught to anyone. Eventually, he would like to produce a scalable, online course to spread the methods. "Then things get really interesting," he predicts, in part because traditional peer review has failed to catch so many problems. "In short, peer review misses all the hard stuff, and a worrying amount of the easy stuff."

For the moment, however, the pair is content to have helped start a conversation about publicly confronting potentially problematic results, however uncomfortable it might be for some researchers—and science writ large. "The black flag has been hoisted," Heathers has written. "It isn't coming down." ■

Adam Marcus and Ivan Oransky are co-founders of Retraction Watch. This story is the product of a collaboration between Science *and Retraction Watch.*

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PHOTO: SEAN BAGSHAW/GETTY IMAGES

THE CARBON HARVEST

Vast bioenergy plantations could suck up carbon and stave off climate change. They would also radically reshape the planet

By **Julia Rosen**

On a sunny day this past October, three dozen people file into a modest, mint-green classroom at Montana State University (MSU) in Bozeman to glimpse a vision of the future. Some are scientists, but most are people with some connection to the land: extension agents who work with farmers, and environmentalists representing organizations such as The Nature Conservancy. They all know that climate change will reshape the region in the coming decades, but that's not what they've come to discuss. They are here to talk about the equally profound impacts of trying to stop it.

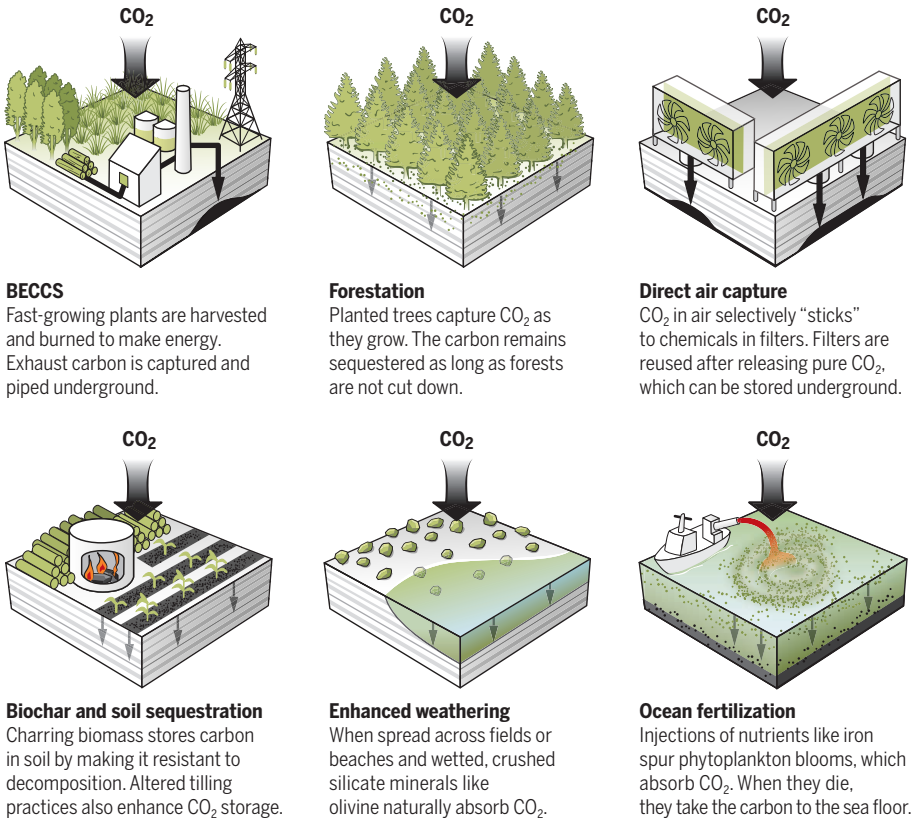
Paul Stoy, an ecologist at MSU, paces in front of whiteboards in a powder blue shirt and jeans as he describes how a landscape already dominated by agriculture could be transformed yet again by a different green revolution: vast plantations of crops, sown to sop up carbon dioxide (CO_2) from the sky. "We have this new energy economy that's necessary to avoid dangerous climate

A poplar tree farm in Oregon is a fast-growing bioenergy source.

Take it back

Researchers are pursuing a handful of negative emissions technologies (NETs) that would mitigate global warming by pulling carbon dioxide (CO_2) out of the atmosphere. A prominent NET is bioenergy with carbon capture and storage (BECCS), because it combines existing technologies.

Six ways to pull CO_2 out of the air



BECCS
Fast-growing plants are harvested and burned to make energy. Exhaust carbon is captured and piped underground.

Forestation
Planted trees capture CO_2 as they grow. The carbon remains sequestered as long as forests are not cut down.

Direct air capture
CO_2 in air selectively "sticks" to chemicals in filters. Filters are reused after releasing pure CO_2, which can be stored underground.

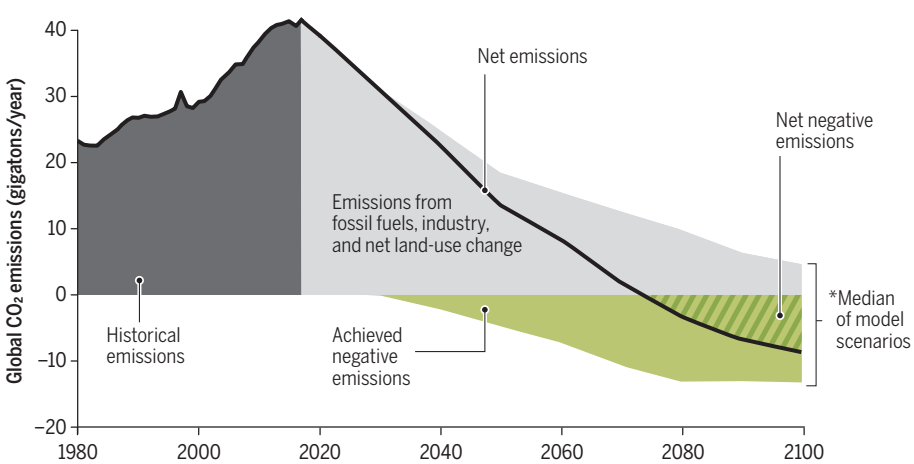
Biochar and soil sequestration
Charring biomass stores carbon in soil by making it resistant to decomposition. Altered tilling practices also enhance CO_2 storage.

Enhanced weathering
When spread across fields or beaches and wetted, crushed silicate minerals like olivine naturally absorb CO_2.

Ocean fertilization
Injections of nutrients like iron spur phytoplankton blooms, which absorb CO_2. When they die, they take the carbon to the sea floor.

A global unwinding

In order to prevent the world from warming more than 2°C, models count on the fast development of NETs. But many scientists question whether they can be scaled up in time.



*Median values at 10-year time steps of 18 scenarios evaluated by six models using shared socioeconomic pathways assessed in the next report of the Intergovernmental Panel on Climate Change.

change, but how is that going to look on the ground?" he asks.

In 2015, the Paris climate agreement established a goal of limiting global warming to "well below" 2°C. In the most recent report of the Intergovernmental Panel on Climate Change, researchers surveyed possible road maps for reaching that goal and found something unsettling. In most model scenarios, simply cutting emissions isn't enough. To limit warming, humanity also needs negative emissions technologies (NETs) that, by the end of the century, would remove more CO_2 from the atmosphere than humans emit. The technologies would buy time for society to rein in carbon emissions, says Naomi Vaughan, a climate change scientist at the University of East Anglia in Norwich, U.K. "They allow you to emit more CO_2 and take it back at a later date."

Whether that's doable is another question. Some NETs amount to giant air-purifying machines, and many remain more fiction than fact. Few operate at commercial scales today, and some researchers fear they offer policymakers a dangerous excuse to drag their feet on climate action in the hopes that future inventions will clean up the mess. "In many ways, we're saying we expect a bit of magic to occur," says Chris Field, a climate scientist at Stanford University in Palo Alto, California, who instead favors drastic emissions reductions. Others say we no longer have a choice—that we have dallied too long to meet the Paris targets solely by tightening our belts. "We probably need aggressive and immediate mitigation, plus some negative emissions," says Pete Smith, a soil scientist and bioenergy expert at the University of Aberdeen in the United Kingdom.

One particular technology has quietly risen to prominence—thanks to global models—and it is the one on tap in Bozeman. The idea is to cultivate fast-growing grasses and trees to suck CO_2 out of the atmosphere and then burn them at power plants to generate energy. But instead of being released back into the atmosphere in the exhaust, the crops' carbon would be captured and pumped underground. The technique is known as bioenergy with carbon capture and storage, or—among climate wonks—simply as BECCS.

Few at the Bozeman meeting have heard of BECCS, and most are suspicious; it sounds like a far-fetched scheme that might disrupt the world as they know it. During a break, Martha Kauffman, a regional director for the World Wildlife Fund in Bozeman, wonders whether BECCS might encroach on lands used to graze cattle. In grasslands like this, she says, "It's the pri-

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mary way people make a livelihood while keeping habitat."

She's not the only one who's wary. Although BECCS is relatively cheap and theoretically feasible, the sheer scale at which it operates in the models alarms many researchers. In some future scenarios, BECCS would remove up to a trillion tons of CO_2 from the air by the end of the century—about half of what humans have emitted since the start of the Industrial Revolution—and it would supply a third of the globe's energy needs. Such a feat would require growing bioenergy crops over an area at least as large as India and possibly as big as Australia—half as much land as humans already farm. "It is easy to say, 'Hey, globally, how about we just do this, guys?'" Stoy says to the room. "But what is actually going to happen?"

Stoy and a team of researchers hope to provide answers gleaned from the Upper Missouri River Basin, which includes parts of Montana, Wyoming, and the Dakotas. They have just launched a $6 million effort to study the impacts of BECCS on such things as local food production, water use, and biodiversity. In other words, what happens when you pluck BECCS from the idealized realm of global carbon accounting and plop it into a real place, with patchwork lands, messy politics, and interconnected ecological, physical, and economic systems? "Nobody's evaluated what these assumptions mean at the regional scale," says Ben Poulter, a carbon cycle modeler at NASA's Goddard Space Flight Center in Greenbelt, Maryland, and a leader of the project. "It's really important that we try to figure that out."

After all, the future of climate policy—and possibly the planet—hangs on the answer.

A bioenergy field trial in Wisconsin is evaluating how switchgrass, *Miscanthus*, corn stover, poplar trees, and native prairie grasses stack up against each other.

PHOTO: GREGG SANFORD/GREAT LAKES BIOENERGY RESEARCH CENTER/FLICKR/CC BY-NC-ND 2.0

IN EARLY FALL, Montana's Gallatin Valley is a study in gold. Flame-leafed cottonwoods burn like candles along the narrow country lanes, and the hills wear a mantle of thick, honey-colored grass. Dale Flikkema, a third-generation farmer, almost blends into the landscape. With sandy hair and a sun-bronzed face, he surveys his field on the outskirts of Bozeman. Beneath the yellow canola stubble at his feet, stray seeds have sprouted into tiny sprigs of green. "These spilled from my combine," he says, kneeling to inspect them. Today, this food-grade canola—which can also be used to make biodiesel—is the closest thing to a bioenergy crop being grown in Montana. But under the models' BECCS scenarios, farmers like Flikkema would see big changes.

As BECCS is usually conceived, bioenergy crops would be grown on unused agricultural land. In the Upper Missouri River Basin, that could mean conscripting fields set aside as part of the U.S. Department of Agriculture's Conservation Reserve Program (CRP), which pays farmers to leave fields fallow for environmental benefits. Given the right incentives, farmers could pull these lands back into production—something that has already happened in the region as demand for corn and soy have grown. "Farmers are no different than anyone else. We are profit-driven," Flikkema says.

Here in Montana, farmers' bioenergy crop options are limited for now. Only a few adventurous growers like Flikkema are experimenting with canola and other oilseeds. As the climate warms, however, the entire region is projected to become more hospitable to plants such as switchgrass, a towering grass called *Miscanthus*, and vigorous poplar trees. These "second-generation" bioenergy crops are often seen as the future of bioenergy because, as perennials, they are far better at storing carbon in the soil and in their biomass than traditional fuel crops like corn and canola. They can also grow on marginal lands with less fertilizer and water, making it less likely they will compete with food production.

Once harvested, these crops would get ferried by truck or train to power plants and other industrial facilities where, along with waste from food crops and timber harvests, they would be burned for heat or electricity, or converted to ethanol and other liquid biofuels. The CO_2 given off by either process would be siphoned off and compressed into a fluid. That concentrated CO_2 would be piped away and pumped underground into porous rock formations, which abound in the Upper Missouri River Basin. Because of its long history of oil and gas production, the area is perforated with wells. Lee Spangler, an MSU chemist involved with the project, is studying whether any of the 11,000 wells near the Colstrip Power Plant in eastern Montana, for instance, would be good conduits for injecting carbon underground. The final result? Carbon is transferred from the atmosphere back to the geologic reservoirs from which it came.

BECCS isn't the only route to negative emissions. But alternative approaches, like capturing CO_2 directly from the air using chemical reactions or absorbing it with ground-up minerals added to soils, are just beginning to see their first real-world tests (see graphic, p. 734). These techniques could one day surpass BECCS, but for now, they cost more, Vaughan says. "BECCS will pay for itself to some extent because it generates energy."

BECCS isn't a total technological reach, either; its two components—bioenergy and CCS—are already happening to some degree today. Power plants around the world are burning biomass for energy, either alone or together with fossil fuels. CCS has been slow to take off, but dozens of projects are underway, including numerous pilots in the Great Plains, many of which pump CO_2 from fossil fuel power plants into dwindling wells to drive out residual oil. One of the longest-running operations is in the North Sea, where the Norwegian oil company Statoil has been separating CO_2 from natural gas and sequestering it underground for more than 2 decades.

To put the brakes on climate change, however, these tools would have to be deployed on an entirely unproven scale.

AS FLIKKEMA DRIVES BACK from his canola field, his blue pickup rumbles across a narrow irrigation canal. "Our lifeblood," he

A farmer harvests a poplar plantation in Germany. Wood chips can be burned to produce energy at power plants, where emissions can be captured.

remarks. Water is a scarce commodity in Montana, and irrigated crops are by far the biggest consumer of it, although lately, there is growing demand from the oil and gas industry. Poulter says BECCS could divert precious water that would otherwise support crops or native ecosystems. "Water already defines land use in the West and is bound to be an issue," Poulter says. According to one global assessment, using switchgrass to sequester 3.7 billion tons of CO_2 would use almost as much water as is in Lake Michigan, and many scenarios require that much carbon or more to be removed each year. (The same study concluded that BECCS would eat up the equivalent of a quarter of the world's annual nitrogen fertilizer production, too.)

Critics are also concerned about BECCS's big footprint. "It worries me that the landscape already has to produce food, and now we will rely on it to produce energy, too," says Meghann Jarchow, an ecologist at the University of South Dakota in Vermillion. The prairies of the Upper Missouri River Basin are home to iconic species such as the prairie dog and provide critical habitat for many grassland birds, but they are losing ground to food production and, increasingly, to bioenergy crops. BECCS could make the problem worse.

Some BECCS advocates disagree, saying that if it were done right, it could be a boon for the environment. Today, much of the abandoned farmland where second-generation bioenergy crops could grow is degraded and dominated by invasive plants, says Phil Robertson, an ecologist at Michigan State University's W. K. Kellogg Biological Station in Hickory Corners. "Generally, it doesn't have high conservation value," he says. But field studies in the Midwest suggest that planting native switchgrass, with a few other plant species thrown in for good measure, could actually help restore the grassland ecosystems that once covered the middle of the continent. With smart policies in place, Robertson envisions a world in which farmers could turn the profits from bioenergy harvests back into restoring more land. "I think it could underwrite conservation," he says.

Worldwide, there is no shortage of farmland that's been abandoned because of low productivity or fickle markets. A conservative estimate by Field and his colleagues suggests an area at least the size of India is available globally, and others suggest there is several times that—plenty to support a robust BECCS industry. But more farmland may also be needed to feed a global population that could peak between 8 billion and 12 billion people sometime this century. Most model scenarios make a big assumption: that rising agricultural productivity and vegetable-based diets will limit the need for new farmland. But the real world, where demand is growing for meat and dairy products that require lots of land, could be a different story.

Researchers like Vaughan worry that without strong regulations, surging demand for bioenergy could displace food crops—causing prices to rise—or push farmers into uncultivated lands. Past experiments with biofuels also brought new land into cultivation, which not only threatened biodiversity, but also undermined some of

the climate benefits of bioenergy in the first place. That's because cutting down trees to make new farmland, for example, releases far more carbon into the atmosphere than bioenergy crops can sequester. "That can wipe out any future benefit for years to come," Robertson says. Even planting crops on abandoned fields, like CRP land, can create a sizable carbon debt if soil is tilled, which releases CO_2.

Then there are the economics. Getting farmers to grow specialized crops will require proper incentives. "The markets will have to come for guys to change," Flikkema says. Farmers here didn't start growing soy until a local elevator started buying it, he says. To establish BECCS in the Upper Missouri River Basin and worldwide, governments will have to set a price on carbon—through something like a tax or a cap-and-trade program—and use the proceeds to incentivize individual farmers to grow bioenergy crops on their land.

These headwinds lead many researchers to conclude that the amount of BECCS in models is unrealistic. "Nobody is actually saying it's coherent," says David Keith, an engineer and climate policy expert at Harvard University who wrote some of the early papers on BECCS. Keith, who has since helped launch a direct air capture company, says the modelers seized on BECCS because it was one of the few ways to simulate negative emissions—and negative emissions were one of the few ways to try to keep warming below 2°C.

Modelers stress that scenarios are not projections of the future, and shouldn't be treated as such. "They're what-if pathways," says Katherine Calvin of the Pacific Northwest National Laboratory in College Park, Maryland. But Keith says that hasn't stopped BECCS from attracting undue attention. The result, he says, is a perilous mismatch between models and reality that presents a "moral hazard" by committing future generations to technological solutions that may not work in the end.

It's an accusation that has often been lobbed at Keith's main area of study: geoengineering Earth's climate to counteract warming by, for instance, injecting particles into the sky to reflect sunlight. Keith is miffed that many policymakers see geoengineering as a "completely crazy, risky, way-out-there thing we shouldn't talk about" while remaining sanguine about massive reliance on negative emissions. "If moral hazard is sweeping the problem under the rug, and pushing more of it to future generations, and making it look like you are meeting the targets when you are not," he says, "that is for sure what's happening with BECCS now."

A pilot project in Ketzin, Germany, is monitoring the long-term storage of carbon in a porous layer of sandstone hundreds of meters underground.

PHOTO: NESTOR BACHMANN/DPA/PICTURE-ALLIANCE/NEWSCOM

BY THE END OF THE DAYLONG MEETING in Bozeman, Stoy and Poulter have made progress on their first goal: spreading the word about this arcane acronym, BECCS. But most of the work, and the loftier questions, lie ahead. Stoy raised one earlier that day: "How can we not just run roughshod over the entire northern Great Plains?" Or, by extension, the world?

To that end, the team will use detailed physical models to construct a handful of scenarios for the region. At one end of the spectrum is a world that goes long on BECCS, with farmers using CRP land, and maybe even existing cropland or virgin prairie, for bioenergy. At the other end is a future that sacrifices some amount of carbon storage for the benefit of conservation, food production, and other local values. In this future, there would be only a small amount of BECCS. Instead, most carbon would be stored by protecting forests, adopting no-till farming practices, and taking other climate-friendly approaches to land stewardship. A recent study found that such actions, carried out on a global scale, could provide a cheap and easy way to accomplish a third of the CO_2 mitigation needed in the next decade to be on track to meet the Paris goals.

The team doesn't know which of its scenarios will come to pass. But it does know that, as atmospheric CO_2 continues to rise and the world warms apace, time is running out for countries to decide whether to count on negative emissions. If we are going to rely on technologies like BECCS in the future, we need to start ramping them up now, says Sabine Fuss, an economist at the Mercator Research Institute on Global Commons and Climate Change in Berlin. "It's a little bit dangerous if it's conceived as something that you just switch on." So far, only one commercial plant is doing anything close to BECCS—a bioethanol refinery in Decatur, Illinois, that each year sequesters 1 million tons of CO_2 released from fermenting corn.

The researchers repeatedly try to impress this upon the audience in Bozeman—that despite its many risks and drawbacks, they should take BECCS seriously. Some amount of BECCS, or some other carbon-eating technology, is probably coming. "Even though it's very fantastical at this point to think it could happen," Poulter says, "it's one of only a few remaining options we have to deal with this problem."

BECCS would bring sweeping changes to the region, but then again, so will climate change. Indeed, among all the options the team will consider in its study, there is one it won't include: allowing the Upper Missouri River Basin to stay the same. ■

Julia Rosen is a journalist in Portland, Oregon.

ECOLOGY

Is evolution predictable?

Simple traits may not have simple, predictable evolutionary paths

By **David Reznick**[1] *and* **Joseph Travis**[2]

Forty years ago, Anderson (*1*, *2*) and Poole (*3*, *4*) debated the value of predictive models for understanding population dynamics in a temporally varying environment. Poole argued that he could predict the future with high confidence if he had a good record of the past. Anderson (*1*) expressed doubts. He pointed out that long-term predictions will hold only if past conditions persist into the future. He also argued that although sophisticated statistical models may be able to predict the future, they do not tell us why they succeed or, more pointedly, why they fail. Without deep biological understanding of the system under study, predictive models are not likely to offer much insight into either the past or future. On page 765 of this issue, Nosil *et al.* (*5*) apply the same scrutiny to evolution.

Evolution is like population dynamics because evolutionary change over time can be governed by multiple factors, the relative influence of which vary over time. Nosil *et al.* used a series of observational data taken over 25 years on natural populations in combination with experiments to show that in one case, evolution can be predicted very well, but in another, it cannot. More generally, they show that without deep biological knowledge, we cannot understand either past or future, much less predict the future from the past.

The authors worked on the stick insect *Timema cristinae* in the chaparral biome of California. There are three color combinations: uniform green, green with a white stripe, and melanic (dark gray) (see the photos). These insects feed and live on *Adenostoma fasciculatum* (chamise, or greasewood) or *Ceanothus spinosus* (greenbark or redheart). They are small (2 to 3 cm), wingless, and not very mobile, so each shrub or clump of shrubs is a semi-isolated community. The striped morph is most cryptic (camouflaged) and abundant on *Adenostoma*, whereas the green form is most cryptic and abundant on *Ceanothus*, but both morphs can be found on both plants. The melanic morph is found at low frequencies on both types of shrubs but predominantly on the gray trunks of *Adenostoma* (*6*).

This species has become a model for the study of local adaptation (*6*, *7*). The poor

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PHOTO: MORITZ MUSCHICK

A green-striped stick insect rests on chamise, the host plant on which this color morph is most abundant (left). Green, unstriped, and melanic color morphs of the stick insect are shown (right).

PHOTO: MORITZ MUSCHICK

mobility of the stick insect, the patchy distribution of host plants, and the visual predators of these insects combine to maintain the associations between morph frequencies and host plant (*6*). In addition, local populations are under strong selection to adapt to the chemistry of the host plant; this contributes to reduced interbreeding and possibly incipient reproductive isolation between populations adapted to either species of plant, which can be a step to forming new, host-specific species (*8*).

Nosil *et al.* demonstrate that these stick insects undergo direct selection based on color and pattern (the presence or absence of the stripe). They identified a region of the genome in which variants are associated with the color and pattern morphs. There are three alleles at this "mel-stripe" locus, corresponding to unstriped (u), striped (s), and melanic (m). U is dominant to s, and s is dominant to m. The u/u, u/s, and u/m genotypes are green and unstriped, the s/s and s/m genotypes are green and striped, and the m/m genotype is melanic. In three experimental field studies, they found that the short-term changes in allele frequencies at this locus were significantly faster than those in similarly sized segments of the genome, indicating ongoing selection.

Because they could genotype all individuals, they could estimate the relative fitness of each genotype, not just the fitness of the different morphs. In an experiment on adult survival within a generation, they found that the s/s genotype had the highest fitness, but the s/m genotype had close to the lowest relative fitness among the six genotypes. In an experiment that spanned two generations (2 years) of stick insect, they found that s/s and s/m were nearly equal in fitness and both had higher fitness levels than the other four genotypes. The two genotypes s/s and s/m have the same phenotype (green striped), so the dramatic change in fitness of s/m between experiments indicates that there is more at stake with this portion of the genome, either because the color locus affects more than color or because there is a closely linked locus that in turn has a large effect on fitness.

The authors then investigated whether the past can predict the future. Using an 18-year data set of morph frequencies from one locality, they examined whether temporal patterns early in the series predict the patterns later in the series. When they applied the analysis to color by comparing the abundance of green (both striped and unstriped) versus melanic, they were able to predict the abundance of the color morphs. Although the data were a significant match to the predictions, the match was weak: The past predicted, on average, 14% of the variation occurring years in the future. The predictive power improved slightly when the authors incorporated spring temperatures in the model because warmer, drier springs were associated with an increase in the abundance of the melanic morph.

The past was far more successful in predicting the future in the relative abundance of green striped versus green unstriped morphs. It accounted for 80 to 95% of the variation in future abundances. The trajectory had a distinctive, sawtooth pattern, with the frequency of the striped morph consistently rising then falling on alternate years. This pattern suggests negative frequency-dependent selection (NFDS), or selection in favor of a phenotype when it is rare but against the phenotype when it is common. This type of selection on color pattern has been described in earlier studies of other animals, such as the snail *Cepaea nemoralis* or guppies (*Poecilia reticulata*) (*9*, *10*). It happens because some predators preferentially feed on the most common morph, which gives rare color morphs an advantage, but only for as long as they are rare (*11*, *12*).

Nosil *et al.* tested the NFDS hypothesis by introducing striped and unstriped morphs on to *Adenostoma* in either 1:4 or 4:1 ratios. Striped morphs had much higher survival when rare, but the two morphs did not differ in survival probability when striped was more common, fulfilling half of the conditions for NFDS. The authors suggest that perhaps the ratios needed to be more extreme for striped morphs to lose their advantage when common.

Questionable predictability is not specific to stick insects. Nosil *et al.* analyzed data sets for other long-term studies of evolution in various species, including Galapagos finches and the peppered moth, and show that they also offer low temporal predictability. In these cases, the likely cause is also multiple forms of selection the strength of which varies over time.

These results show that an iconic example of a simple trait subjected to a single agent of strong selection is actually much more complicated. Similar lessons have been taught by other seemingly simple phenomena. For example, the complex ways in which known agents of selection on the color polymorphism of *Cepaea* snails meant that "each population is subject to a unique explanation" (*10*). This is in stark contrast to studies of microbial, viral, and immune system selection, for which evolution seems to be highly predictable (*13*). Why this is the case, when it is not so in organisms such as stick insects and others, is a new challenge for evolutionary biologists. ■

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NEUROSCIENCE

Controlling learning and epilepsy together

Silencing dentate gyrus mossy cells affects spatial learning as well as seizures

By **Helen E. Scharfman**[1,2]

The dentate gyrus (DG) is a region in the hippocampus of the brain that is important for many cognitive functions, such as spatial learning and memory, and understanding our environment or context (*1*). The DG is also considered to be important in many diseases, some of which surprisingly do not appear to be related to memory, such as temporal lobe epilepsy (TLE) (*2*). One explanation is based on the idea that the DG is an inhibitory filter or gate (*3*, *4*), preventing too much information from corrupting memory formation as well as preventing seizures. However, it is unclear exactly how and when the DG limits the influence of afferent input to the hippocampus, and when the DG is permissive, because the DG has powerful excitatory and inhibitory characteristics. For example, the DG contains mossy cells (MCs), which have both characteristics (*5*). On page 787 of this issue, Bui *et al.* (*6*) show that silencing MCs impairs a spatial memory task and also terminates seizures in an animal model of TLE, which could improve our understanding of TLE as well as cognitive comorbidities.

MCs project primarily to excitatory granule cells (GCs), which are the principal cell type and major output of the DG (see the figure). GCs project to the CA3 area of the hippocampus, which in turn activates other areas of the hippocampus and extrahippocampal regions to carry out functions related to memory and also to cause seizure spread throughout the brain. Because MCs produce the excitatory neurotransmitter glutamate, they can activate GCs. However, MCs also activate neurons that produce the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and these GABAergic neurons, such as basket cells, can inhibit GCs (*5*).

Many of the hypotheses for the functions of MCs have come from studies in animal models of TLE-like conditions in which MCs are reduced in number, so the normal function of MCs can potentially be inferred. The dormant basket cell hypothesis proposes that without MCs, basket cells lack sufficient input to maintain GC inhibition (*7*). By contrast, the irritable MC hypothesis suggests that when MC numbers are reduced by brain injury, the surviving MCs become "hyperexcitable" and cause hyperactivity of GCs (*8*).

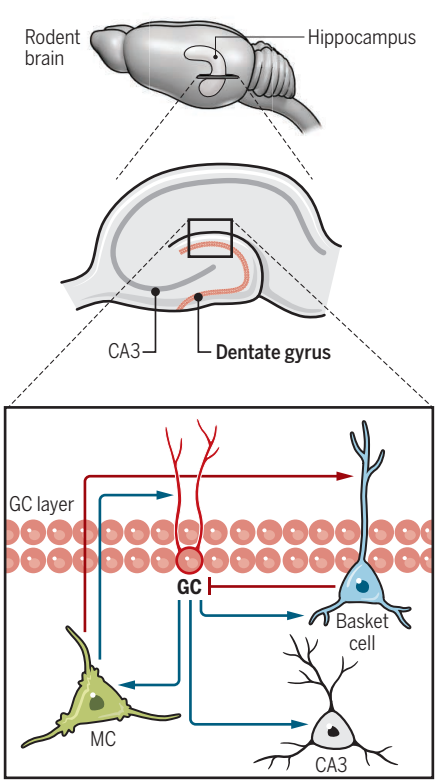
After these hypotheses were proposed, MC manipulations brought new insights (*9*), but the roles of MCs in normal DG function and TLE remained unclear. Bui *et al.* used several approaches to investigate. They induced a TLE-like condition in mice by injecting the glutamate receptor agonist and excitotoxin kainic acid into the dorsal DG to create a seizure focus. Kainic acid induces many changes to the DG, including damage to MCs, and ultimately these changes transform the brain into one that has spontaneous intermittent seizures (chronic epilepsy). Some of these seizures can be severe, causing convulsions. By pulsing light over the DG using implantable optic fibers, Bui *et al.* determined if exciting or inhibiting residual MCs, engineered to respond to light, would alter seizures. They also used closed-loop optogenetics, an ingenious method in which an algorithm identifies the onset of a seizure and triggers pulses of light to try and stop the seizure. MC excitation reduced the duration of electrographic seizures, which are unaccompanied by convulsions. Activating MCs also reduced the propensity for a seizure to become convulsive. This suggests that MCs primarily inhibit GCs, preventing persistent activation of downstream areas in the hippocampus, consistent with the dormant basket cell hypothesis.

In an effort to understand how MCs control seizures and convulsions, the authors activated or silenced the GCs. Surprisingly, silencing GCs did not stop the emergence of convulsive seizures. The likely explanation of this apparent paradox lies—as the authors suggest—in anatomical connections. A single MC projects to GCs that are in both the ipsilateral and contralateral DG, but a single GC only projects locally within the hippocampus. This explanation is incomplete, however, because GCs in one small region project to both MCs and CA3 pyramidal cells that have wide-ranging projections. Even some GABAergic neurons project for long distances and they are often lost or altered after epilepsy (*10*, *11*), possibly disinhibiting neurons outside the DG that are part of a circuit that underlies a seizure. These complexities may be explained after additional aspects of the circuitry and physiology in the TLE model become clear.

An important clinical concern in patients with TLE is cognitive comorbidities, which accompany chronic seizures. Bui *et al.* investigated this by optogenetically silencing MCs in normal mice to see if impairments could be induced in tasks that test cognitive ability. Silencing MCs caused deficits in a task that tests spatial memory, where a mouse must detect changes in the location of an object. Interestingly, they had to silence MCs during the learning phase of the task to see an effect, suggesting that learning (or encoding) of an object's location, but not the memory of it, is dependent on MCs. How MCs affect learning could be related to their unique sensitivity to cortical afferent input (*5*). It will be interesting to determine

Linking seizures and memory

MCs excite GCs and GABAergic neurons, which inhibit GCs. Thus, MCs can activate many GCs or they can inhibit them, via GABAergic neurons such as basket cells. This cellular circuitry can excite many parts of the DG, potentially leading to activation of CA3 pyramidal cells in the hippocampus and their downstream targets, to initiate a seizure.



GRAPHIC: A. KITTERMAN/*SCIENCE*

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if deficits in the TLE mice can be alleviated by activating MCs during learning.

Thus, Bui *et al.* provide some answers but also leave us with some questions. For example, how do MCs control only the duration of electrographic seizures? The reason may be similar to the reason MCs control convulsive seizures—in each case they terminate the seizure prematurely. It could be that activating surviving MCs might strengthen the DG inhibitory gate sufficiently to stop a seizure that has begun. However, how could a very small number of MCs stop a seizure that involves so many neurons in different brain regions? A possible explanation is that MCs that survive in the mouse model of TLE begin to grow additional connections (sprouting), which is known to happen in other cell types, such as GCs (*2*). Indeed, what would occur if all MCs survived in this model? Would MCs still inhibit GCs, or would they activate them? And would seizures be affected?

Other aspects of the DG that affect object location memory and convulsive seizures are also intriguing. For example, the DG is one of the few areas of the brain where GC neurogenesis occurs throughout life. Remarkably, new GCs influence the ability to distinguish novelty (*12*), which seems related to the functions of MCs to encode new object locations, identified by Bui *et al.* Reduction of new GCs in an adult mouse also enhances the susceptibility to convulsive seizures induced by systemic kainic acid injection (*13*). MCs make the first excitatory synapses on new GCs (*13*), so MC interactions with new GCs could play a role in spatial encoding and seizure susceptibility. Interestingly, GCs release peptides and even GABA, as well as undergoing many other changes, after seizures in mice (*14*). This might help explain why MC and GC manipulations had some different consequences in TLE mice. Further investigation should advance our understanding of how the DG contributes to memory and its role in epilepsy. ■

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ECOLOGY

The value of pollinator species diversity

Most crop-visiting species are needed to ensure high levels of crop pollination

By **Claire Kremen**

In a 1991 experiment that would be unlikely to pass a human-subject review today, eight intrepid adventurers were enclosed in a hermetically sealed structure (Biosphere 2), along with 3000 species of plants and animals and several habitats, including a coral reef, rainforest, mangrove, and wetland. However, most vertebrates and all pollinating insects went extinct, whereas ants and cockroaches multiplied. Carbon dioxide concentrations fluctuated wildly, and oxygen concentrations declined (*1*). The results highlighted how little we know about what it takes to maintain Earth's life-support system. On page 791 of this issue, Winfree *et al.* (*2*) investigate an important aspect of this problem: How many pollinators are needed to ensure crop pollination?

The question of how many species are needed to support ecosystem functioning has occupied an army of ecologists over the past 20 years (*3*). Experimental evidence is mainly based on randomly assembling grassland plant communities to comprise different numbers of species in small, replicated field plots. The results from these experiments increasingly suggest that large numbers of species are needed to support ecosystem functioning (*4*, *5*). But it remains unclear whether the relationship between biodiversity and ecosystem functioning scales up from small plots to produce benefits to humans (or ecosystem services) in real, working landscapes, which are considerably more difficult to study (*5*).

In the experimental communities, species are picked randomly from a common species pool, and abundances are set to be similar from species to species (even). By contrast, natural communities are neither randomly assembled nor even. Instead, they typically consist of a few highly abundant (dominant) species and many rare ones. In the few studies that have looked at biodiversity–ecosystem functioning relationships in real-world settings, these dominant species were far more important for determining ecosystem functions than was the number of species (*6*, *7*). Winfree *et al.* now take a fresh look at the role of dominance in ecosystem services, examining how many species are needed to supply crop pollination across a farming region.

High dominance (the presence of a few dominant species) tends to reduce the number of species needed to ensure ecosystem functioning (*7*), but species turnover (the replacement of one species for another across space or time) might increase it. When both properties occur in a real-world landscape, which one of them is more important in determining the relationship between biodiversity and ecosystem functioning? The answer will illuminate whether humanity's survival depends on a few or on many species. It will also help to resolve a long-standing conundrum (*8*): Should conservationists use ecosystem-service arguments to garner support from a broader array of people for biodiversity conservation, or would such an approach potentially undermine biodiversity conservation, if it turns out that relatively few species are needed to supply these services? Winfree *et al.*'s study helps to resolve these questions.

> ***"...understanding how much pollination a farmer would get at any point in the landscape is the relevant metric for assessing ecosystem services..."***

Pollinators are necessary to increase the production of 75% of our crop species. Honey bee colonies are often managed to supply crop-pollination services, but relying only on honey bees for pollination has become increasingly risky as beekeepers experience higher and higher rates of colony losses each year because of the combined effects of pesticides, diseases, and changes in habitat and climate. Native bee species can

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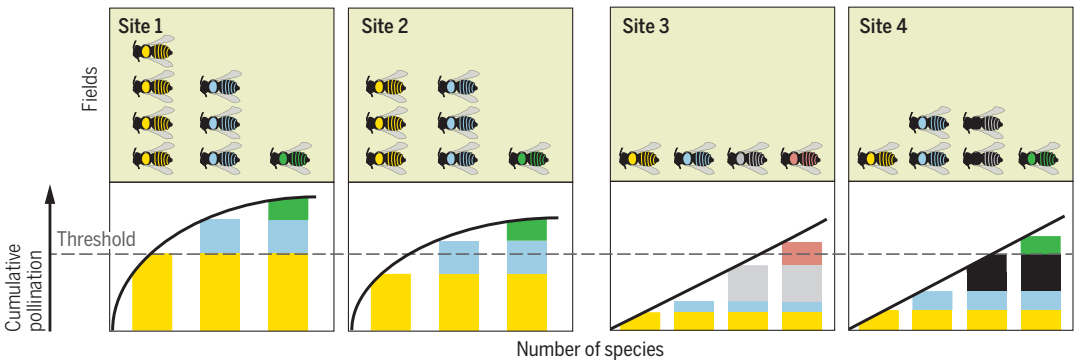
Bee diversity needed for pollination

Pollinating species vary from site to site; numbers of individuals indicate abundances at the site for each species type.



Dominant species contribute most to pollination function at sites 1 and 2, and only one or two species, respectively, are needed to surpass the threshold required for full pollination. Dominant species occur at all sites, but because of their low abundance at sites 3 and 4, most species are needed for pollination function. Species turnover between such sites means that most species in the species pool are needed to supply pollination function across the entire array of sites.

substitute for honey bees and often provide superior services (*9*). Of 20,000 bee species worldwide, 12% are estimated to contribute to crop-pollination services (*6*).

Winfree *et al*. elegantly disentangle the effects of species dominance from turnover in how different native bee species contribute to pollination of three crops (watermelon, blueberry, and cranberry) in the U.S. mid-Atlantic region. High functional dominance exists in the system, with just a few species supplying a large proportion of the pollination overall (*10*). The authors determine this by measuring both the typical amount of pollen that each species delivers on a single visit and the visit rate of each species at a given farm site, and then estimating the contribution of each species to the total amount of pollen delivered. However, as the team considered a larger and larger array of sites, they found that many more species were required to reach a threshold level of pollination (25, 50, or 75% of the mean total pollination per site).

Further, the authors quantified the relative importance of species turnover and species dominance with a null model that removed the effect of dominance. In this model, they effectively apportioned the pollination provided at a site evenly among all species present. The surprising result was that the effects of species turnover were, on average, 14 times more important than dominance effects for pollination function (at the largest scale of analysis), even though high levels of dominance occurred at individual sites and dominant species were widespread. Thus, achieving the 50% pollination threshold at a single farm site required, on average, 5.5 bee species, but 55 species were needed across the entire study region. At the 75% threshold, most bee species in the pool of crop-visiting species would be needed across all sites.

Why are these results so different from previous studies, including studies of crop pollination, which concluded that only a few dominant species are needed to supply ecosystem functions? A partial answer is that this is the first study to disentangle the contrasting effects of species dominance and turnover.

Equally important is how exactly the service was measured. Previous studies, including those by Winfree and co-workers (*6, 10*), looked at the relative contributions of functionally dominant and nondominant species to ecosystem function without considering the actual amount of pollination needed by farmers to reach critical pollination thresholds. In the current study, Winfree *et al*. instead looked at the magnitude of the service and whether a given threshold (25, 50, or 75%) is achieved at each site on the basis of the bee-community composition. Critically, at sites where the dominant, widespread pollinators are low in abundance, almost all or even all pollinator species may be needed (see the figure). At such sites, relatively rare species provide essential contributions to pollination function. Species turnover among such sites, then, is the reason why so many species are needed, regionally, to provide pollination.

Even though rare species make a small contribution overall across sites, identifying their contributions to reaching a threshold on a farm-by-farm basis shows how important they are. Arguably, understanding how much pollination a farmer would get at any point in the landscape is the relevant metric for assessing ecosystem services to real people in real landscapes (*11*).

The growing chorus, both from plot-based experimental studies (*3*) and now from a large-scale natural experiment (*2*), strongly supports the importance of maintaining a large amount of biodiversity to support human well-being sustainably. But maintaining this biodiversity in agricultural landscapes, both for pollination services and for other ecosystem functions and services that support crop production, is likely to require substantial changes in management. Specifically, it will require moving away from monocultures and fencerow-to-fencerow farming that rely extensively on external inputs of pesticides and fertilizers, as well as managed honey bees that may compete with wild bee species (*12*), and toward farms that generate much of the needed pest and disease control, soil fertility, and pollination services through crop and noncrop diversification and "ecological intensification" (increasing crop productivity through management practices that promote the organisms producing ecosystem services, rather than through increased use of pesticides and fertilizers) (*13, 14*). For example, planting diverse crops, flowering strips, and hedgerows can restore wild pollinator populations, enhance species turnover, and supply pollination services (*15*).

Winfree *et al*.'s study helps to show that there may be much more alignment than previously thought between ecosystem-service arguments for biodiversity conservation and intrinsic-value arguments (conserving biodiversity for its own sake). Given the key role of biodiversity for human well-being and sustainability, it is crucial that human societies better protect and restore biodiversity. ■

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GRAPHIC: N. CARY/*SCIENCE*

APPLIED PHYSICS

Capsules made from prefabricated thin films

Droplets become encapsulated after falling into floating polymer films

By **Esther Amstad**

Capsules are composed of a core, typically a liquid containing active substances, and a surrounding shell. They are used to delay the degradation of active ingredients, protect them from reacting or interacting with substances contained in the surrounding shell, or to prevent premature consumption of encapsulants (*1*, *2*). The performance of capsules is often determined by their permeability toward encapsulants and stability against rupture; these parameters can be adjusted with the composition, structure, and thickness of the shell (*3*, *4*). Mechanically robust capsules with a minimal permeability even toward low molecular weight substances often have rather thick shells (*5*). On page 775 of this issue, Kumar *et al.* (*6*) report an elegant process to fabricate capsules with very thin, rigid shells that display a low permeability even toward small encapsulants.

The degree of control over the dimension and composition of capsules depends on the processing method and parameters (*3*, *7*, *8*) and must usually be traded off with the throughput and hence with the production costs. The shells of capsules are most often produced during the encapsulation process, for example, by partially solidifying emulsion drops (*4*, *9*, *10*). These processes can produce relatively thick homogeneous shells (*11*) or shells composed of polyelectrolyte multilayers (*12*, *13*) but offer limited tuning of the structure and local composition of capsules made of multiple materials.

Kumar *et al.* report an elegant approach to enclose reagent-containing liquids in prefabricated solid sheets. The composition of these sheets can be adjusted to the requirements of the specific application, and the sheets can be as thin as 50 nm. Encapsulation is achieved by splashing a reagent-loaded drop onto a thin film that floats on the surface of a bulk liquid. They demonstrate that for a sufficiently high impact of the drop, the thin sheet deforms and enwraps the drop. Thereby, the two-dimensional (2D) sheet forms a 3D capsule whose size and shape depend on the size and contour of the 2D sheet.

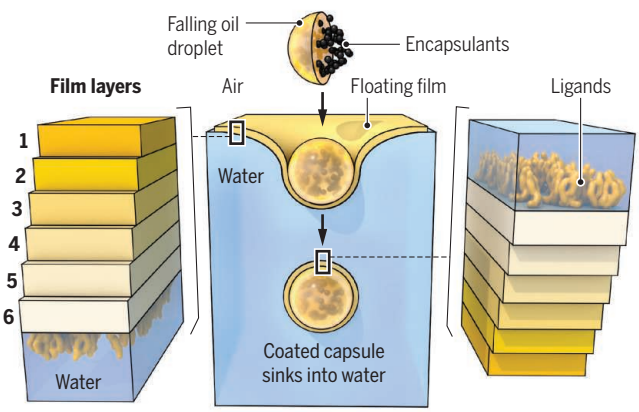
A prerequisite for this encapsulation process is that the sheet deforms upon impact of the drop. Moreover, the density of the impacting drop must exceed that of the bulk fluid so that the enwrapped drop sinks. These prerequisites can be fulfilled by tuning the composition and thickness of the sheet as well as by adjusting the involved fluids and processing conditions. Hence, these prerequisites do not impose any fundamental limits for the material selection. Capsules could be fabricated with very thin shells from a wide variety of materials, including composites of functional multilayers.

The main difference in the technology presented by Kumar *et al.* over conventional encapsulation technologies is that they use prefabricated 2D sheets. In most other cases, 3D shells are formed in situ during the encapsulation process. The use of prefabricated thin 2D sheets offers the distinct advantage that the extensive library of methods for the production of thin films can be exploited to form multifunctional capsules. The ability to use thin 2D sheets opens up new avenues to fabricate capsules from a much wider range of materials. In addition, it offers new possibilities for fabricating capsules composed of thin multilayered shells that encompass multiple functionalities (see the figure). This method facilitates the controlled modification and detailed characterization of the surface chemistry of these capsules because well-established techniques can be used to characterize flat surfaces. Superior control over the surface chemistry would be of particular importance for targeting capsules to desired sites to locally release encapsulants.

Many opportunities can be explored to design multifunctional capsules of well-defined structures and compositions. However, a better understanding of the encapsulation process of Kumar *et al.*, as well as of the processing technology, are needed. A knowledge of mechanisms involved in the wrapping of the impacting drops would allow tuning size and shape of the capsules over a wider range. It could provide insights into control of their stability and permeability and facilitate its scale-up. Once these points are addressed, the presented method has the potential to offer many exciting opportunities to develop multifunctional capsules whose applications range far beyond the encapsulation of active ingredients to prolong their storage time. ■

Custom coating

An oil drop containing encapsulants (for example, drug molecules) becomes a coated capsule when it impacts a floating multilayer thin film. The various layers of the film help preserve the drug and target delivery on the capsule in the body.



1 Is compatible with the encapsulants within oil droplet

2 Has responsive materials triggering capsule rupture

3 Contains oxygen scavengers

4 Has low permeability to hydrophilic substances

5 Has low permeability to hydrophobic substances

6 Displays ligands that target capsules

GRAPHIC: C. BICKEL/*SCIENCE*

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ATMOSPHERIC CHEMISTRY

The changing face of urban air pollution

Volatile organic compounds in U.S. urban air increasingly derive from consumer products

By **Alastair C. Lewis**

The atmospheric chemistry that leads to photochemical smog and climate-active aerosols requires the presence of volatile organic compounds (VOCs) (*1*, *2*). The VOCs in urban air typically derive from the prevailing energy and transport technologies as well as the use of petrochemical-derived products. On page 760 of this issue, McDonald *et al.* (*3*) report that a notable change in emissions may be underway in U.S. cities, with effects on secondary pollutants such as organic aerosols. Shifting from an urban atmosphere dominated by transport-related VOCs to one dominated by VOCs from coatings, adhesives, and consumer products would alter predictions of urban air quality and challenge the existing policy framework for emissions control.

The composition of VOCs in urban air has historically been influenced by the presence or absence of a natural gas network or refining industries; the relative balance in the urban transport fleet between gasoline, diesel, public, and private (*4*, *5*); and, more recently, the extent of vehicle electrification. Natural emissions from plants and trees can also be important in the warmer months of the year. Transport, industrial, and natural emissions can be predicted with some precision, but estimating highly diffuse VOC sources from consumer products is very challenging and often depends on predictions of air exchange between indoor and outdoor environments.

Many countries already regulate the emission of VOCs from sectors such as fuel storage and distribution, transportation, and industrial solvent use. International conventions such as the Gothenburg Protocol set limits on the transboundary export of VOCs between some countries. Multidecadal reductions in carcinogenic benzene and 1,3-butadiene have been particularly notable in North America and Europe, along with a more general decline in those regions in the total amount of short-chain hydrocarbons in ambient air.

The modern three-way catalytic converter has been particularly effective at eliminating tailpipe VOC emissions from gasoline vehicles. An outlier to this long-term global decline has been a recent rise in atmospheric ethane across the Northern Hemisphere, thought to result from the expansion of unconventional hydrocarbon industries in the United States (*6*).

Although it is tempting to treat VOCs as a single pollutant, they have enormously diverse chemistries; each compound follows a unique pathway from initial emission through atmospheric degradation to an end product. They are short-lived in the atmosphere and are susceptible to oxidative attack by hydroxyl radicals (during daytime) and nitrate radicals (during the night); some also react with ozone. Lifetimes range from several months to only a few minutes, with oxidation occurring through multiple steps that ultimately produce CO_2 and water. The complexities of VOC degradation can be staggering: Atmospheric oxidation of isoprene (C_5H_8) is estimated to involve 1928 different steps and 602 unique intermediate organic species before CO_2 and water are finally formed (*7*). Most of this chemistry is hidden from experimental view, and there is a reliance on theoretical predictions provided by the detailed chemical models used for air pollution forecasting (*8*). Only in 2012 was one of the most fundamental species in VOC oxidation chemistry, the Criegee intermediate, experimentally detected for the first time (*9*).

As VOCs oxidize, they can form other stable organic compounds that are functionalized with oxygen- and nitrogen-containing groups. Functionalized intermediates of VOC oxidation often have a lower vapor pressure than the starting compound and therefore tend to condense to aerosols, rather than staying in the gas phase. They can participate in heterogeneous processes that form or modify aerosol properties. Understanding these degradation processes is therefore vital for both air quality and climate applications.

Models that represent some of this chemistry predict formation of thousands of dif-

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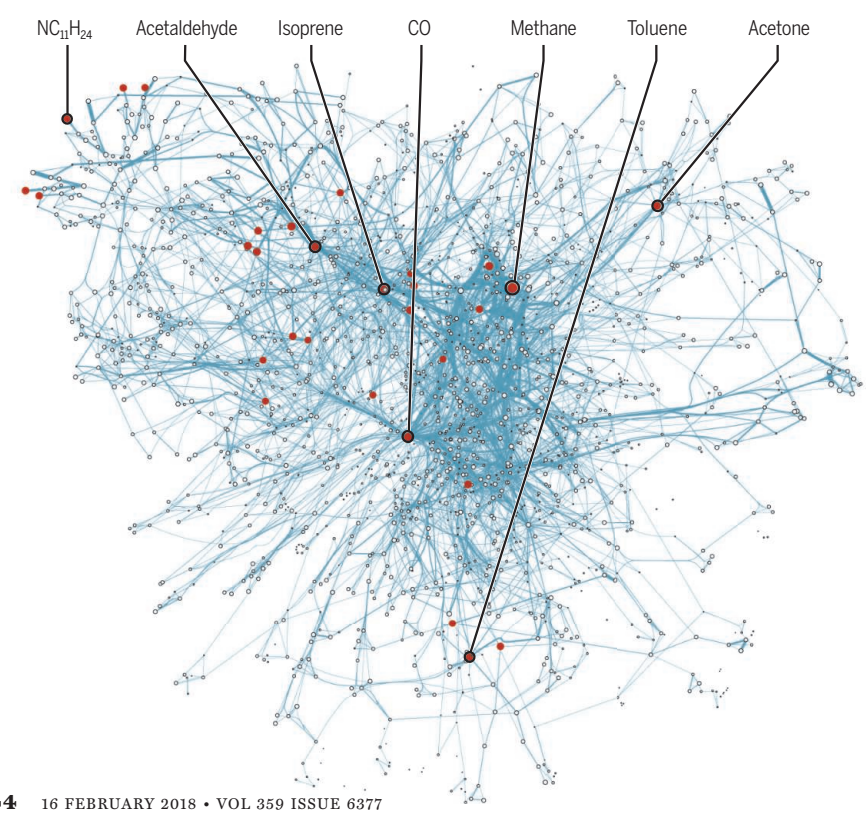
A complex network of VOC reactions

A small number of initial emitted VOCs (red dots) react in the atmosphere to form a vast number of secondary compounds (white dots). In this graph representation, blue lines denote the reactions between compounds. See (*8*) for details.



GRAPHIC: V. ALTOUNIAN/*SCIENCE*

ferent potentially condensable compounds in a complex web of reactions from a small number of initial VOC emissions (see the figure). Changing the blend of those starting VOC compounds in cities could generate a different suite of condensable products, in turn affecting how much ozone and secondary aerosols are formed.

The development of analytical techniques has played a very important role in advancing knowledge of VOCs in air. Mass spectrometry, in particular, can now provide exceptional detail on the amounts and exact chemical structures of VOCs released into air. Goldstein and Galbally (*10*) estimated that VOCs in the air may comprise more than 10,000 different structures. This diversity is daunting, but not necessarily beyond the capabilities of the very latest high-resolution instruments.

The shift in U.S. VOC sources that McDonald *et al.* report highlights the need for continued surveillance of VOCs as pollutants. Changing patterns of VOC emissions may potentially be seen most clearly by analyzing indoor air—a type of atmosphere that has received considerably less research attention than outside air (*11*). Volatile chemicals in cleaning products, such as limonene, can dominate the air in modern homes, displacing solvents such as xylenes that have been reduced in paints, glues, and coatings (*12*). Yet, few operational air pollution models include VOCs that are specific to sources such as personal care products, and none take into account synthetic forms of VOCs such as cyclic volatile siloxanes (*13*). These models must be adapted to capture the changing pattern of emissions. As knowledge of VOC chemistry improves, it will become possible to develop more targeted approaches to reducing impacts. Prioritizing those VOCs with the greatest aerosol formation potential—for example, through reformulation of consumer products—would be one option. Industry sectors that have until now been left outside of VOC emissions controls may, in a cleaner electrified future, receive more direct attention from regulators. ■

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TUMOR IMMUNOLOGY

Chromatin regulation and immune escape

Deficiency in a chromatin remodeling complex enhances tumor immunotherapy

By **Ehsan Ghorani** *and* **Sergio A. Quezada**

Antigens expressed by cancer cells target them for elimination by tumor-infiltrating T cells (*1*). But, despite T cell recognition, advanced malignancies are often fatally progressive. T cell inhibitory (checkpoint) receptors, including programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte–associated protein 4 (CTLA-4), contribute to immune suppression and dysfunction in tumors. Checkpoint inhibitors (CPIs) developed to block these pathways and derepress T cell activity have considerably improved outcomes for various cancer types. However, beyond certain rare and highly sensitive tumors (*2*), responses remain limited to a fraction of patients, and both primary and acquired resistance are frequently observed. Although much work has focused on defining and overcoming T cell–intrinsic inhibitory mechanisms, such as checkpoint expression, less is known about what regulates tumor cell sensitivity to T cell attack. On pages 801 and 770 of this issue, Miao *et al.* (*3*) and Pan *et al.* (*4*), respectively, find that chromatin remodeling pathways contribute to cancer cell immune resistance through control of interferon-stimulated gene (ISG) expression. This has implications for our understanding of why CPIs fail and suggests that targeting these pathways may enhance tumor immunotherapy.

"...the findings of Pan et al. and Miao et al. pave the way for clinical trials combining small-molecule inhibitors of chromatin remodeling pathways and [checkpoint inhibitors] as a new synergistic combination."

The interferons (IFNs) are a group of cytokines with antitumor effects, mediated by activation of Janus kinases (JAKs) and signal transducers and activators of transcription (STATs). STATs bind ISG promoters to drive transcription and thus gene expression. ISGs promote programmed cell death and antiproliferative effects in addition to enhancing tumor cell immunogenicity by increasing the expression of tumor antigen processing and presentation machinery. Thus, ISG expression is usually tumor suppressive. Of the three types of IFN, type II or IFN-γ is a key effector of antitumor T cell function with its tumor suppressive effects mediated predominantly through activation of STAT1 and the expression of a subset of ISGs. Deficient IFN-γ signaling enhances tumorigenesis in mice, and loss-of-function mutations in downstream signaling pathways are well characterized in tumor cell lines and tumor tissues (*5*). In melanoma, inactivating mutations of genes that encode members of these pathways are enriched in CPI-resistant tumors (*6*).

STAT binding to ISG promoters is regulated by multiprotein complexes that remodel chromatin to control DNA accessibility. The switch/sucrose nonfermentable (SWI/SNF) family consists of BRG1- or hBRM-associated factors (BAF) and polybromo-BAF (PBAF) subgroups with distinct roles in regulating transcriptional programs driving a broad range of cellular processes. Although sharing a core set of subunits, PBAF complexes are distinguished by the inclusion of bromodomain-containing protein 7 (BRD7), AT-rich interactive domain–containing protein 2 (ARID2), and polybromo 1 (PBRM1) (*7*). SWI/SNF complex genes are commonly inactivated through mutation in ~20% of human cancers. Specifically, *PBRM1* is mutated in ~40% of patients with clear cell renal cell cancer (ccRCC) and acts as a tumor suppressor gene with roles in DNA repair, maintenance of genome stability, and control of cell proliferation (*8*).

Miao *et al.* and Pan *et al.* validate a role for IFN-γ signaling in cancer cell

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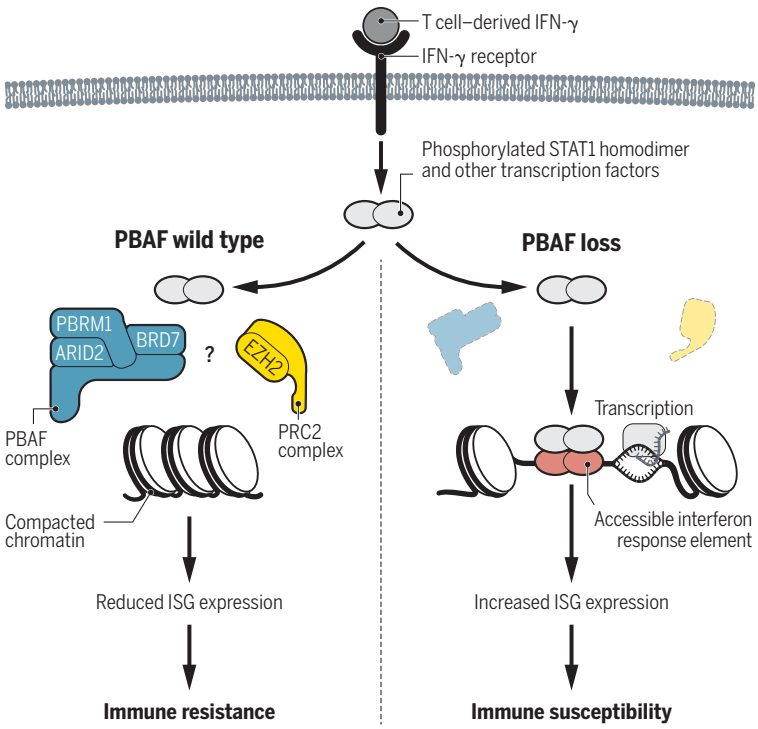
sensitivity to antitumor immune responses and further characterize chromatin remodeling as a regulator of this. Miao *et al.* found that truncating loss-of-function mutations in *PBRM1* were significantly enriched in ccRCC patients who respond to anti–PD-1 or anti–PD-1 ligand 1 (PD-L1) CPIs. Exploring the potential transcriptional consequences of PBAF loss in a *PBRM1*-deficient ccRCC cell line and in patients with *PBRM1* loss-of-function mutation, the authors found that immunostimulatory ISGs were strongly expressed in the absence of PBAF. Moreover, they observed an intriguing increase in the expression of genes downstream of STAT3 and STAT5. In addition to driving oncogenic gene transcription, both STAT3 and STAT5 (*9*) interfere with STAT1 mediated antiproliferative effects of IFN-γ signaling, suggesting induction of these factors to counterbalance the tumor-suppressive effects of STAT1.

Sensitizing cancer cells to antitumor immunity

Loss of PBAF is proposed to alter chromatin structure so that IFN-γ response elements in ISG promoters are more accessible to transcription factors, increasing their expression. When PBAF is intact, it might cooperate with EZH2 to modify chromatin and reduce the accessibility to IFN-γ response elements.



Using a CRISPR screen in a CPI-resistant mouse melanoma cell line, Pan *et al.* confirmed that genes involved in antigen presentation and IFN-γ signaling are important for immune sensitivity. All three PBAF-specific genes (*BRD7*, *ARID2*, and *PBRM1*) were identified in the screen, suggesting a role in conferring resistance to T cell attack. Gene expression and chromatin accessibility analyses of PBAF-deficient cell lines revealed increased ISG transcription in concordance with greater accessibility of DNA at target promoters. *Pbrm1*-deficient melanomas in mice had greater T cell infiltration and sensitivity to combined anti–PD-1 plus anti–CTLA-4 CPIs, in agreement with the findings of Miao *et al.*

Together with recently published CRISPR screens that similarly attribute immune resistance to genes involved in IFN-γ signaling (*10*), these studies add further in vivo and clinical data to support the importance of the IFN-γ pathway in the response to CPIs. The remaining key question is what other tumor cell–intrinsic pathways play a role in CPI resistance? Tumor metabolic properties are emerging as potential regulators of immune activity, and putative resistance genes in these pathways were found by Pan *et al.* The contribution of these pathways to control of immune susceptibility is not well characterized, and further work is required to understand this.

SWI/SNF complexes have previously been implicated in enhancing ISG transcription (*11*). By what mechanisms may loss of PBAF function have the same effect? The epigenetic silencer polycomb repressive complex 2 (PRC2) is overexpressed in cancer cells and mediates repression of multiple IFN-γ–stimulated genes (*12*). The recent demonstration that PBRM1 cooperates with the PRC2 subunit enhancer of zeste homolog 2 (EZH2) to promote silencing of ISGs (*13*) suggests a possible mechanism to explain why PBAF loss is associated with the induction of ISG expression, but further work is required to validate this (see the figure).

Given the tumor suppressive effects of PBAF, the finding that inactivating mutations in PBAF subunits sensitize cancer cells to T cell–mediated destruction suggests a trade-off between concurrently enhanced tumorigenicity and tumor suppressive immunogenicity. The finding by Miao *et al.* that PBAF deficiency is associated with increased STAT3 and STAT5 signaling suggests the deployment of cell-intrinsic mechanisms to counteract mutant PBAF-mediated enhancement of immune susceptibility. Agents with activity against these STATs are either approved or in development (*14*) and may additionally synergize with CPIs.

As PBAF loss-of-function mutation or decreased expression is seen in multiple cancer types other than ccRCC, the finding that PBAF deficiency may enhance tumor cell susceptibility to immune control could have wider translational importance. In tumor types with greater CPI sensitivity, such as ccRCC, PBAF deficiency may serve as a biomarker of treatment response and thereby aid patient selection. Together with the recent demonstration that EZH2 inhibition enhances CPI efficacy in mouse models of melanoma (*15*), the findings of Pan *et al.* and Miao *et al.* pave the way for clinical trials combining small-molecule inhibitors of chromatin remodeling pathways and CPIs as a new synergistic combination. Looking beyond tumor cell–intrinsic mechanisms that contribute to CPI sensitivity in the context of altered chromatin remodeling, one important question for future work is whether there are reciprocal effects of tumor cell chromatin regulation on T cell function and the landscape of immune checkpoint expression that may enable further refinement of therapeutic strategies. ■

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POLICY FORUM

HISTORY OF SCIENCE

Was there ever really a "sugar conspiracy"?

Twists and turns in science and policy are not necessarily products of malevolence

By **David Merritt Johns**[1]
and **Gerald M. Oppenheimer**[1,2]

Over the past quarter-century, historical research has revealed how major industries from tobacco to lead to petroleum have meddled in science to conceal the hazards of their products. Drawing on secret industry documents, these studies have shown how special interests have used financial incentives to influence scientists, fabricate doubt, and delay regulation (*1*). Recently, similar allegations have been made against the sugar industry, with claims that prominent industry-backed researchers in the 1960s downplayed or suppressed evidence linking sugar and heart disease. Building on a newly popular narrative holding that the low-fat campaign of the 1980s was not based on solid science, these allegations have suggested that if not for the machinations of the sugar industry and its cadre of sponsored researchers, the history of U.S. dietary policy might have unfolded very differently. In this article, we argue that the historical evidence does not support these claims. Although we do not defend the sugar industry and cannot address every aspect of this history, we believe recent high-profile claims come from researchers who have overextended the analogy of the tobacco industry playbook and failed to assess historical actors by the norms and standards of their time. Our analysis illustrates how conspiratorial narratives in science can distort the past in the service of contemporary causes and obscure genuine uncertainty that surrounds aspects of research, impairing efforts to formulate good evidence-informed policies. In the absence of very strong evidence, there is a serious danger in interpreting the inevitable twists and turns of research and policy as the product of malevolent playbooks and historical derailments. Like scientists, historians must focus on the evidence and follow the data where they lead.

The current controversy over sugar has its origins in the rise of obesity as a policy issue near the turn of the 21st century and concomitant concerns that existing dietary guidelines were not achieving their intended ends. As nutrition scientists increasingly acknowledged benefits of "healthy fats" and possible metabolic dangers of added sugars, critical new accounts questioned whether the architects of the low-fat campaign had placed too much faith in weak epidemiologic findings and brushed aside countervailing evidence. Some scientists particularly lamented the fate of John Yudkin, a British nutrition scientist from the 1960s who they noted had "preached in the wilderness" about the dangers of sugar, only to be sidelined and ignored (*2*). One article called this historical failure by low-fat enthusiasts to heed Yudkin's Cassandra-like warnings "the sugar conspiracy" (*3*).

The case for industrial malfeasance builds on this revisionist foundation, expanding and enlarging the size and seriousness of the "sugar conspiracy." In September 2016, researchers with the University of California, San Francisco (UCSF), announced that they had uncovered archival documents showing that in the mid-1960s, the sugar industry secretly paid nutrition scientists at Harvard to write a key literature review downplaying the evidence linking sugar and coronary heart disease (CHD) (*4*). As the UCSF authors recounted, "By the 1960s, 2 prominent physiologists were championing divergent causal hypotheses of CHD: John Yudkin identified added sugars as the primary agent, while Ancel Keys identified total fat, saturated fat, and dietary cholesterol." But according to the authors, after the sugar industry "paid off" a Harvard review team led by D. Mark Hegsted, the effect was to "derail" scientific discussions of sugar's potential role in heart disease, with the dietary fat hypothesis subsequently coming to dominate the field.

PHOTO: EDELMAR/ISTOCK.COM

Marion Nestle, a nutrition professor and authority on corporate influence, suggested that the documents were a "smoking gun" (*5*). The Harvard scientists "knew what the funder expected, and produced it," she said, accepting a "bribe" that may have shaped the field for years. A *New York Times* report asserted that, "five decades of research into the role of nutrition and heart disease, including many of today's dietary recommendations, may have been largely shaped by the sugar industry." Recently, a new study by the UCSF group claimed that the sugar industry "suppressed" damaging research it had funded.

We believe that these narratives are wrong. There was no "smoking gun." There was no "sugar conspiracy"—at least not one which we have identified. Here, we offer a brief

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review of postwar nutrition research on fat and sugar and attempt to explain the emergence of these conspiratorial stories.

A NEW FOCUS ON NUTRITION

In the United States, a new movement to develop knowledge about nutrition emerged in the context of World War II, at a time when health officials believed deficiency diseases posed a threat to economic productivity and military fitness. Concurrently in late 1941, the Rockefeller Foundation gave $100,000 (~$1.6 million in 2018, adjusted for inflation) to Harvard to create a nutrition unit, and 15 food firms amassed nearly $1 million (~$16 million in 2018) to launch a research organization called the Nutrition Foundation to fund studies and prepare for rationing. At the center of both was Frederick J. Stare, a clinician and biochemist hired by Harvard to chair its new department and by the Nutrition Foundation to edit its journal.

Nutrition research thus began at Harvard at a moment when the interests of nutritionists and food executives seemed to be aligned; deficiency diseases presumably would be addressed through fortified products or efforts to increase distribution and consumption. Initially, the department focused on war-related research commissioned by the U.S. Army and other federal agencies. But in the years after the war, with circulatory diseases accounting for roughly 40% of U.S. deaths, Stare decided to focus on two conditions commonly linked with the "rich" American diet: obesity and heart disease (*6*).

By 1951, Stare had secured 27 funders, including the U.S. Public Health Service, the Nutrition Foundation, the American Meat Institute, the National Dairy Council, the American Cancer Society, the Eli Lilly Company, and the Sugar Research Foundation (SRF). According to Bernard Lown, a cardiologist hired by Stare in 1958, it was "natural" and "proper" for Stare to turn to the food industry in accord with the mores of the time. "There was no sense of 'being bought,'" recalled Lown, who later accepted, along with a Soviet colleague, the 1985 Nobel Peace Prize awarded to International Physicians for the Prevention of Nuclear War. Nor were there demands from journals that authors provide financial disclosures, Lown said. "It wasn't required. It never entered my mind!" (*7*).

DEVELOPING THE LOW-FAT PARADIGM

As nutrition scientists at Harvard began to examine the possible link between diet and heart disease, the group initially looked askance at the claims of researchers such as Ancel Keys, an eminent physiologist, who believed heart attack prevention should begin with a diet low in fat. Such beliefs threatened the "sound American diet, where nutritional adequacy is built around meat, milk and eggs."

But within a few years, the Harvard team became deeply engaged in research contributing to a new causal paradigm in which heart attacks were the end result of a long-term accumulation of fatty material in the coronary arteries, suggesting possibilities for prevention. Many heart disease sufferers had high serum cholesterol levels, and various investigators had produced arterial disease in animals by feeding foods such as eggs. Wartime data appeared to show European populations deprived of fatty animal foods experienced a decline in coronary deaths. Influential early studies of this emerging dietary fat hypothesis were supported by the U.S. dairy industry.

During the 1950s, Harvard nutritionists participated extensively in collaborative field investigations: a study involving four research centers to test the predictive value of blood lipid assays by examining 15,000 workers at Chrysler, Kodak, Met Life, and two dozen other organizations; international studies examining the diets and cholesterol levels of populations in Guatemala, Costa Rica, and Nigeria. These investigations added to insights gained from ambitious cohort studies such as Framingham that would eventually identify multiple "risk factors" (such as elevated blood cholesterol) by following thousands of individuals prospectively over time.

Despite broad agreement that more evidence was needed, the dietary fat hypothesis seemed scientifically plausible to many researchers. As the media queried experts for guidance in the wake of U.S. President Eisenhower's heart attack in 1955, some tentatively backed the low-fat diet. Stare himself did so in a 1956 magazine column, joining with the President's eminent heart consultant, Paul Dudley White, in recommending that, "perhaps less fat in the American diet... would be desirable."

By 1960, a dominant paradigm was forming around the belief that replacing saturated "animal fats" with vegetable oils could lower serum cholesterol levels and possibly fight heart disease. Reflecting this view was a new statement from the American Heart Association (AHA), coauthored by Stare, recommending that the "coronary-prone" consider limiting intake of foods such as whole milk, butter, and meat (*8*). Hoping to demonstrate causality, scientists began organizing a pilot study for a large "definitive" trial.

THE SUGAR HYPOTHESIS

By the time John Yudkin emerged as an outspoken critic of the fat theory, he was well aware he was fighting an uphill battle. Trained in medicine and biochemistry like Stare, Yudkin had taught nutrition at London University since 1946. Situated in a college of household science, however, he was initially unable to obtain funding from the government's Medical Research Council (MRC). Yudkin thus turned to industry for support. "I've always been a consultant to the food industry," said Yudkin in a 1979 interview, arguing that it would be "highly illogical" for a nutrition scientist to refuse to work with food companies.

Yudkin's entry in the diet-heart debates began with a 1957 paper challenging prevailing interpretations of the widely discussed hypothesis that countries that consumed more fat had higher rates of coronary mortality. He argued that several modern exposures correlated with coronary deaths as well or better than fat, including animal protein, sugar, and access to radio and television. Focused on writing a popular diet book, Yudkin did not initially implicate sugar in heart disease, seeking merely to establish that his recommended low-starch slimming regimen, rich in meat and cheese, was not a recipe for cardiac arrest. (He actually endorsed saturated fat restriction for the coronary-prone.)

But after learning of a study that attributed elevated rates of heart disease among some immigrants to their transition from a meaty diet to more sugar-laden fare, and new claims suggesting a sugar-sensitive constituent of the blood called triglycerides might predict heart attacks better than serum cholesterol, Yudkin sought to refine his hypothesis. In 1964, he performed a case-control study that used questionnaires to assess the sugar intake of 25 men without known heart disease, 20 coronary patients, and 25 men with arterial disease. Finding a significant difference in sugar intake between his cases and controls, Yudkin proposed in the *Lancet* that "people who take a lot of sugar—for example in their tea or coffee—are far more likely to have a heart attack than those who take little" (*9*).

The publication stimulated 20 letters to the editor, several of them with questions about Yudkin's failure to adjust for factors such as smoking and body weight. MRC scientists asked why Yudkin's controls averaged 77 grams of sugar per day when his own data suggested the typical Englishman ate 139. But Yudkin's sugar theory attracted wide press attention, as well as new offers from book publishers.

AN INDUSTRY-SPONSORED REVIEW

Despite Yudkin's work, the central focus of diet-heart research remained on fat. At Harvard in 1962, Stare's top scientist, Mark Hegsted, launched a controlled feeding study at Danvers State Hospital, a Massachusetts psychiatric institution. Backed by a new dairy industry fund created to give producers a

firsthand look at the possible role of dairy fats in disease, the Danvers study involved feeding 20 schizophrenic men various diets in which intake of vegetable oils, butterfat, eggs, starch, sugar, and lactose were manipulated so as to quantify their impact on blood cholesterol levels.

Over his 20 years at Harvard, Hegsted had earned a reputation as a data-driven scientist. Among his first Harvard studies was an analysis of adult protein requirements that disappointed its sponsor, the American Meat Institute, by concluding that the National Research Council's recommended daily allowance was much too high and that even vegetarian diets could supply adequate protein. Under the Reagan administration, Hegsted would be fired from his job developing the first U.S. Dietary Guidelines after his low-fat approach provoked the ire of the beef industry.

Enjoying ice cream in the 1960s, when battle lines were being drawn over the roles of dietary fat and sugar.

PHOTO: BETTMANN/GETTY IMAGES

The Danvers study would become another example of Hegsted's independence. In a talk on 6 May 1965, at a meeting of the Nutrition Foundation, Hegsted began by addressing recent findings linking carbohydrates with heart disease, acknowledging that Yudkin's claims were "worth considering" but hard to credit "without controlled laboratory data" (*10*). He expressed skepticism about new claims that triglycerides might be a better risk indicator than cholesterol. Moving to the Danvers data, Hegsted said the results suggested that the link between dietary carbohydrates such as starch or sugar and serum cholesterol elevation was "rather minimal" compared with the "abundant evidence implicating dietary fat." The Danvers data buttressed the case against saturated fats, providing the basis for a new formula relating fat intake to serum cholesterol that came to be called the "Hegsted equation." The findings helped nudge the AHA to extend its warning about dietary fat to the entire U.S. population.

It was a disaster for the dairy industry. But for sugar executives—one attended Hegsted's talk—the findings appeared to constitute a scientific basis for countering the claims of Yudkin. One month after Hegsted's presentation, an SRF executive reached him by phone to discuss his research and the prospect that SRF might hire him to conduct a review of those articles "which find some special metabolic peril in sucrose." Hegsted agreed to cover SRF's "particular interest," but only within the context of a review "sufficiently broad to make it worth doing."

For Hegsted, the sugar review was but one of several Danvers-related articles to be written, including one that expanded on his Nutrition Foundation talk—a draft of which he shared with SRF. In it, he argued that practical manipulations of the American diet should focus on dietary fat, noting that the "potent role" of fats had been "amply demonstrated," but that such a role for carbohydrates had "not yet been shown." The SRF-sponsored review, published in the *New England Journal of Medicine* in 1967, expanded on these themes and reviewed additional studies but did not disclose that it had been commissioned by SRF (*11*).

THE BATTLE OVER SUGAR AND FAT

Increasingly challenged by his scientific peers, Yudkin continued to gather evidence on sugar: examining national patterns in diet and disease, refining his questionnaire-based study linking sugar and heart disease, and conducting clinical studies of the effect of elevated sugar intake on insulin and platelet adhesiveness. Assisting him in amplifying his ideas was a group of powerful commercial entities whose interests aligned with his beliefs. In 1966, Yudkin reported that he was receiving ~£25,000 per year (~$530,000 in 2018) from "the big food manufacturers."

Yudkin was an asset because he brought scientific legitimacy to events such as the high-protein breakfast promotion organized in 1966 by the British Egg Marketing Board. The next month, for International Milk Day, he joined the National Dairy Council to publicize its new "seventeen day milk diet." He conducted research showing the "value of taking milk before alcoholic drinks"—an implicit test of the "Drive Safely on Milk" slogan the dairy industry had used since 1961. As a dairy consultant, he toured the United States, promoting his sugar theory and an industry statement he had written titled "Sense and Nonsense about Dairy Foods." In one industry meeting, Yudkin would later note that his research on sugar could also be viewed as "diversion tactics" that might "prove beneficial by freeing butterfat from any 'guilt.'"

By the eve of the 1970s, Yudkin had acquired some critics. "I regard Yudkin as a menace and a deterrent to good nutrition policy," wrote Hegsted to a colleague in 1969. That year, the sugar industry convened a panel of heart disease consultants, including a National Institutes of Health (NIH) scientist, which debated a possible "anti-Yudkin" effort because "although British scientists are critical of him and his flimsy data, he does have the interest of the press." Indeed, British government scientists had become sufficiently concerned about Yudkin's sugar hypothesis that they decided to put it to an authoritative test. Multiple government research teams, some of them part of a multicenter working party organized by MRC, tried without success to replicate Yudkin's finding that heart attack sufferers tended to be heavy sugar users. The eminent MRC panel reported in 1970 that the evidence in favor of the sugar hypothesis was "extremely slender" (*12*).

These publicly funded studies, along with other forceful critiques, marked the beginning of the end for Yudkin's sugar hypothesis. In 1971, he retired and began summarizing his case against sugar in a popular book. Proponents of the fat hypothesis soon faced disappointment as well: NIH declined to fund the "definitive" trial, despite persis-

tent exhortations that if strong trials could not be mounted, then dietary advice would have to be promulgated based on the best existing evidence.

By the 1970s, nutrition had become a subject of heated public discussion, and a U.S. Senate committee—after extensive expert testimony and stern warnings from several well-credentialed skeptics who simply did not believe the evidence was sufficient to warrant the issuance of high-profile congressional recommendations for dietary change—embraced the low-fat concept as one aspect of a broad program of healthy eating (*13*). The committee's 1977 report *Dietary Goals for the United States*, which set the model for the low-fat policy paradigm, mentioned Yudkin's theory only in passing. Written by committee staff but edited mainly by Hegsted, the *Dietary Goals* did not, however, overlook sugar. Taking note of sugar's link with tooth decay and possibly diabetes, the report recommended a 40% reduction in sugar intake.

CAUGHT IN THE CROSS FIRE

As we have shown, by the 1960s the paradigm that dietary fat was a likely risk factor for heart disease prevailed among a coalition of scientists closely linked with NIH and AHA and was based on extensive research. By contrast, the sugar theory was developed by a small number of researchers, was supported by limited evidence, and was not accepted by key authorities. Normal science is a social project in which a community of scientists develops consensus over theory. Heart disease epidemiology, in adopting a multifactorial model, could plausibly have accommodated sugar if the theory had withstood testing. But Yudkin's claims were seen as weak and antagonistic, and his signature finding could not be replicated. Moreover, sugar did not appear to meaningfully affect serum cholesterol—the only then-accepted lipid pathway to coronary disease.

As we have also shown, the sugar industry approached Hegsted only after learning of the results of his dairy industry–backed study suggesting that fat and not sugar was a factor in heart disease. "There was no, 'We'll get money from them and make the results come out this way,'" recalled Lown, who worked in the department. "It didn't happen that way," he said. "The sugar industry didn't find researchers at Harvard who would make up a story they didn't believe in order to cash in on the sugar industry money," asserted Gary Taubes, author of *The Case Against Sugar*, a 2016 book that delves deeply into the sugar industry's involvement in nutrition research. "What industry does is find people who already believe something that that industry finds convenient, and then they pay those people to make those beliefs known" (*14*).

During the period in question, food industry funding of nutrition research was routine, and disclosures were "rarely required," as Marion Nestle has written. When NIH moved to defund Framingham in 1968, its former director rescued it by soliciting grants from the Oscar Mayer Foundation and other private entities—none of which were routinely disclosed in publications. Today, food industry funding of research remains common, although most journals require disclosure of conflicts of interest. Compliance is inconsistent, however, and some argue existing policies do not address important sources of bias such as investigators' dietary habits and beliefs.

Our study raises questions about how to assess the historical influence of special interests on nutrition science and policy. Certainly, there is ample evidence that various sectors have tried to influence scientists, and we agree with those who suggest that food companies fund research with an eye toward marketing. (Indeed, an internal sugar industry document states that SRF was created "for the basic purpose of increasing the consumption of sugar.") We do not claim the sugar industry had no influence on nutrition work at Harvard, nor on the field in general. But we believe that there is no good reason to conclude that SRF's sponsorship of a literature review meaningfully shaped the course of dietary science and policy. Moreover, we think it is an error to demonize, almost as a reflex, scientists and their research when there is evidence of private funding. Such a response can create an intellectual template that short-circuits a fuller investigation of alternative explanations. For example, arguments that the sugar industry "suppressed" evidence should be tested against alternative hypotheses.

Our history also underscores the fallacy of emphasizing the machinations of one commodity sector when multiple food industries were deploying similar techniques of influence in the battle for market share. It is notable that during the low-fat era of the 1980s, when suspicion fell heavily on the meat and dairy industries, it was argued that, "The 'fat lobby' has not only influenced our nation's food and nutrition policies, it has *determined* those policies" [emphasis original] (*15*). Nearly 40 years later, at a moment when some have said "butter is back" and sugar is toxic, "Big Sugar" is the behemoth accorded these dramatic powers. Caught in the cross fire of these "diet wars" have been the reputations of historical nutrition scientists, whose statures have risen or fallen based on the extent of their contribution to current theories.

Interpreting history requires attention to the logic and tools of the period under study. Over the course of the diet-heart debates, the techniques of epidemiology and causal inference evolved substantially. The randomized controlled trial had not yet attained the hegemonic "gold standard" status it is often accorded today. It is thus peculiar to reject as unscientific the beliefs of those who pressed for action on the basis of then cutting-edge epidemiologic theory and research. As the great historian of science Thomas Kuhn once wrote, "Out-of-date theories are not in principle unscientific because they have been discarded."

Historical investigations of "merchants of doubt" have been invaluable in showing that scientific uncertainty is sometimes the product of deliberate acts of deception. Such studies underscore the essential insight that the existing evidence base is powerfully shaped by social forces and political choices, and that had decisions unfolded differently, our areas of knowledge (such as genomics) and blind spots (such as obesity prevention or gun violence) would be shifted. But ahistorical accounts thwart our ability to critically evaluate the often long and zigzag process of scientific conjecture and refutation. They provide spurious cover for changes to policy by suggesting that old ideas are illegitimate. And, they advance a false impression that doing the "right" kind of science will somehow avert the messy business of making policy based on incomplete evidence, public values, and democratic politics (*16*). ■

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/359/6377/747/suppl/DC1

10.1126/science.aaq1618

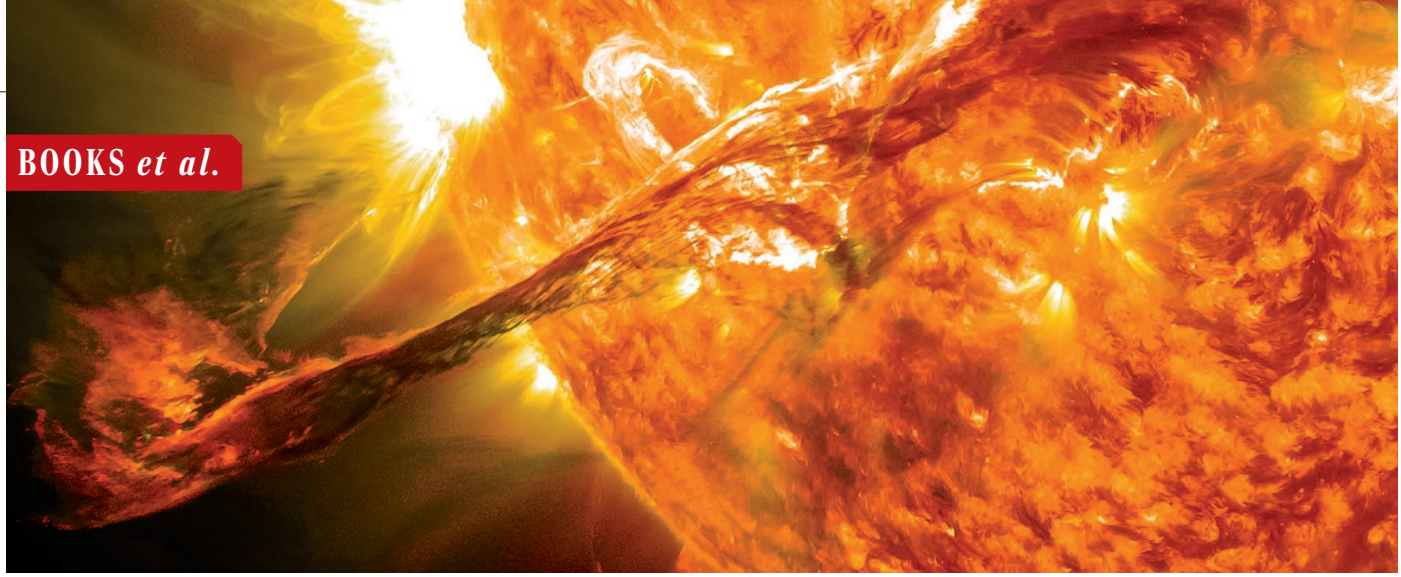

PHOTO: NASA/GSFC/SDO

Power systems are vulnerable to solar flares (shown) and storms when magnetic fields are weakened.

GEOMAGNETISM

Electrical chaos

A candid portrait of the scientists studying Earth's declining magnetism warns of potential peril if the poles swap places

By **Bruce Buffett**

Earth's magnetic field can be approximated as a dipole with north and south magnetic poles slightly misaligned with the geographic poles. This field protects the environment from the harsh conditions of space, yet its strength has been declining since Carl Friedrich Gauss first devised a method to measure the absolute intensity in the 1830s.

Fluctuations in the rate of decline are small compared with the average trend, suggesting that the dipole might vanish in less than 2000 years. This trend has led some researchers to speculate that our planet may be entering the early stages of a magnetic reversal. The outcome would be a substantial lowering of our protective shield.

The last time the north and south poles flipped orientation was about 780,000 years ago. The remoteness of this event in time limits what we have been able to infer about it, but the available geological record suggests that the magnetic field remained in a weakened state for 10,000 years or more until it was finally reestablished in the opposite orientation. Should a similar scenario play out today, the weak magnetic field would wreak havoc on our power grids and other infrastructure.

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The Spinning Magnet
Alanna Mitchell
Dutton, 2018. 333 pp.

The prospect of an impending magnetic reversal sets the backdrop for Alanna Mitchell's new book, *The Spinning Magnet*, which begins with a historical tour of the theory of electricity and magnetism. She also recounts the story of Bernard Brunhes, a French physicist who, in 1906, was the first to suggest that Earth's magnetic field had once been in the opposite polarity. His conclusions were based on the magnetization acquired by certain minerals in rocks as they are heated and cooled through the "Curie point" (the temperature at which a material develops permanent magnetism from a state of induced magnetism).

At that time, it was easier to believe that the rocks were faulty recorders of the ambient magnetic field than to imagine the colossal change required to flip the polarity of Earth's magnetic field. As a result, Brunhes's ideas languished. By the middle of the 20th century, however, magnetic reversals had become widely accepted, having played an important role in the development of the theory of plate tectonics.

At this point in Mitchell's retelling, the focus of the narrative sharpens on the question of an impending reversal of Earth's magnetic poles. She interviews leading researchers in the field of geomagnetism and describes their efforts to understand the processes that govern the evolution of Earth's magnetic field. New satellite observations are offering fresh insights. She also interviews space scientists to understand how charged particles from the Sun and beyond interact with the magnetic field and how the present-day magnetic field shields our modern electrical infrastructure.

Recent examples of failures in this protective barrier (*1*) serve to highlight the problem. A large solar storm in March 1989 sent high levels of charged particles streaming toward Earth. These particles impinged on the magnetic field and induced electric currents through power grids in Quebec, Canada. The ensuing blackout affected 6 million customers. A reduction in the field strength would allow charged particles to penetrate deeper into the Earth system, causing greater damage with even modest solar storms. A substantial and sustained collapse of the magnetic field during a reversal would likely end our present system of power distribution.

Throughout the book, there is a clear and effective attempt to cast a spotlight on the individuals who have contributed to our understanding of Earth's magnetic field. Mitchell has a sharp eye for mannerisms and a vivid way of bringing personalities to the page. Her explanations are aimed at a nontechnical audience, and the analogies she uses to describe complex scientific ideas are always entertaining. For example, a crowded washroom at a "beer-soaked" sporting event serves as the starting point for an illustration of Pauli's exclusion principle. Her enthusiasm for the book's subject matter shines throughout.

There is little doubt that the magnetic field will reverse again. In the meantime, *The Spinning Magnet* gives readers a nontechnical description of electromagnetism and a measured assessment of the possible consequences for our modern world if it does so in the near future. ■

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ECOLOGY

Look to the locals

A field scientist reflects on how indigenous knowledge can enhance tropical forest management

Managing the Wild
Stories of People and Plants and Tropical Forests
Charles M. Peters
Yale University Press, 2018.
208 pp.

By **J. Leighton Reid**

To the untrained eye, an indigenous orchard can look like a trackless wilderness. In truth, many places that Westerners think of as "wild" are far from it. In many parts of the tropics, for example, local people have produced and managed forests consciously and precisely, often in ways that have been sustained for hundreds or thousands of years.

In *Managing the Wild*, botanist and tropical ecologist Charles Peters tells rich stories about indigenous forest management, which he accumulated over nearly four decades of fieldwork in Latin America, Africa, Asia, and Australasia. Through an engaging blend of natural history, ethnobotany, and personal anecdote, Peters aims to change the perception that local people exploit natural resources with no regard for the future.

A Dayak woman carries farm equipment in a rattan basket. Dayak gardens look wild but are carefully cultivated.

Traveling chronologically through his career, Peters begins with an investigation of an ecological enigma in southern Mexico, where ramón trees (*Brosimum alicastrum*) grow in unusually dense stands over Mayan ruins. This pattern, he discovers, is best explained as a relic of careful phenotype selection by ancient Mayan foresters (with temple-dwelling fruit bats playing a contributing role).

In lowland Amazonia, he studies the effects of fruit harvesting on the camu-camu (*Myrciaria dubia*), a small tree that is submerged by flood waters for half of the year, when its vitamin C–packed fruits are eaten by fish. He finds that the population is resilient to intense harvesting but is naturally ephemeral, shifting as the river's course migrates.

In the greater Mekong region of Laos, Cambodia, and Vietnam, Peters and his colleagues study the sustainability of wild-collected rattan—a commodity worth billions of dollars. And in New Guinea, Brazil, and Myanmar, he works with locals to develop, or try to develop, scientific timber inventories and sustainable management plans.

Peters's stories are engaging and memorable, evoking the style of Forsyth and Miyata's *Tropical Nature* and Plotkin's *Tales of a Shaman's Apprentice*. Like those works, *Managing the Wild* is more than a naturalist's autobiography. Throughout his rollicking tales, Peters expressly highlights rural people collecting, analyzing, and applying sophisticated forest inventory and growth data—producing homegrown scientific information to sustainably manage their resources.

In the dry forests in southern Mexico, for example, locals harvest the sugary leaf bases of several species of wild agave to produce mescal, a smoky liquor. In the absence of data, the practice looks bad: The agaves, which only flower once before they die, are dug up before they have a chance to reproduce. Overharvesting could decimate agave populations, leaving little incentive for a community to conserve local patches of dry forest—the most threatened ecosystem in Mexico. With guidance from Peters, one such community collected data on the stock and production of wild agave populations over 5 years. At the end of the study, they were able to demonstrate that their practices were maintaining the agave populations (giving cause for a celebratory toast). When incorporated into a sustainable management plan, such data can form the basis for locals to shore up their land tenure situations.

Through such examples, Peters builds a case in favor of governments giving rural people greater control over their local forests. A long attention span is not needed; the vignettes are as short as a few pages. But for readers who find the contents light, technical manuscripts are cited in the endnotes.

The book is not all lighthearted. Some stories relate cases where traditional practices were lost—such as a rural community in Mexico that overexploited tree bark for artisanal paper and caused the local extirpation of the best bark-producing tree species; or a community in Myanmar that discontinued the planting of thatch palm (*Livistona jenkinsiana*) around rice fields because the people thought that they might be displaced, again, by the military before they could harvest it; or the Miao farmers in China whose fallow cycle was disrupted when they were offered cash to plant exotic monocultures in one of the largest payment-for-ecosystem-services projects ever undertaken. The somber implication is that sustainable management systems are difficult to restore once they are lost.

Indeed, *Managing the Wild* relates confirmatory stories about the sustainability of traditional management practices and describes aspirations about sustainability in the future, but examples of communities that transitioned from overexploitation to robust, sustainable management are lacking.

Peters's stories and his overarching message that local people can be good for nature are likely to resonate with resource managers, conservation advocates, researchers, students, and policy-makers, but *Managing the Wild* should be accessible to anyone curious about tropical forest ecology. ■

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PHOTO: ELLISPHOTOS/ALAMY STOCK PHOTO

Edited by **Jennifer Sills**

Salton Sea: Ecosystem in transition

Each year at least a billion birds migrate down the west coast of North America along what is known as the Pacific Flyway (*1*). For the aquatic species, large, open bodies of water are important oases. For more than a century, the Salton Sea in southern California has been a vital component of this flyway for fish-eating birds (*2*, *3*), including pelicans, cormorants, skimmers, mergansers, herons, egrets, terns, and gulls. In California, 96% of the historic wetlands have been lost to agriculture and development (*4*). The delta of the Colorado River, in Mexico just south of California, was once a verdant wetland but is now shrunken and dry. In most years, not a drop of water in the river reaches the Gulf of California in Mexico (*5*).

In January 2018, mitigation water that had been flowing to the Salton Sea to maintain its level and salinity began to be diverted, which will cause the sea to shrink in volume and increase in salinity (*6*, *7*). These changes will eliminate fish. The Salton Sea will shift from an ecosystem in which fish are the trophic level on which birds feed, to one in which birds feed on invertebrates.

It is far from clear how birds of the American West will respond to this shift (*4*). It may lead to fewer bird species overall, but some species will likely increase in number, such as the eared grebe, ruddy duck, northern shoveler, California gull, and ring-billed gull. Populations of saline lake specialists, such as black-necked stilts, Wilson's and red-necked phalaropes, and American avocets, will likely increase as well.

The human-induced ecological transition of the Salton Sea has profound implications for continent-wide avian populations (*8*), as well as for human communities exposed to toxic dust rising from the drying shores (*9*). Currently, the State of California has not adequately addressed the ecological consequences and public health impacts of a shrinking and salinizing sea (*10*). It is important to plan for an ecosystem-wide transition that minimizes the impacts on birds and on the hundreds of thousands of human inhabitants living adjacent to the shrinking sea. Steps toward restoration include building and maintaining suitable habitats on the periphery of a smaller Salton Sea that will reduce dust emission and create more habitats for birds; monitoring the quality of shallow water habitats; and minimizing the release of dust from newly exposed lake bottom sediments through a variety of wind-abatement techniques pioneered at Owen's Lake (*11*).

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Fund the Biological Survey Unit

The Biological Survey Unit (BSU) is administered by the U.S. Geological Survey (USGS) and located in the Smithsonian Institution's National Museum of Natural History (NMNH) (*1*, *2*). Since 1889, the BSU has managed the

The shrinking Salton Sea serves as an important stop for fish-eating migratory birds.

North American collections of non-fish vertebrates. The proposed budget for 2018 eliminates the BSU and transfers personnel to the Patuxent Wildlife Research Center campus in Maryland, far from the collections central to the Unit's mission (*1*–*3*). This erosion of collection-based expertise further undermines U.S. leadership in science.

The BSU has been instrumental in tracking biotic diversity in North America and beyond as well as anthropogenic impacts on plant and animal life (*1*–*3*). This mission is more timely now than ever before—we face likely future extinctions linked to human activities (*4*–*6*), and conversion of natural habitats for human use places a premium on understanding the distributions and dynamics of wild taxa (*6*, *7*).

BSU activity over the past 5 years has included collection of many thousands of specimens from multiple states and foreign countries, loans of scientific specimens to institutions in the United States and abroad, hosting visiting researchers, and publication of seminal scientific contributions (*8*). Scientists from any part of the world using scientific specimens from this region will almost invariably work directly or indirectly with the BSU.

On behalf of our memberships, we express deep concerns over these budgetary decisions, and we urge reconsideration of budget priorities to maintain and, indeed, to revitalize the BSU. This small unit collects and curates foundational resources upon which untold future discoveries will be based. The American Society of Mammalogists, American Ornithological Society, and American Society of Ichthyologists and Herpetologists consider it imperative that these resources be preserved intact for future generations, and that their growth and continued use be established as a priority for scientists of today and the future.

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§B.I.C. and K.S.C. are President and President-elect, respectively, of the American Society of Ichthyologists and Herpetologists.

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10.1126/science.aas9289

TECHNICAL COMMENT ABSTRACTS

Comment on "Selective anaerobic oxidation of methane enables direct synthesis of methanol"

J. A. Labinger

The Comment and Response concerning the report of oxidation of methane to methanol by water (Reports, 5 May 2017, p. 523) do not fully capture the implications of thermodynamic limitations. A nonisothermal process in which each cycle requires a large temperature swing and permits only substoichiometric methane conversion surely could not be carried out on any practical scale.

Full text: dx.doi.org/10.1126/science.aar4968

Response to Comment on "Selective anaerobic oxidation of methane enables direct synthesis of methanol"

Vitaly L. Sushkevich, Dennis Palagin, Marco Ranocchiari, Jeroen A. van Bokhoven

Labinger argues that stepwise reaction of methane with water to produce methanol and hydrogen will never be commercially feasible because of its substoichiometric basis with respect to the active site and the requirement of a large temperature swing. This Comment is not touching any new ground, beyond describing the thermodynamic feasibility, thermal cycling, and the role of water as discussed previously. Most important, it does not have a solid numerical basis.

Full text: dx.doi.org/10.1126/science.aar6868

ONLINE BUZZ

As autonomous vehicles approach

On 14 December 2017, *Science* posted two News stories about the status and potential of autonomous vehicles (AVs): "Are we going too fast on driverless cars?" by J. Mervis (http://scim.ag/AVrisks) and "People don't trust driverless cars. Researchers are trying to change that" by M. Hutson (http://scim.ag/AVtrust). The stories, and an accompanying video and podcast, explored how riders and businesses might use AVs, how government might regulate them, what determines how much people trust the technology, and how safe the AVs would have to be to gain users' trust. On Facebook and Youtube, readers left hundreds of comments expressing their hopes and fears about AV technology. Below are some excerpts from a few comments that went beyond whether to trust the technology and addressed a broader concern. Submit your own thoughts about AVs at science.sciencemag.org/359/6377/755.

A selection of your thoughts:

Ultimately, insurance will change the acceptance of self-driving cars. The technology can be improved...drivers generally can't. Commercial airliners are pretty much on autopilot after takeoff up to landing, so the concept is sound and will gain ground. How quickly is another matter.... *—Allen McPherson*

Who will be to blame when a machine kills a person in an accident? Furthermore, with the current sentiment of changing net neutrality, what's to stop future governments restricting where your vehicle is "allowed" to go? *—Branislav Džepina*

When they are hack-proof, I'll trust them more. [As] anyone who's ever owned any smartphone, PC, or other such tech knows, they're not always reliable. Who is culpable in this scenario? *—Aidan Quinn*

I think we'd do better to double down on fast and efficient mass transit and (generally) redesign such that private cars (if any) and pedestrians do not coexist in the same spaces.... *—Joshua Eric Turcotte*

10.1126/science.aat1490

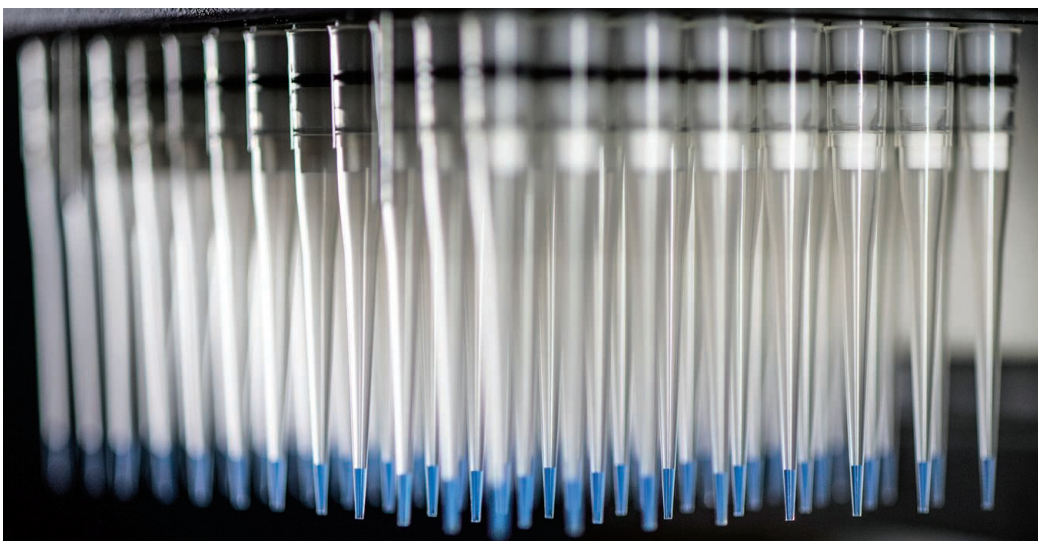
RESEARCH

Toward predicting evolution in stick insects

Nosil et al., *p. 765*

IN *SCIENCE* JOURNALS

Edited by **Stella Hurtley**



INFLUENZA

Investigating flu vaccine effectiveness

Seasonal influenza vaccines have been recommended for decades, but studies focused on antigen-specific lymphocytes in humans are sparse. Koutsakos *et al.* examined longitudinal samples of influenza-vaccinated individuals to determine what responses generate protective immunity. Vaccination could induce circulating T follicular helper memory cells, antibody-secreting cells, and memory B cells, but it did not seem to affect other types of lymphocytes. Existing antibodies against influenza at the time of vaccination dampened these responses. The authors probed different tissues for influenza memory B cells, which they found outside the circulation. Better targeting of these cells might improve influenza vaccine efficacy. —LP

Sci. Transl. Med. **10**, eaan8405 (2018).

Studying samples after flu vaccination suggests that immunological memory cells reside outside the vasculature.

BIOCHEMISTRY

How lipopolysaccharides bridge the gap

The outer membrane of Gram-negative bacteria is composed of lipopolysaccharide, a large glycolipid that prevents drugs from entering the cells. Disrupting lipopolysaccharide assembly hypersensitizes bacteria to antibiotics. Sherman *et al*. used biochemical tools to observe lipopolysaccharide transport. Seven proteins, which are conserved in all Gram-negative bacteria, appear to form a protein bridge that uses adenosine triphosphate to power transport of lipopolysaccharide from one membrane to another. The ability to monitor intermembrane transport of lipopolysaccharide will help in efforts to develop and characterize inhibitors. —SMH

Science, this issue p. 798

CANCER

SNF'ing out antitumor immunity

Immune checkpoint inhibitors induce durable tumor regressions in some, but not all, cancer patients. Understanding the mechanisms that determine tumor sensitivity to these drugs could potentially expand the number of patients who benefit (see the Perspective by Ghorani and Quezada). Pan *et al*. discovered that tumor cells in which a specific SWI/SNF chromatin remodeling complex had been experimentally inactivated were more sensitive to T cell–mediated killing. The cells were more responsive to interferon-γ, leading to increased secretion of cytokines that promote antitumor immunity. Miao *et al*. examined the genomic features of tumors from patients with metastatic renal cell carcinoma who had been treated with immune checkpoint inhibitors. Tumors harboring inactivating mutations in *PBRM1*, which encodes a subunit of the same SWI/SNF complex, were more likely to respond to the drugs. —PAK

Science, this issue p. 770, p. 801; see also p. 745

MICROBIOLOGY

CRISPR-Cas accelerates phage evolution

Despite the growing use of the CRISPR-Cas system for targeted mutagenesis, little attention has been paid to understanding the basic biology of this defense system in bacteria-phage relationships. Rao *et al.* suggest that the system is a driver of phage, and perhaps bacterial, evolution. The authors characterized phage escape mutants restricted by high- and low-restriction spacers. Although the frequency of phage mutants that escaped high-restriction sequences was predictably low, the mutation frequency of phages that escaped low-restriction sequences was extremely high, about six orders of magnitude

greater than spontaneous mutation frequencies. —TM

Sci. Adv. 10.1126/sciadv.aar4134 (2018).

STRUCTURAL IMMUNOLOGY

Recognizing danger signals

In the classical complement pathway, the C1 initiation complex binds to danger patterns on the surface of microbes or damaged host cells and triggers an immune response. Immunoglobulin G (IgG) antibodies form hexamers on cell surfaces that have high avidity for the C1 complex. Ugurlar *et al*. used cryo–electron microscopy to show how a hexamer of C1 complexes interacts with the IgG hexamer. Structure-guided mutagenesis revealed how C1 is activated to trigger an immune response. —VV

Science, this issue p. 794

APPLIED PHYSICS

It's a wrap

Whether an object has a regular or irregular shape, wrapping it with a thin film can be challenging. Kumar *et al*. released droplets of oil above thin polymer sheets floating on water (see the Perspective by Amstad). With sufficient impact force, the polymer wrapped around the droplet with near perfect seams. The shape of the resulting enclosed drop depended on the shape of the sheet initially placed at the air-liquid interphase. —MSL

Science, this issue p. 775; see also p. 743

QUANTUM OPTICS

Forming photonic bound states

Photons do not naturally interact with each other and must be coaxed into doing so. Liang *et al*. show that a gas of Rydberg atoms—a cloud of rubidium atoms excited by a sequence of laser pulses—can induce strong interactions between propagating photons. The authors could tune the strength of the interaction to make the photons form dimer and trimer bound states. This approach should prove useful for producing novel quantum states of light and quantum entanglement on demand. —ISO

Science, this issue p. 783

NEUROSCIENCE

A way to prevent generalized seizures?

Temporal lobe epilepsy is the most common form of epilepsy in adults. Patients have spontaneous seizures and risk developing serious cognitive impairment. Bui *et al*. studied an animal model of temporal lobe epilepsy (see the Perspective by Scharfman). Selective opto-genetic inhibition of dentate gyrus mossy cells increased the likelihood of electrographic seizures generalizing to full behavioral convulsive seizures. Activation of mossy cells reduced the likelihood. Thus, the activity of mossy cells might serve to inhibit seizure propagation. —PRS

Science, this issue p. 787; see also p. 740

ATMOSPHERIC CHEMISTRY

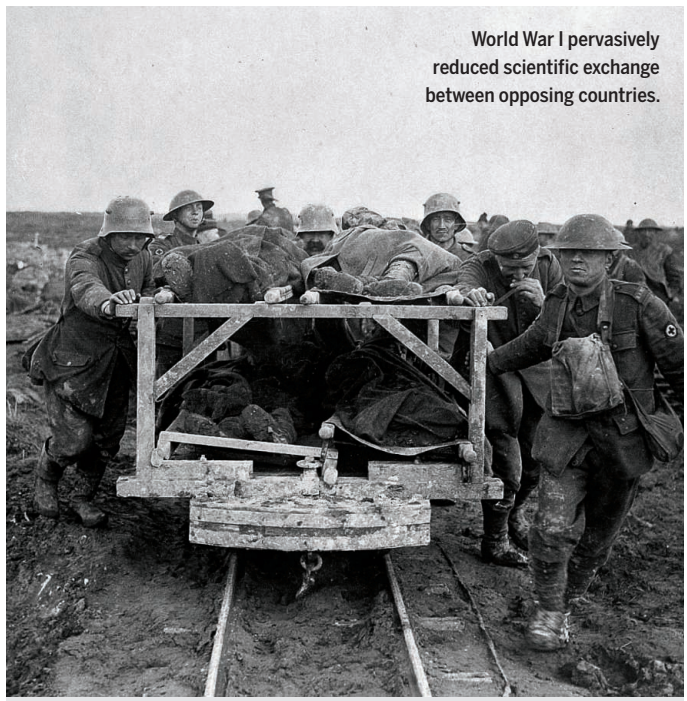
Air pollution evolution

Transport-derived emissions of volatile organic compounds (VOCs) have decreased owing to stricter controls on air pollution. This means that the relative importance of chemicals in pesticides, coatings, printing inks, adhesives, cleaning agents, and personal care products has increased. McDonald *et al*. show that these volatile chemical products now contribute fully one-half of emitted VOCs in 33 industrialized cities (see the Perspective by Lewis). Thus, the focus of efforts to mitigate ozone formation and toxic chemical burdens need to be adjusted. —HJS

Science, this issue p. 760; see also p. 744

IN OTHER JOURNALS

Edited by **Caroline Ash** *and* **Jesse Smith**



World War I pervasively reduced scientific exchange between opposing countries.

PHOTO: WELLCOME COLLECTION

COLLATERAL DAMAGE

A world at war on science

As casualties mounted along the frontlines of World War I, the international scientific frontier was no exception. Iaria *et al*. show that the war drove down both citations of and similarities to research from scientists in the opposing camp (Allied versus Central nations). Leading-edge science was most affected. Relative to researchers whose prewar work referenced the most highly cited 5% or 3% of research from the opposing camp, prolific researchers who depended on the top 1% from behind enemy lines showed the steepest declines during the war in terms of publications in top journals, Nobel-nominated breakthroughs, introducing new scientific terms, and having those new terms mentioned in granted patents. —BW

Quart. J. Econ. 10.1093/qje/qjx046 (2018).

IMMUNOLOGY

Innate receptor sees cancer growth factor

Innate lymphoid cells (ILCs) and natural killer (NK) cells express receptors that recognize ligands associated with pathogens and cellular stress. One such human receptor, NKp44, has been implicated in recognizing transformed cells, but its actual target has remained elusive. Barrow *et al*. report that a member of the platelet-derived growth factor (PDGF) family, PDGF-DD, is a ligand for NKp44. Notably, cancer cells use PDGFs to promote their survival, growth, and dissemination. PDGF-DD induced ILC and NK cell cytokine secretion in vitro. Furthermore, the expression of PDGF-DD in tumors promoted increased rejection in NKp44-expressing transgenic mice. This was further enhanced by anti-CD96 checkpoint blockade.

Dinosaurs followed a classic pattern of adaptive radiation as they spread across the planet.

PALEONTOLOGY

Around the world in 170 million years

Dinosaurs were the dominant vertebrate on the planet for more than 170 million years. During that time, they dispersed and diversified into the myriad of forms that we recognize from fossils today. O'Donovan *et al.* use a phylogenetic modeling approach, in combination with fossil locations, to reconstruct locations of origin and map the path of dinosaur evolution and radiation from their emergence to their demise. The authors find that dinosaurs followed a classic pattern of evolutionary radiation from their origin in what is now South America. Dinosaur speciation rates were faster early in their history and slowed toward the end. Further, the authors conclude that early speciation was likely due to vicariance, whereas later speciation events were shaped by ecological pressures and niche filling. —SNV

Nat. Ecol. Evol. 10.1038/s41559-017-0454-6 (2018).

A meta-analysis of human cancer data hints that NKp44–PDGF-DD interactions may have positive clinical outcomes for certain cancers, such as glioblastoma. —STS

Cell 10.1016/j.cell.2017.11.037 (2018).

GEOPHYSICS

Hot mantle rushes in to fill the void

Volcanism in the western United States over the past 20 million years is tied to the subducting Juan de Fuca and Farallon slabs and mantle dynamics. Zhou *et al.* present a geodynamic model of the region using past plate motion, current seismic tomographic imaging, and volcanic history. They find that the large amount of intraplate volcanism in the past required the intrusion of hotter mantle below the western United States. This intrusion was driven by the sinking of the ancient Farallon slab beneath the region. —BG

Nat. Geosci. 10.1038/s41561-017-0035-y (2018).

TISSUE HOMEOSTASIS

Checks and balances at a cellular level

To stay healthy, tissues must maintain proper ratios of their constituent cell types. Adler *et al.* developed a framework for describing a range of circuit topologies between two cell types where each secretes a signal that is sensed by the other. Without regulation, both cell types grow to a stable cell number close to the carrying capacity of the system. To maintain one cell type at lower numbers, production of the signal that it senses could be down-regulated by the signal that it secretes, or it could remove its cognate signal by endocytosis. Endocytosis allows a faster response and is more robust to parameter variation. The concepts also apply to three- and four-cell circuits and provide a basis for understanding tissue homeostasis. —VV

Proc. Natl. Acad. Sci. U.S.A. 10.1073/pnas.1714377115 (2018).

CLIMATE CHANGE

Cities feel the heat of climate change

Many climate change studies aim to determine how the global annual mean surface air temperature has changed or will change over time. Since 1975, this temperature has changed at a rate of about 0.15° to 0.2°C per decade. But as Papalexiou *et al*. show, this figure does not capture the rising extremes in heat that many people living in cities around the world are experiencing. In the past three decades, the highest temperatures of the year at 9000 stations have risen by an average of 0.25°C per decade. In many big cities, the rise has been even larger, with Houston, Moscow, and Paris experiencing rises of more than 0.8°C per decade. These fast rises in the most extreme temperatures increase the risk of heat-related fatalities. —JFU

Earth's Future 10.1002/2017EF000709 (2018).

MOLECULAR BIOLOGY

Retrotransposons acting as lightning rods

Long interspersed nuclear elements–1 (L1s) are abundant retrotransposons in the human genome. L1s can duplicate and jump in the genomes of neural progenitor cells in a process called retrotransposition. High levels of retrotransposition are associated with neuronal diversity and pathology. Jacob-Hirsch *et al.* mapped genome-wide retrotranspositions in human brain samples. The majority of L1 insertions in brains of normal donors occur in preexisting L1 elements that serve as "lightning rods" to guide safe landings of potentially harmful retrotranspositions. However, in brains of patients with neurodevelopmental disorders, enhanced transpositions can occur in genes associated with neurologic and psychiatric disorders, increasing the risk of damaging insertions. —SYM

Cell Res. 10.1038/cr.2018.8 (2018).

CREDIT: JULIUS T. CSOTONYI

ALSO IN *SCIENCE* JOURNALS

Edited by **Stella Hurtley**

ORGANIC CHEMISTRY

Left- or right-handed C–H bond activation

Although organic compounds consist mostly of carbon and hydrogen atoms, strategies for chemical synthesis have traditionally targeted the handful of more reactive interspersed oxygens, nitrogens, and halogens. Modifying C–H bonds directly is a more appealing approach, but selectivity remains a challenge. Saint-Denis *et al*. review recent progress in using transition metal catalysis to break just one of two mirror-image C–H bonds and then append a more complex substituent in its place. Ligand design has proven crucial to differentiate these otherwise similar bonds in a variety of molecular settings. —JSY

Science, this issue p. 759

EVOLUTIONARY ECOLOGY

Estimating the predictability of evolution

Evolution results from expected effects, such as selection driving alleles toward fixation, and stochastic effects, such as unusual environmental variation and genetic drift. To determine the potential to predict evolutionary change, Nosil *et al*. examined three naturally occurring morphs of stick insects (see the Perspective by Reznick and Travis). They wanted to determine which selective parameters could be used to foresee changes, despite varying environmental conditions. One morph fit a model of negative frequency-dependent selection, likely owing to predation, but changes in other morph frequencies remained unpredictable. Thus, for specific cases, we can forecast short-term changes within populations, but evolution is more difficult to predict when it involves a balance between multiple selective factors and uncertainty in environmental conditions. —LMZ

Science, this issue p. 765; see also p. 738

PEPTIDE MODIFICATION

Protein backbone, broken and mended

Small, posttranslationally modified peptides are produced by microorganisms as antimicrobial agents or to communicate with neighboring cells. Alterations to the peptide backbone can change the structure of peptides or introduce reactive chemical moieties. Morinaka *et al*. characterized a bacterial enzyme that excises the side chain and α-carbon of a tyrosine residue from a short peptide, leaving behind an α-ketoamide. This backbone functional group is found in some protease inhibitors and is a valuable handle for bio-orthogonal chemistry. The enzyme accepts peptide substrates with a short recognition motif, suggesting that it could be used to generate libraries of modified peptides. —MAF

Science, this issue p. 779

ECOSYSTEM SERVICES

Many, many more pollinators needed

Numerous studies have shown that biodiversity is necessary for ecosystem function. The majority of these, however, have taken place at relatively small experimental scales. Winfree *et al*. looked across more than 3000 square kilometers for relationships between biodiversity and crop pollination (see the Perspective by Kremen). The number of wild bee species required for successful pollination rapidly increased with spatial scale, largely owing to variation in the species present across sites and the degree to which the most abundant species played a role. In the end, more than an order of magnitude more species than predicted by smaller-scale experiments were required for full ecosystem functioning. —SNV

Science, this issue p. 791; see also p. 741

DEVELOPMENT

A primitive role for ATF6

The unfolded protein response (UPR) preserves endoplasmic reticulum (ER) homeostasis in mature cells. However, inactivating mutations in the UPR-associated transcription factor ATF6 cause congenital vision defects, suggesting a developmental role for ATF6 as well. Kroeger *et al.* found that ATF6 was critical to stem cell differentiation into the mesodermal lineage, in part by promoting ER expansion during cell differentiation. Activating ATF6 in cultured stem cells resulted in the generation of functional vascular endothelial cells, suggesting a potential strategy to facilitate mesodermal tissue production for research or therapy. —LKF

Sci. Signal. **11**, eaan5785 (2018).

REVIEW SUMMARY

ORGANIC CHEMISTRY

Enantioselective C(sp^3)–H bond activation by chiral transition metal catalysts

Tyler G. Saint-Denis, Ru-Yi Zhu, Gang Chen, Qing-Feng Wu, Jin-Quan Yu*

BACKGROUND: The ultimate goal of synthetic chemistry is the efficient assembly of molecules from readily available starting materials with minimal waste generation. The synthesis of organic molecules—compounds containing multiple carbon-hydrogen (C–H) and carbon-heteroatom (such as oxygen or nitrogen) bonds—has greatly improved our quality of life. Pharmaceuticals that can treat disease, agrochemicals that enhance crop yields, and materials used in computer engineering are but three illustrative examples. And yet more often than not, the syntheses of these substances have proved challenging because of restrictions on how molecules can be constructed.

Major advances in organic chemistry have relied on the discovery of reactions that dramatically altered chemists' approach to building molecules. Canonical organic reactions typically rely on the high reactivity of functional groups (with respect to a C–H bond) in order to introduce new functionality in a target molecule. However, there are times when the accessibility of certain functional groups at particular carbon centers may be restricted; in these cases, the installation of functionality may require several steps and can lead to undesired side reactions, delaying the production of as well as decreasing the overall yield of a synthetic target.

Considering that organic molecules possess an abundance of C–H bonds, it should be unsurprising that C–H functionalization (the conversion of C–H bonds into C–X bonds, where X ≠ H) has garnered considerable attention as a technique that could alter synthetic organic chemistry by enabling relatively unreactive C–H bonds to be viewed as dormant functionality. And yet, to date applications of C–H functionalization logic are hindered by considerable limitations in terms of regioselectivity and stereoselectivity (the construction of chiral centers).

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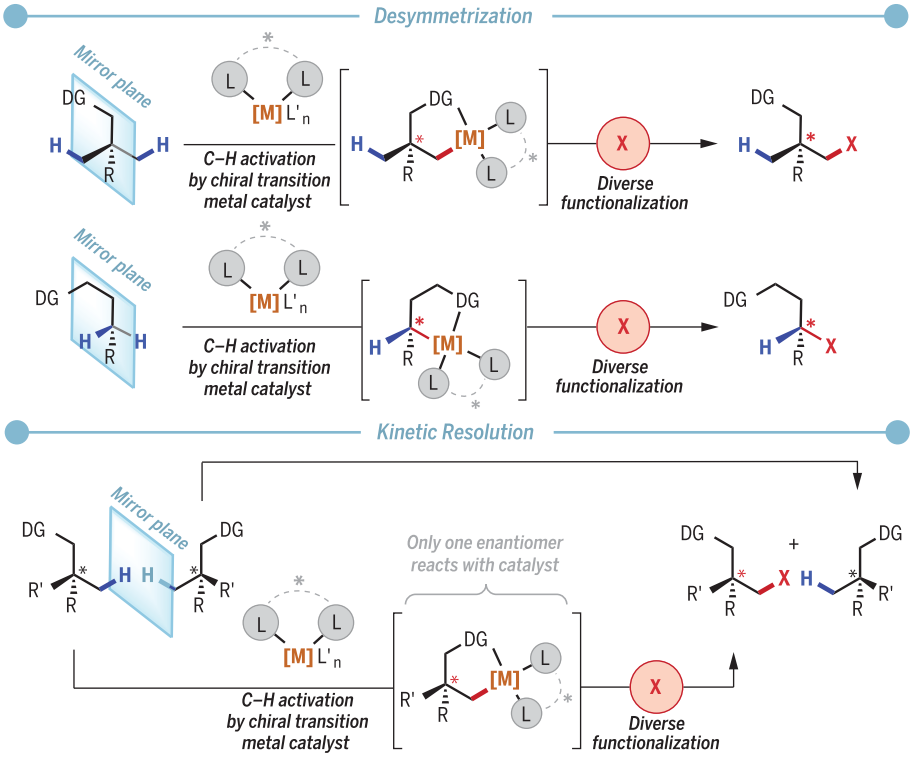
ADVANCES: Although numerous approaches to regioselective C–H functionalization have been extensively reported, only recently has attention been placed on addressing the issues of stereoselectivity. One such solution entails chiral transition metal catalysts in which a metal complexed to a chiral ligand reacts directly with a C–H bond, forming a chiral organometallic intermediate that is then diversely functionalized. A variety of transition metal catalysts have been shown to affect the asymmetric metallation of C–H bonds of enantiotopic carbons (C–H bonds on different carbons) or enantiotopic protons (C–H bonds on the same carbon). The major driving force behind the development of enantioselective C–H activation has been the design of chiral ligands that bind to transition metals, creating a reactive chiral catalyst while also increasing the reactivity at the metal center, accelerating the rate of C–H activation.

OUTLOOK: In order for enantioselective C–H activation to become a standard disconnection in asymmetric syntheses, the efficiency of catalyses and breadth of transformations must be improved. Although the specific requirements to achieve these goals are unclear, we argue that improved ligand design will be instrumental to further progress until any C–H bond of any molecule can be converted into any functionality in high yields with high enantioselectivity. The impact of such progress will no doubt have rippling effects in seemingly disparate fields, such as medicine, by enabling the syntheses of previously inaccessible forms of matter. ■



Enantioselective C(sp^3)–H activation. Chiral transition metal catalysts can selectively functionalize both (Top) enantiotopic carbons and (Middle) enantiotopic protons through asymmetric metalation. (Bottom) Racemic mixtures (1:1 mixtures of enantiomers) may also be differentiated through kinetic resolution/C(sp^3)–H activation.

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REVIEW

ORGANIC CHEMISTRY

Enantioselective C(sp^3)–H bond activation by chiral transition metal catalysts

Tyler G. Saint-Denis, Ru-Yi Zhu, Gang Chen, Qing-Feng Wu, Jin-Quan Yu*

Organic molecules are rich in carbon-hydrogen bonds; consequently, the transformation of C–H bonds to new functionalities (such as C–C, C–N, and C–O bonds) has garnered much attention by the synthetic chemistry community. The utility of C–H activation in organic synthesis, however, cannot be fully realized until chemists achieve stereocontrol in the modification of C–H bonds. This Review highlights recent efforts to enantioselectively functionalize C(sp^3)–H bonds via transition metal catalysis, with an emphasis on key principles for both the development of chiral ligand scaffolds that can accelerate metalation of C(sp^3)–H bonds and stereomodels for asymmetric metalation of prochiral C–H bonds by these catalysts.

One of the long-standing objectives of organic chemistry is the selective functionalization of carbon-hydrogen (C–H) bonds (*1*). This is because organic molecules consist of carbon frameworks (occasionally containing heteroatoms such as oxygen, nitrogen, and sulfur) bearing hydrogen atoms on the majority of carbon centers. Traditionally, the synthetic manipulations possible in organic synthesis have been limited by the availability of distinct functional groups at specific carbon centers; consequently, synthetic transformations are not possible at the majority of carbon centers containing inert C–H bonds. Such limitations have often forced synthetic chemists to pursue indirect, multistep manipulations to introduce functionality in a reaction sequence, and have restricted the use of simple starting materials in synthetic endeavors.

The intrigue of C–H functionalization in the synthesis of complex synthetic targets thus stems from the potential to view inert C–H bonds as masked reactive functionalities, which may be unlocked by a reagent under the appropriate reaction conditions. By virtue of the abundance of C–H bonds in organic molecules, C–H bond functionalization, in principle, could allow structural modification at any carbon center of an organic molecule, altering synthetic chemistry's modus operandi by shortening synthetic routes, increasing atom and step economy, enabling novel disconnections, and expediting the production of target molecules. Further, in the arenas of drug discovery and drug design C–H functionalization may allow chemists to take relatively complicated molecules and in a single step introduce a diverse range of functionalities to previously inaccessible carbon centers so as to afford analogs with potentially improved biological properties.

The greatest hindrance to the widespread application of C–H activation is selectivity: In molecules with multiple C–H bonds of comparable bond strengths and steric environments, it has been traditionally difficult to control chemo-, regio-, and stereoselectivity in C–H activation processes. Although recent advances have been made in the regioselective metalation of both proximal and remote C–H bonds by using directing effects or electronic biases by several different groups (*2*–*4*), practical stereoselective C–H activation has received considerably less attention. The lack of attention toward enantioselective C–H activation is striking, given the paramount importance of chirality in organic molecules; for example, pharmaceuticals often require chiral components, owing to the inherent chirality of life (*5*). The development of such enantioselective C–H activation methodologies would make it possible to precisely modify C–H bonds and generate new stereocenters in a single step, providing synthetic chemists with the power to specify where, what, and when stereocenters are introduced in a reaction sequence.

To date, several different approaches have been developed to enantioselectively modify C–H bonds (Fig. 1). These include biomimetic approaches (*6*), akin to the H-atom abstraction of cytochrome P450 (*7*), as well as other enzymatic processes (metal-oxo H-atom abstractions) (Fig. 1A) (*8*, *9*); metallonitrene (*10*) and metallocarbene (*11*, *12*) insertions (Fig. 1B); and transition metal–mediated C–H activation (Fig. 1C) (*13*), which is typified by a C–H cleavage event preceding generation of a well-characterized carbon-metal bond and is the topic of this Review (*14*, *15*). Two main methods have emerged for this latter approach, including desymmetrizing C–H activation [such as isopropyl desymmetrization, in which the chiral carbon center is not bound to the transition metal (Fig. 1C)] and transition metal complex recognition of enantiotopic methylene C–H bonds [in which the chiral carbon center is bound to the transition metal (Fig. 1C)]. Further, C–H activation–based kinetic resolution of racemic (a one-to-one ratio of enantiomers) substrates has been demonstrated and is an active area of research (Fig. 1C). Transition metal–catalyzed C–H activation has largely been enabled by select catalytic cycles, including palladium (Pd)(II/0), Pd(II/IV), Pd(0/II), Pd(II/II), and rhodium (Rh) or iridium (Ir)(I/III), although other preliminary examples do exist (*16*). Here, we highlight recent major achievements (Fig. 1D) in the development of enantioselective C–H bond activation, with an emphasis on stereochemistry-generating C–H activation (as opposed to enantioselection occurring in other non-C–H activation steps) and the design of chiral ligands and stereomodels to enable these technologies. For a comprehensive review covering enantioselective C(sp^2)–H and C(sp^3)–H activation reactions up to 2016, we suggest Newton and Wang (*13*).

Enantioselective C–H activation through desymmetrization

Enantioselective desymmetrization C–H activation reactions primarily fall into two categories: the desymmetrization around a point (a single atom) in a substrate and the desymmetrization of a plane or axis of a substrate, exemplified by the desymmetrization of metallocene compounds (*17*, *18*) and atroposelective C–H activation (*19*), respectively. That said, because planar and axial desymmetrization do not encompass C(sp^3)–H activation, the corresponding stereomodels will not be discussed here. Enantioselective C–H point desymmetrization involves the generation of a stereocenter either distal (more than two bonds away) to the C–H bond undergoing activation, as is the case with C(sp^2)–H desymmetrization, or adjacent (two bonds away/vicinal) to a C(sp^3)–H bond undergoing activation (Fig. 2A). These examples are in contrast to methylene C–H activation, in which the newly formed stereocenter is on the same carbon of the C–H bond that was functionalized (Enantioselective methylene C–H activation, below). The earliest examples of enantioselective catalytic C–H activation relied on the use of mono-*N*-protected amino acid (MPAA) ligands to desymmetrize pyridine-containing substrates by means of Pd(II)/Pd(0) catalysis (*20*). This work exploited the well-established directing group (DG) nature of pyridine (*21*) in order to direct palladation of both C(sp^2)–H and C(sp^3)–H bonds as well as chiral carboxylates in order to induce asymmetric cyclopalladation. MPAA ligands were investigated given their easy preparation from commercially available and naturally occurring amino acids as well as their ability to coordinate Pd(II) and serve as chiral carboxylate surrogates, as originally proposed by Sokolov *et al.* (*22*), or as bidentate ancillary ligands, as studied by Navarro *et al.* (*23*) (Fig. 3A). Initial stoichiometric studies with $Pd(OAc)_2$ yielded a racemic

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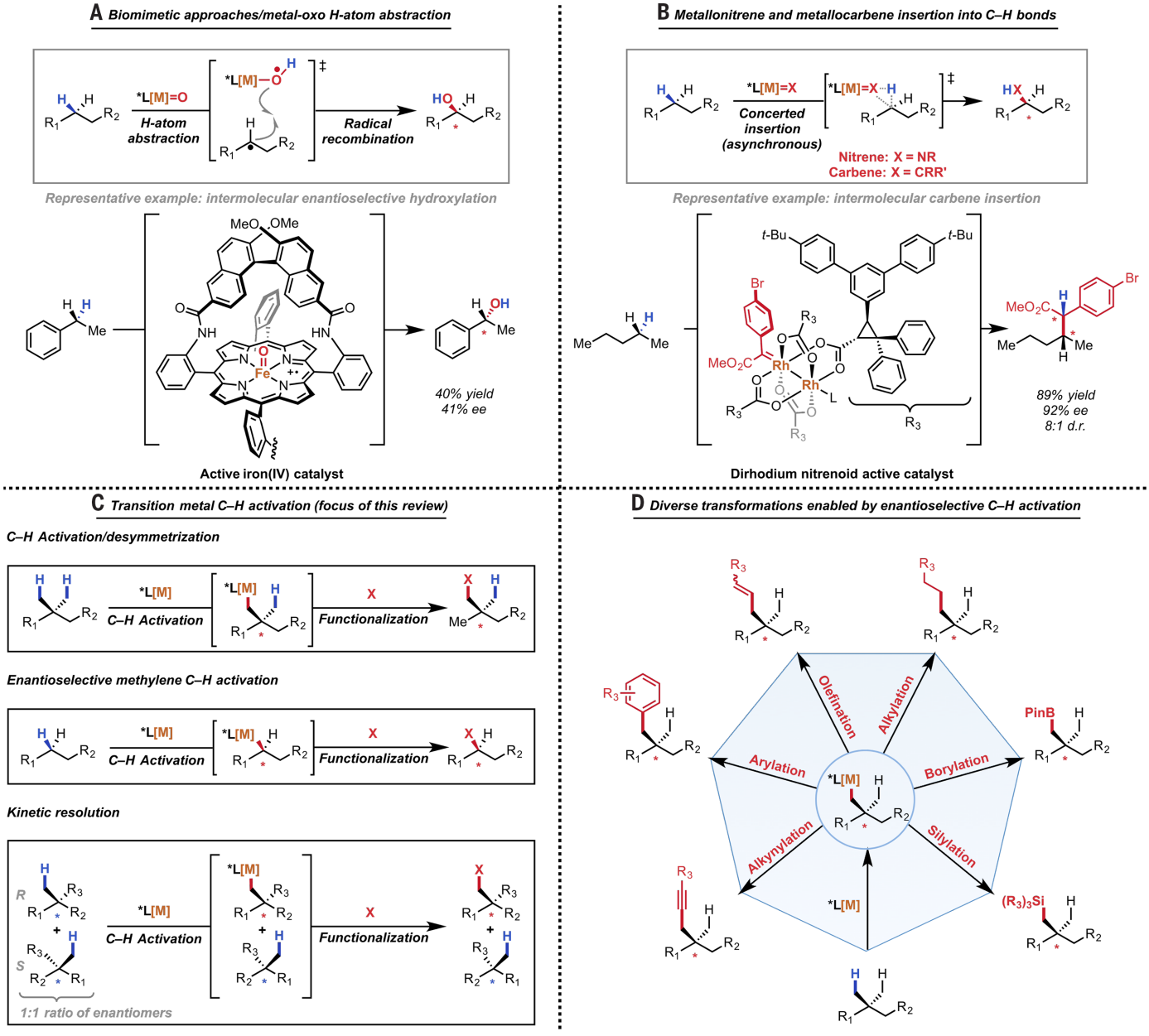

Fig. 1. Overview of mechanistic differentiation in transition metal–mediated enantioselective C–H functionalization. Me, methyl; *t*-Bu, *tert*-butyl; *L, chiral ligand; [M], transition metal; BPin, pinacolatoboron; X, aryl, alkyl, alkynyl, N, O, B, or Si.

cyclometallated dimer in 85% yield (Fig. 3A), and it was proposed that replacing the bridging acetates with amino acid ligands would lead to the formation of a chiral cyclometallated dimer; however, thorough variation in amino acid substitution elucidated a different mechanism for stereocontrol: Unprotected leucine amino acids (entry 1) suppressed catalysis and double *N*-protected amino acids (entry 2)—though affording product in high yield—gave minimal stereocontol [7% enantiomeric excess (ee)]. Mono-*N*-protection was critical for both yield and enantiocontrol (entry 3, 90% ee), and conversion of the carboxylate to the corresponding methyl ester (entry 4) afforded racemic product in 86% yield. Entries 2, 3, and 4 suggest that the operative mechanism of enantiocontrol induced by MPAAs relies on bidentate coordination by both the carboxylate and the mono-protected amine to the metal center. Although bidentate cyclopropyl MPAA (entry 5) was capable of moderate enantiocontrol and yield, the C_2-symmetric bidentate cyclopropyl MPAA (entry 6) only afforded racemic product. This was a surprising and important finding, given the dominance of C_2-symmetric ligands in transition metal catalysis (*24*) and suggested that a radically different ligand architecture would be needed to effectively induce stereocontrol in C–H activation (monodentate C_2 ligands are discussed later). Further optimization of ligand design yielded the (–)-menthol derivative of leucine (entry 7) as the most effective ligand. ^{1}H nuclear magnetic resonance, mass spectroscopy, and density functional theory computational studies elucidated the mechanism of stereoinduction in these reactions (*25*) and have led to the proposal of a stereomodel that is consistent with the reactivity and stereochemistry observed in this reaction as well as the necessary requirements (Fig. 3B). The pretransition state intermediate, in which Pd is bound both to the MPAA ligand as well as the directing group of the substrate, may proceed through two distinct pathways: In the disfavored pathway (*S*), it is proposed that a high-energy transition state is formed in which there is steric clashing between the bulky chain of the MPAA ligand and a large aryl group of the substrate; in

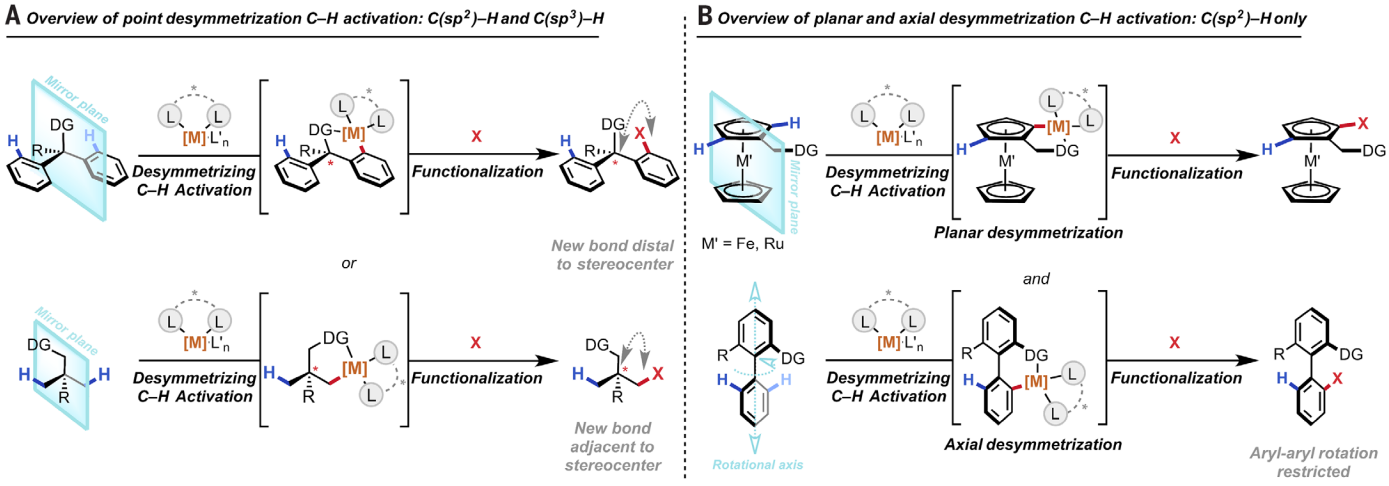

Fig. 2. Overview of desymmetrization C–H activation. DG, Directing group; [M], transition metal; L*–L, chiral ligand; M′, Fe or Ru.

the favored pathway (*R*), this steric clashing is avoided, resulting in a lower-energy transition state and thus the major product.

The original report of MPAA ligands for enantioselective C–H activation also disclosed the enantioselective C(sp^3)–H activation of 2-isopropyl pyridine (Fig. 3C) (*19*); however, both the yield and the ee reported were low (38 and 37%, respectively). One reason the alkyl substrate has such poor selectivity may be that the catalyst has to differentiate between a methyl group and a hydrogen atom, which are relatively close in size compared with the differentiation required in Fig. 3B (between an aryl group and a hydrogen atom). Additionally, pyridine-directed C–H activation persisted in the absence of chiral ligand (a racemic background reaction proceeds). This example underscores two substantial pitfalls of conventional directed C–H activation: Typically, innate functionality (carboxylic acids, amines, alcohols, and ethers) fails to interact sufficiently with a transition metal catalyst to direct metallation, so that strong directing groups must be installed before C–H activation so as to effectively direct metallation. When strong directing groups (such as pyridine or 8-amino quinoline) (Fig. 4B) are present in a substrate, the substrate may outcompete ligand binding to a transition metal center (substrate is usually an order of magnitude greater in concentration than ligand) and/or undergo a reaction in the absence of a chiral ligand, affording racemic product (Fig. 4A). Moreover, strong directing groups may lead to a thermodynamically stable cyclopalladation intermediate, hindering subsequent functionalization steps.

These so-called background reactions are detrimental to enantiocontrol; one solution to this problem has been the use of weakly coordinating monodentate directing groups (*26*), which ideally in the absence of a chiral bidentate ligand fail to afford any product. The key principles of ligand design for enantioselective C–H activation reaction are thus twofold; ligands must both be capable of creating a steric environment that affords stereocontrol and must increase reactivity of a transition metal catalyst, accelerating the rate of the reaction.

Fortunately, it was discovered early on that MPAAs are capable of dramatically accelerating a wide variety of C–H activation transformations (*27*, *28*). This discovery, compounded with the facile syntheses of diverse MPAAs, motivated the use of MPAA ligands in the presence of weakly coordinating monodentate directing groups for the desymmetrization of cyclopropyl and cyclobutyl compounds by using Pd(II)/Pd(0) catalysis (Fig. 5A) (*29*, *30*). Cyclopropyl and cyclobutyl compounds were chosen as substrates because the requisite C(sp^3)–H bonds have similar electronic properties to C(sp^2)–H bonds and because these rigid systems would allow for precise elucidation of the mechanism of stereoinduction. Because of the conformation of the substrates, only single *cis*-diastereomers were observed, and through fine-tuning of MPAA ligand side chain and *N*-protecting group, enantioselective cross-coupling of cyclopropyl compounds could be achieved in up to 70% yield with up to 94% ee (*29*). Further modification of MPAA ligand side chain to a 2,6-diarylated phenyl compound as well as conversion of the carboxylate to an *N*-hydroxamic ester (Fig. 5A) allowed for the desymmetrization of cyclobutyl compounds in up to 77% yield as well as 95% ee (Fig. 5A) (*30*). The stereomodels proposed to rationalize stereochemical induction in these systems (Fig. 5A) are based on computational studies (*31*) as well as assignment of the absolute configuration; in both cases, it is believed that the repulsive interaction between the sterically bulky *N*-protecting group and the large MPAA side chain forces the MPAA side chain to be orthogonal to the square plane of Pd(II), and that the rigid position of the MPAA side chain also forces the substrate cyclobutane orthogonal to the square plane and trans to the MPAA side chain, in order to avoid unfavorable steric clashing as shown in the disfavored intermediate (Fig. 5A). These models have also proven reliable in rationalizing enantioinduction imparted by MPAA ligands for Pd(II)/Pd(IV) C(sp^3)–H arylation of cyclopropylmethylamines (*32*), which has different steric requirements in the functionalization step [a high-energy octahedral Pd(IV)] compared with those of Pd(II)/Pd(0) catalyses.

Several complementary approaches to the aforementioned enantioselective Pd(II)/Pd(0) or Pd(II)/Pd(IV) catalyses for C(sp^3)–H desymmetrization have been developed, including enantioselective aziridine formation through Pd(II)/Pd(IV) intramolecular cyclization (*33*), Pd(0)/Pd(II) catalyses (*34*–*37*), as well as Rh(I)/Rh(III) (*38*, *39*) catalyses and, more recently, Ir(I)/Ir(III) catalysis (*40*). The only examples of these point desymmetrizations are intramolecular [the target C(sp^3)–H bond and the to-be-installed functionality are linked by a covalent tether]; because of the rigidity imparted by intramolecularity, C_2-symmetric ligands have had success in these catalytic arenas. In the Pd(0)/Pd(II) systems, oxidative addition by Pd(0) to substrate aryl–iodides, –bromides, or –triflates generates a Pd(II) intermediate that then proceeds to cleave an intramolecular C(sp^3)–H bond (Fig. 5B). In this regard, the aryl–iodide, –bromide, or –triflate serves as a pseudo-directing group, but one that is consumed during the course of the reaction; the aryl–iodide, –bromide, or –triflate both relay chiral transition metal catalysts to a target C–H bond and serve as the source of functionality installed during a reaction.

These catalytic regimes are capable of desymmetrizing *gem*-dimethyl substrates, as well as cyclic substrates with high ee (up to 93 and 95%, respectively). Preliminary studies to elucidate the role of ligand in the stereochemical outcomes of these reactions have been performed (*41*, *42*); in almost all cases, the ligands required to enable reactivity and enantioselectivity are monodentate phosphines, phosphoramidites, or *N*-heterocyclic carbenes (NHCs), which enable Pd(0) to oxidatively add to substrates, although a single example of the bidentate phosphine (*R*,*R*)-Me-DUPHOS imparting enantioselectivity

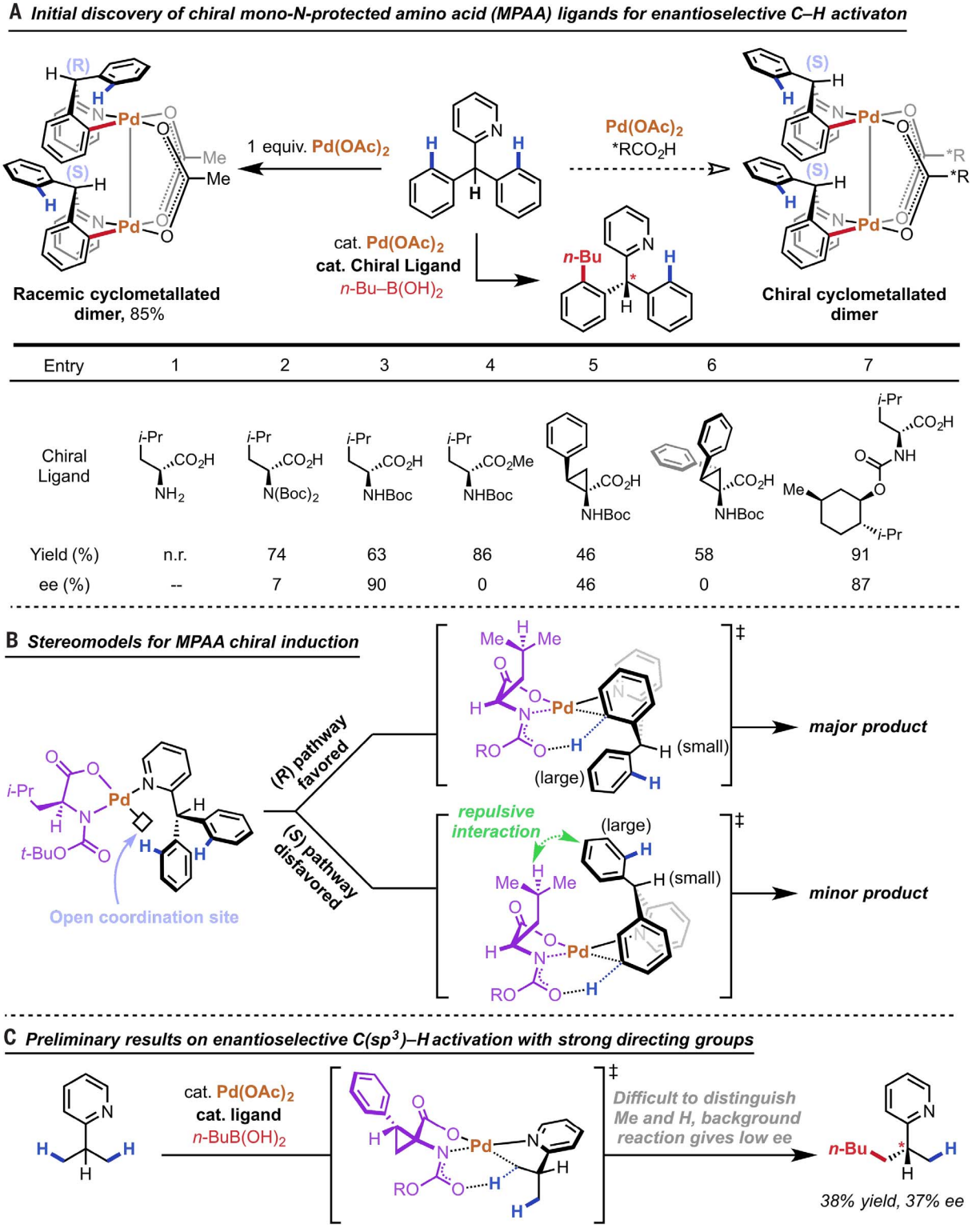

Fig. 3. Discovery of mono-*N*-protected amino acid ligands. *n*-Bu, *n*-Butyl; Boc, *tert*-butyloxycarbonyl; *i*-Pr, isopropyl; OAc, acetate.

has been reported (*35*). In the few examples of enantioselective Rh(I)/Rh(III) C(sp^3)–H activation, bidentate C_2-symmetric ligands have afforded enantioenriched products (Fig. 5C) (*38*, *39*); the most notable example by Hartwig entails the two-step sequence of in situ alcohol protection of cyclopropylmethyl alcohols to the corresponding alkoxysilane, followed by intramolecular C–H cyclization (up to 90% yield and up to 90% ee) (*38*). A similar strategy by use of Ir(I) catalysis in the presence of an *N*,*N*-bidentate chiral ligand enabled intramolecular Si–C bond formation in acyclic systems (Fig. 5C) (*40*). The stereomodels for these Rh(I)/Ir(I)–catalyzed reactions remain to be established, and the precise enantiocontrol imparted by C_2-symmetric/C_2-symmetric–derived ligands is currently under rigorous investigation.

The majority of C(sp^3)–H point desymmetrization has been performed on cyclic systems. Several examples of enantioselective desymmetrization

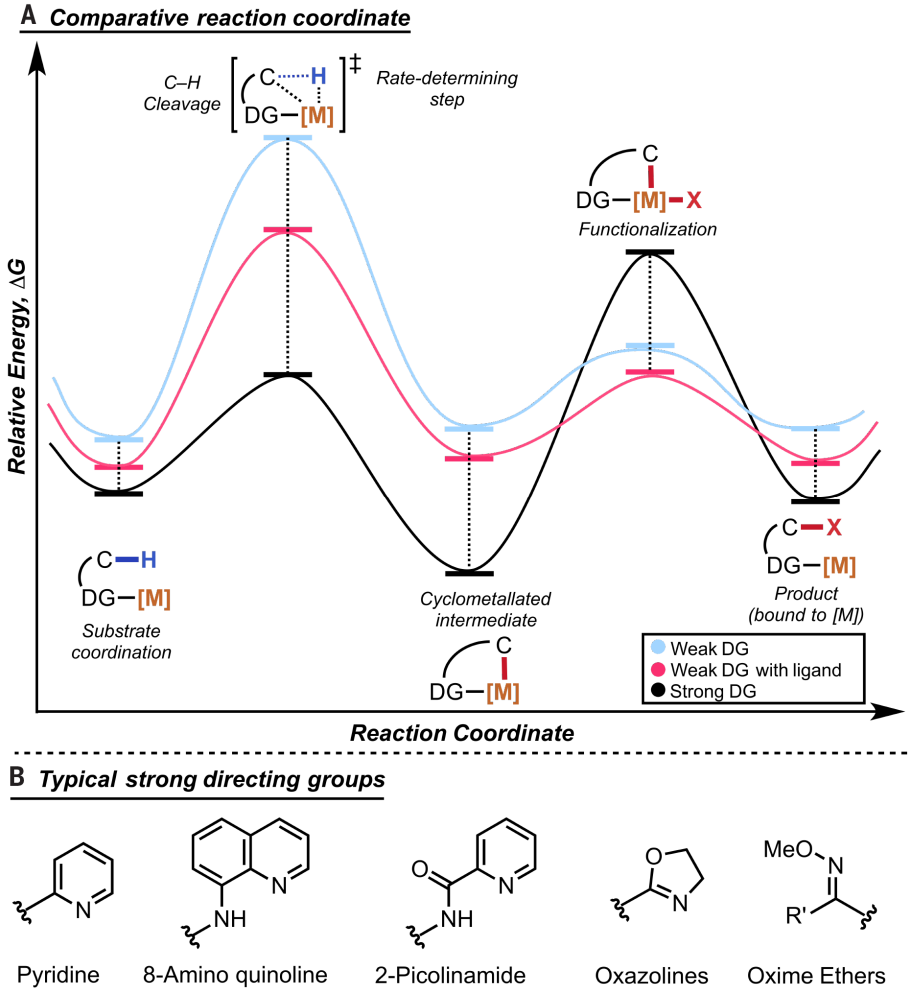

Fig. 4. Ligand-accelerated C–H activation for weak directing groups.

of acyclic systems (*gem*-dimethyl groups) by using the above methodologies were reported (*29*, *39*, *40*); however, yields and enantioselectivities are generally poor for intermolecular desymmetrization of acyclic systems (Figs. 3C and 6A). These results highlight two major challenges of C–H activation enantioinduction of acyclic systems: In cyclic systems, hydrogen atoms and target C–H bonds have restricted rotational freedom and, consequently, restricted conformations; acyclic systems possess many more accessible conformational states. Furthermore, in acyclic systems a catalyst must sterically distinguish relatively similar methyl groups and hydrogen atoms, as opposed to the target C–H bond and the conformationally locked remainder of a cyclic molecule (Fig. 6A). Insofar as the relevance of *gem*-dimethyl desymmetrization is concerned, one of the most important biological pathways used in the synthesis of myriad natural products entails the enzyme-catalyzed enantioselective hydroxylation of isobutyric acid (*43*). Our group engineered a ligand that could enable an analogous transformation—namely, the robust Pd(II)/Pd(IV)–catalyzed desymmetrization of isobutyramides. Inspired by our previous work on the diastereoselective iodination of α-dialkyl groups enabled by a chiral oxazoline auxiliary (Fig. 6B) (*44*), as well as the bidentate coordination mode of mono-*N*-protected amino acids, we synthesized bidentate *N*-acetyl–protected aminomethyl chiral oxazoline (APAO) ligands, which were capable of enantioselective arylation, alkenylation, and alkynylation of isobutyramides in moderate yields with high enantioselectivities (Fig. 6C) (*45*). Because the original report of APAO ligands, they have also been exploited for the enantioselective borylation of cyclic amide substrates enabled by Pd(II)/Pd(0) chemistry (*46*). The proposed stereomodel rationalizing the general high enantioselectivity imparted by the APAO ligands (Fig. 6D) orients the bulky phenyl substituent on the oxazoline ring and the *tert*-butyl group side chain perpendicular to the square plane of Pd(II) in such a way as to evade steric clashing; the *tert*-butyl group then forces the *N*-acetyl group into the square plane of Pd(II), engaging with the target C–H bond. In the disfavored C–H cleavage transition state, the methyl group of the substrate has intense steric clashing with the phenyl substituent of the APAO ligand; in the favored C–H cleavage transition state, this interaction is avoided by positioning of the methyl trans to the sterically encumbering phenyl group. This preliminary stereomodel has yet to be validated and is under computational investigation. The generality of transformations enabled by APAO ligands [including Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalyses] parallels that of MPAA ligands. Further, the ease by which these ligands may be diversely prepared as well as the success so far reported in the steric differentiation of a hydrogen atom and a relatively small methyl group will no doubt provide invaluable insight for the further development of desymmetrizing enantioselective C–H activation.

Enantioselective methylene C–H activation

The C–H activation of methylene (secondary) enantiotopic C–H bonds is a synthetic challenge for two main reasons: First, secondary C–H bonds are substantially less stereoelectronically prone to C–H cleavage/C–H insertion than their primary counterparts because they are both less sterically accessible (kinetic) and possess greater heterolytic bond dissociation energies (thermodynamic). There are several examples of enantioselective point-desymmetrization (presented above) on methylene C–H bonds; however, these do not entail the chiral differentiation of enantiotopic methylene C–H bonds but rather entail the desymmetrization of enantiotopic carbons because only the syn-product can be formed. Moreover, cyclopropane and cyclobutane C–H bonds possess electronic properties comparable with those of aromatic C–H bonds, therefore making these C–H bonds more reactive (*47*). In terms of stereochemical induction in methylene C–H activation of acyclic substrates, a catalyst must be capable of differentiating a relatively small hydrogen atom and a relatively large R-group (Fig. 7A); as the size of this R-group decreases, catalyst differentiation of the hydrogen and R-group becomes increasingly difficult.

Despite these challenges, substantial progress has been made in enantioselective methylene C–H activation; at present, there are three different substrate categories in directed enantioselective methylene C–H activation (Fig. 7A), including C–H bonds α-to-heteroatom, benzylic C–H bonds, and unbiased methylene C–H bonds of linear systems. The majority of methylene C–H activation reactions have been of the first two categories, and various transition metal catalysts and ligands have enabled these reactions. For example, enantioselective Ir(I)/Ir(III)–catalyzed alkylation/olefination of methylene C–H bonds adjacent to nitrogen atoms has been reported in both acyclic and cyclic substrates, affording products in high yield and high ee (Fig. 7B, equation 1) (*48*–*50*). Mechanistically, the target methylene C–H bond undergoes oxidative addition to an Ir(I) catalyst ligated with a C_2-symmetric bidentate phosphine ligand, and the requisite organometallic intermediate then undergoes insertion into olefins or alkynes, affording the alkylated and alkenylated species, respectively. In all of these cases, a precise stereomodel has

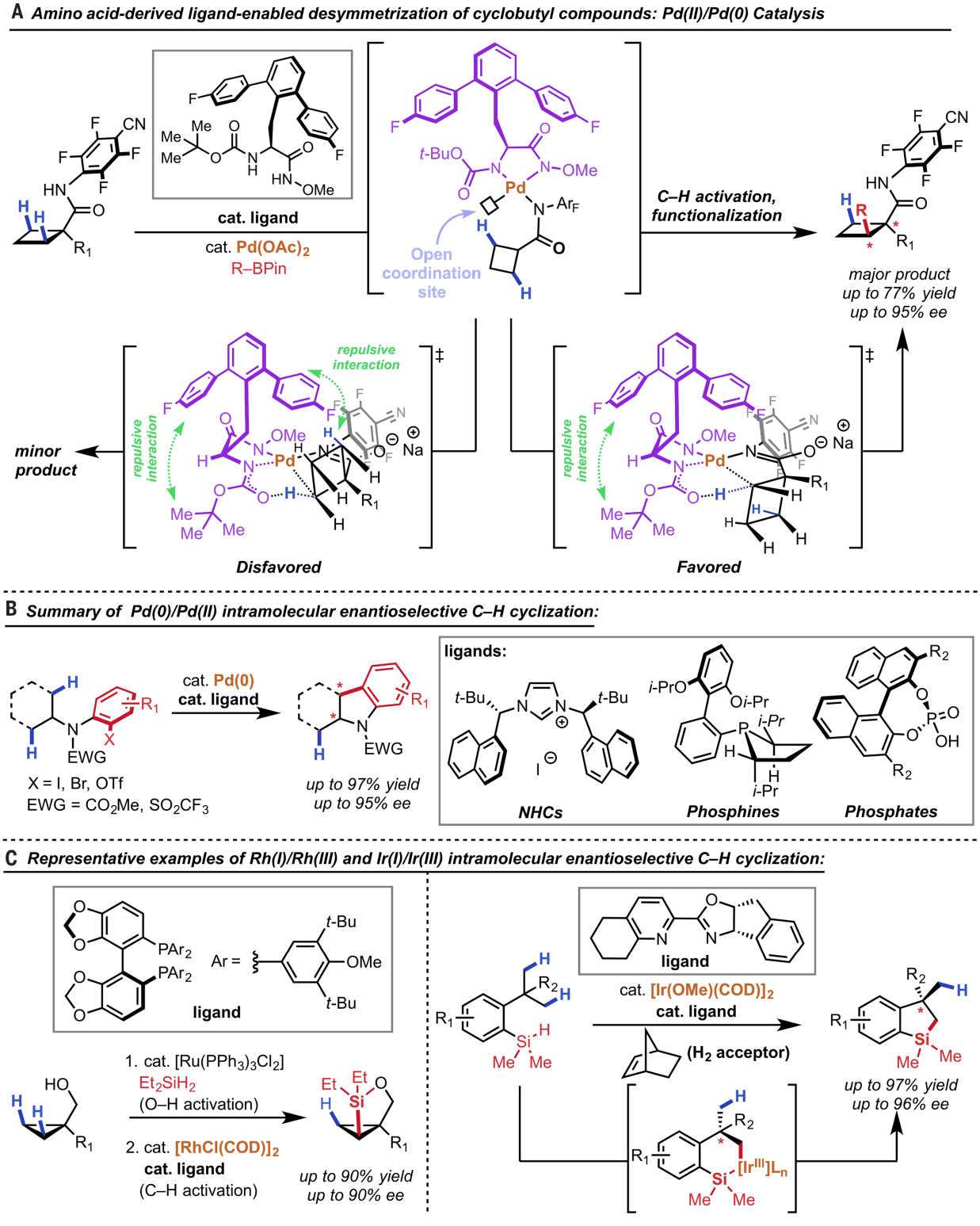

Fig. 5. Representative examples of enantioselective C(sp^3)–H point desymmetrization. *n*-Pr, *n*-propyl; EWG, electron-withdrawing group; COD, 1,5-cyclooctadiene; Ar, aryl; OTf, triflate; NHC, *N*-heterocyclic carbene.

yet to be proposed so as to rationalize stereochemical induction, and as seen above in desymmetrization C–H activation, the role of bidentate C_2-symmetric ligands in imparting stereochemical induction is not well defined, and the hemilabile nature of bidentate phosphines may need to be invoked. Monodentate C_2-symmetric phosphoramidites (*51*) and phosphoric acid (*52*) ligands have been shown to enable Pd(0)–catalyzed intramolecular cyclization and Pd(II)–catalyzed intermolecular arylation of α-methylene C–H bonds, respectively (Fig. 7B, equation 2). Although the yields and enantioselectivities of these reactions are high, the corresponding stereomodels are ambiguous and under investigation.

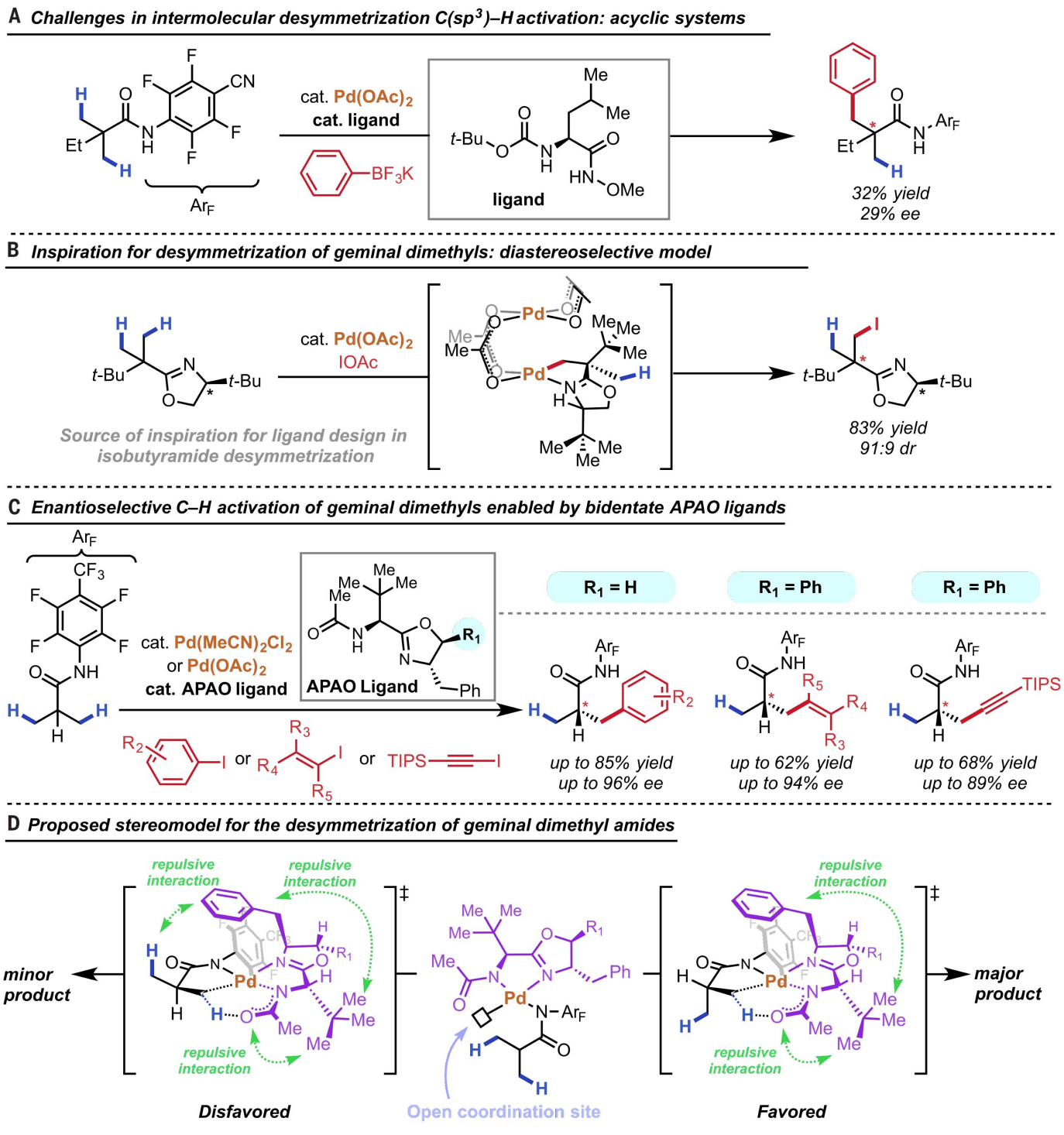

Fig. 6. Desymmetrization of acyclic systems and desymmetrization of *geminal*-dimethyl amides. IOAc, iodoacetate; Ph, phenyl; TIPS, triisopropylsilyl; APAO, acetyl-protected amino oxazoline.

For enantioselective benzylic methylene C–H activation, two distinct approaches have been reported. The first was inspired by the highly enantioselective C–H desymmetrization imparted by amino acid–derived ligands. Our group developed a transient chiral auxiliary approach for enantioselective benzylic methylene C–H activation of 2-alkyl benzaldehyde substrates in which the chiral element is covalently attached to the substrate before the chiral induction step (Fig. 7C, equation 3) (*53*). This technique relied on the in situ formation of an imine intermediate between the amine moiety of amino acids and the aldehyde component of substrates. The corresponding transient aldehyde–amino acid imine intermediates, then ligate Pd(II) and C–H activation and subsequent functionalization proceed in high yield and high enantioselectivity. The stereomodel for this reaction follows the principle of diastereoselection, and it is believed that the steric repulsion between the bulky *tert*-butyl group of the chiral amino acid and the R-group of the substrate forces the two to adopt a *trans*-conformation in the transition

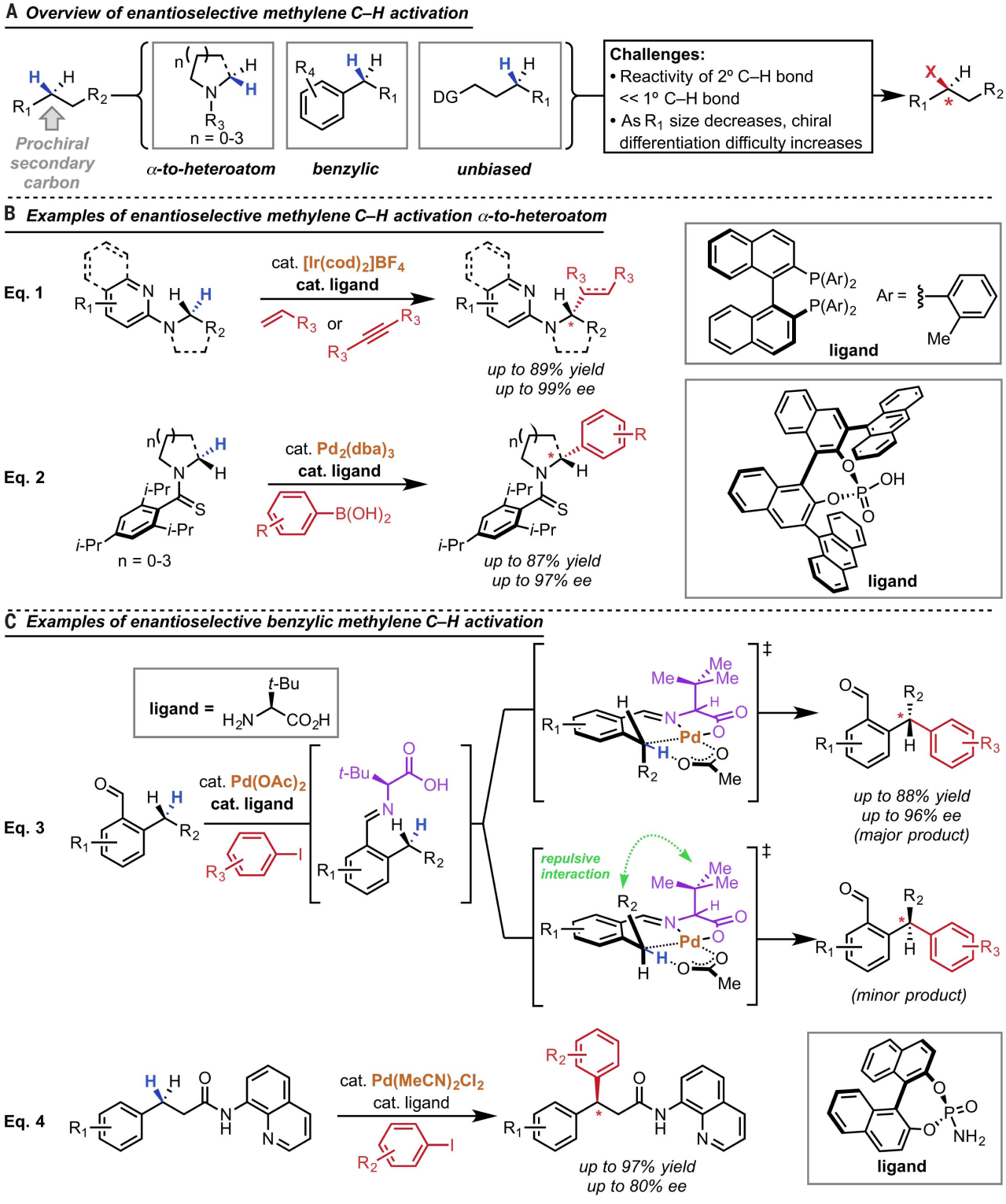

Fig. 7. Overview of methylene C–H activation. dba, dibenzylideneacetone; MeCN, acetonitrile.

state, which proceeds to form product; were the intermediate to adopt a *cis*-conformation (highly disfavored), the opposite enantiomer would be favored.

The second approach to benzylic methylene C–H activation (Fig. 7C, equation 4) has relied on strong bidentate directing groups and monodentate chiral C_2-symmetric phosphoramidites/phosphoric acids (*54*, *55*). The yields and enantioselectivites of these reactions are moderate to good, and the shortcomings of these approaches may be attributed to the strongly coordinating bidentate nature of the directing group, so that background reactions may proceed in the absence of chiral ligand, preventing high stereocontrol. The limitations of strong bidentate directing group/monodentate ligand approaches to enantioselective C–H activation are exemplified by

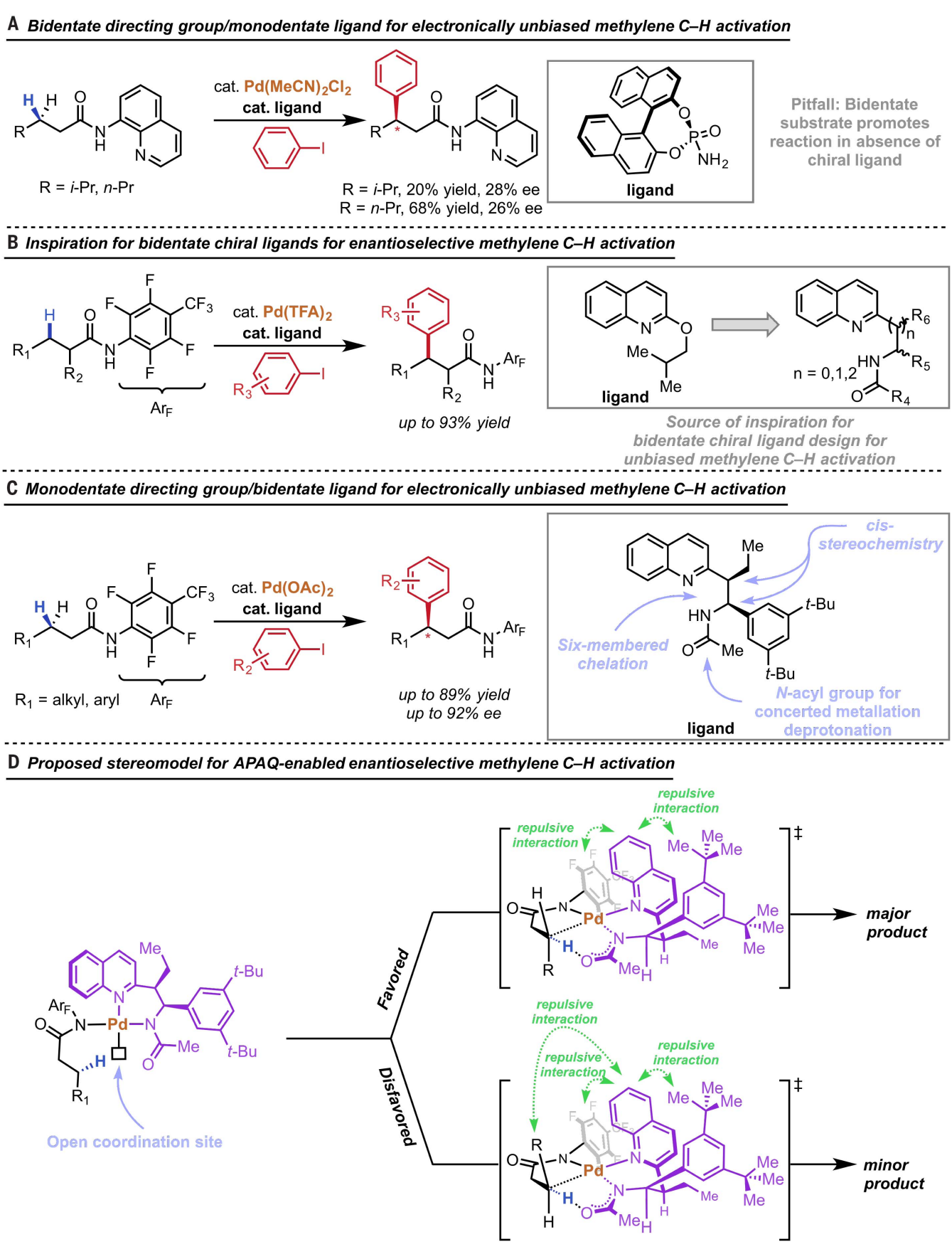

Fig. 8. Unbiased methylene C–H activation. TFA, trifluoroacetic acid; APAQ, acetyl-protected amino quinoline.

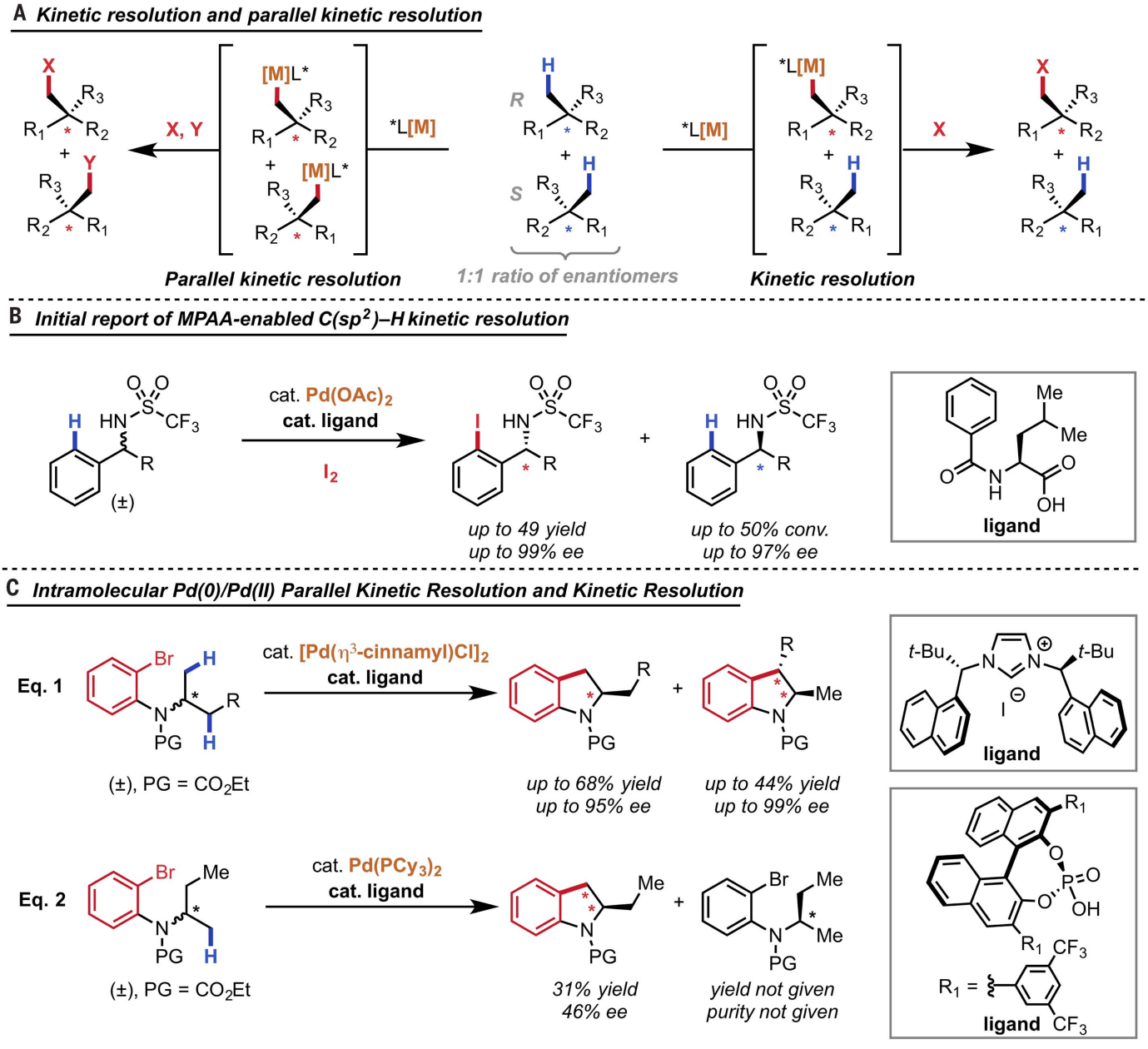

Fig. 9. Kinetic resolution C–H activation. PG, protecting group; Cy, cyclohexyl.

attempts to adopt this approach for electronically unbiased (nonbenzylic) substrates; both yields and enantioselectivities were low, suggesting that substrate-driven cyclopalladation is a major hindrance to high enantioselectivity (Fig. 8A) (*54*). Our group was motivated by our previous successes in the use of monodentate weakly coordinating directing groups/bidentate chiral ligands for enantioselective C(sp^3)–H activation. Inspired by previous reports of monodentate quinoline-enabled Pd(II)–catalyzed racemic methylene C–H activation as well as the privileged structure of bidentate MPAA ligands (Fig. 8B) (*56*), we began a campaign on the synthesis of chiral bidentate quinoline–based ligands (*57*). Extensive ligand design revealed that an acetyl-protected aminoethyl quinoline (APAQ) ligand not only enabled Pd(II)–catalyzed methylene C–H arylation to proceed with a weak directing group but also to afford the corresponding products with high enantioselectivity (Fig. 8C). Systematic ligand modification revealed that six-membered chelation was critical for reactivity (the corresponding five-membered chelating quinoline/acetyl-protected amine ligands failed to afford any product) and that cis-substitution was necessary for high reactivity as well as enantioselectivity; the corresponding diastereomeric ligands failed to afford the desired product in reasonable yields or enantioselectivities. The best ligand for this reaction (Fig. 8C) contains both a bulky 3,5-di *tert*-butyl phenyl group at C1 and an ethyl group at C2. The stereochemical induction imparted by APAQ ligands has been the subject of computational studies (*57*, *58*), and the proposed stereomodel of APAQ-enabled enantioselective methylene C–H activation is shown in Fig. 8D. In the favored transition state, the combined action of the sterically encumbering 3,5-di-*tert*-butyl phenyl of the ligand and the bulky directing group of the substrate is believed to force the quinoline portion of the APAQ ligand perpendicular to the square plane of Pd(II), which in turn forces the bulky R-group of the substrate to orient itself trans to the quinoline. In the

disfavored transition state, the perpendicular quinoline has an intense steric interaction with the cis-situated R-group of the substrate. Although substitution at the C2 position of the APAQ ligands is not a prerequisite for high reactivity (*57*), it is believed that the ethyl group shown in the competing transition states of Fig. 8D helps orient the 3,5-di-*tert*-butyl phenyl group to force the quinoline to adopt a geometry perpendicular to the square planar of Pd(II), affording high enantiocontrol. The breadth of methylene C–H bonds that may be enantioselectively functionalized by APAQ-ligated Pd(II) will no doubt provide invaluable insight for the development of new ligand classes for enantioselective methylene C–H activation on diverse substrates involving both different redox catalytic cycles as well as transformations.

Kinetic resolution

The discussions above on point desymmetrization C(sp^3)–H activation and enantioselective methylene C(sp^3)–H activation involved the recognition—and subsequent functionalization—of prochiral centers by transition metal complexes. By contrast, kinetic resolution entails the differential recognition of enantiomers of a racemic mixture by a chiral catalyst (Figs. 1C and 9A) (*59*). Although kinetic resolution has been established in C(sp^2)–H activation (Fig. 9B) (*60*–*63*), there are considerably fewer examples in C(sp^3)–H substrates. Those examples that do exist involve intramolecular Pd(0)/Pd(II) catalyses, and there are many opportunities for ligand and catalyst design to enable improved C(sp^3)–H activation routes via kinetic resolution. Parallel kinetic resolution has been reported for the regiodivergent synthesis of indolines from racemic carbamates (Fig. 9C and Eq. 1) (*64*). In this reaction, each enantiomer proceeds to form different constitutional isomers. This reaction was enabled with a monodentate C_2-symmetric NHC ligand, and it is believed that the active chiral catalyst forms diastereomeric intermediates when binding with each enantiomer of the starting material and that these diastereomeric intermediates proceed to different products. A single example of kinetic resolution of C(sp^3)–H bonds was recently reported by using intramolecular Pd(0)/Pd(II) catalysis and chiral phosphate ligands, although yield and ee were low (Fig. 9C, equation 2) (*65*). To date, intermolecular kinetic resolution through C–H activation of methylene C(sp^3)–H bonds or point desymmetrization has yet to be reported; through rigorous catalyst and ligand design, such synthetically useful processes will likely reach fruition.

Conclusion

In the past century, asymmetric catalysis has dramatically changed the way chemists construct chiral molecules and has made the synthesis of various pharmaceuticals, agrochemicals, pesticides, materials, and natural products possible (*66*, *67*). Moreover, rationalization of chiral induction in asymmetric catalysis has been one of the most powerful tools to elucidate molecular mechanisms of these reactions and has contributed substantially to our understanding of the underpinnings of catalysis (*68*). Enantioselective C–H activation is currently emerging as a new avenue for developing asymmetric catalysis, and the interest it has garnered, both academic and industrial, has grown enormously over the past decade. The examples of enantioselective C(sp^3)–H activation presented here should attest to this growth and underscore the promise this field holds to enrich synthetic disconnections, expedite chemists' endeavors to make synthetic targets, construct chiral molecules from simple feedstock chemicals, and elucidate various mechanisms of organometallic processes, providing guidance for the development of superior chiral catalysts. Although the field of enantioselective C(sp^3)–H activation by means of chiral transition metal catalysts is young, the breadth of substrates, transformations, catalyses, and ligand platforms involved in these reactions is impressive and will continue to expand. No doubt the field will continue to grow and overcome current limitations, such as scope and reactivity, until any C–H bond of any molecule can be converted into any C–X bond with high yield, regiocontrol, and enantioselectivity. Most importantly, however, is that this growth may have tremendous impact on seemingly disparate fields by enabling the synthesis of hitherto inaccessible forms of organic matter.

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RESEARCH ARTICLE

ATMOSPHERIC CHEMISTRY

Volatile chemical products emerging as largest petrochemical source of urban organic emissions

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A gap in emission inventories of urban volatile organic compound (VOC) sources, which contribute to regional ozone and aerosol burdens, has increased as transportation emissions in the United States and Europe have declined rapidly. A detailed mass balance demonstrates that the use of volatile chemical products (VCPs)—including pesticides, coatings, printing inks, adhesives, cleaning agents, and personal care products—now constitutes half of fossil fuel VOC emissions in industrialized cities. The high fraction of VCP emissions is consistent with observed urban outdoor and indoor air measurements. We show that human exposure to carbonaceous aerosols of fossil origin is transitioning away from transportation-related sources and toward VCPs. Existing U.S. regulations on VCPs emphasize mitigating ozone and air toxics, but they currently exempt many chemicals that lead to secondary organic aerosols.

Exposure to air pollution is the fifth ranking human health risk factor globally, following malnutrition, dietary risks, high blood pressure, and tobacco (*1*). Secondary organic aerosols (SOA), a major component of fine particulate matter ($PM_{2.5}$) in cities around the world (*2*), form through oxidation of volatile organic compound (VOC) precursors. Oxidation of VOCs in the presence of nitrogen oxides ($NO_x = NO + NO_2$) also contributes to tropospheric ozone (O_3), which increases risks of mortality from respiratory diseases (*3*). A recent epidemiological study suggests that adverse human health effects occur below current U.S. standards for $PM_{2.5}$ and O_3 (*4*). It is thus critical to identify and quantify the most important human-produced sources of VOC emissions to effectively mitigate air pollution and improve human health.

Automotive emissions of VOCs have decreased steadily from efforts to control tailpipe emissions in the United States (*5*) and Europe (*6*). As a result, other sources of VOC emissions are likely growing in relative importance (*7*). Transportation emissions of NO_x and VOCs have long been considered major contributors to formation of O_3 (*8*) and SOA (*9*–*11*) in urban areas, although recent studies have suggested the importance of nonvehicular sources as major contributors (*12*–*14*). Emissions from the use of chemical products have been difficult to constrain in models (*15*) or from ambient measurements (*16*). One challenge has been the lack of available atmospheric measurements of oxygenated volatile organic compounds (OVOCs) common in everyday household products (*16*). Here, we focus on volatile chemical products (VCPs), including pesticides, coatings, printing inks, adhesives, cleaning agents, and personal care products. These products contain organic solvents, which lead to substantial emissions of VOCs to the atmosphere.

We show that success in controlling air pollution has changed the proportions of sources of anthropogenic VOC emissions in the United States, decreasing the relative contribution from transportation fuels and increasing the contribution from VCPs. We consider four key pieces of evidence to support this finding: (i) energy and chemical production statistics; (ii) near-roadway measurements of transportation emissions, together with laboratory testing of chemical products; (iii) ambient air measurements away from roads; and (iv) indoor air measurements.

Mass balance of hydrocarbons in the petrochemical industry

We used energy and chemical production statistics, together with near-roadway and laboratory measurements, to construct the mass balance shown in Fig. 1 (*17*). In 2012, the amount of oil and natural gas used as fuel in the United States was ~15 times the amount used as chemical feedstocks (Fig. 1A). Chemical feedstocks are almost entirely derived from fossil hydrocarbons (*18*) and are transformed to chemicals found in everyday household products (tables S1 to S3). We focus on emissions from organic solvents, which consist mostly of intermediate-volatility organic compounds (IVOCs) and higher-volatility VOCs (fig. S1). The evaporation time scales of higher-volatility VOCs range from milliseconds to hours, and for IVOCs from hours to months (*19*). The fraction that can be emitted to the atmosphere depends strongly on product type and use (table S4). For example, a high fraction of organic compounds evaporate from architectural coatings. Most organic compounds in soaps and detergents dissolve in water and end up in sewer systems (*20*), with negligible amounts emitted from wastewater treatment plants (*21*).

Total gas-phase VOC emission factors of mobile source fuels and VCPs are based on field (e.g., near-roadway) and laboratory experiments reported in the literature (Fig. 2). A key finding is that VOC emission factors (emission amount per unit product use) resulting from the use of many chemical products are one to two orders of magnitude higher than from automobile exhaust. The relatively low VOC emission factor for on-road gasoline engines today (Fig. 2) results from (i) combustion oxidizing most hydrocarbons in fuel to carbon dioxide, and (ii) the increasing effectiveness of modern three-way catalytic converters in reducing tailpipe VOC emissions over multiple decades (*5*–*7*). Consequently, the relative importance of VCP emissions has grown. For example, mixing ratios of acetone, a marker of coating-related VCPs in this study and in the past (*16*), increased in ambient air in Los Angeles from 1990 to 2010 (*22*). This is in sharp contrast to VOCs present in gasoline exhaust, which decreased markedly during the same period (*22*), except for ethanol (*23*).

Although U.S. sales of VCPs are substantially smaller than for gasoline and diesel fuel, VOC emissions from VCPs (7.6 ± 1.5 Tg) are twice as large as from mobile sources (3.5 ± 1.1 Tg) (Fig. 1E, light green, dark green, and blue bars) because of differences in emission factors. Emissions from mobile sources and VCPs should scale with driving and population, respectively, and be concentrated in cities. Other fossil sources that occur upstream of end users (i.e., oil and natural gas extraction, oil refineries, and chemical manufacturing facilities)

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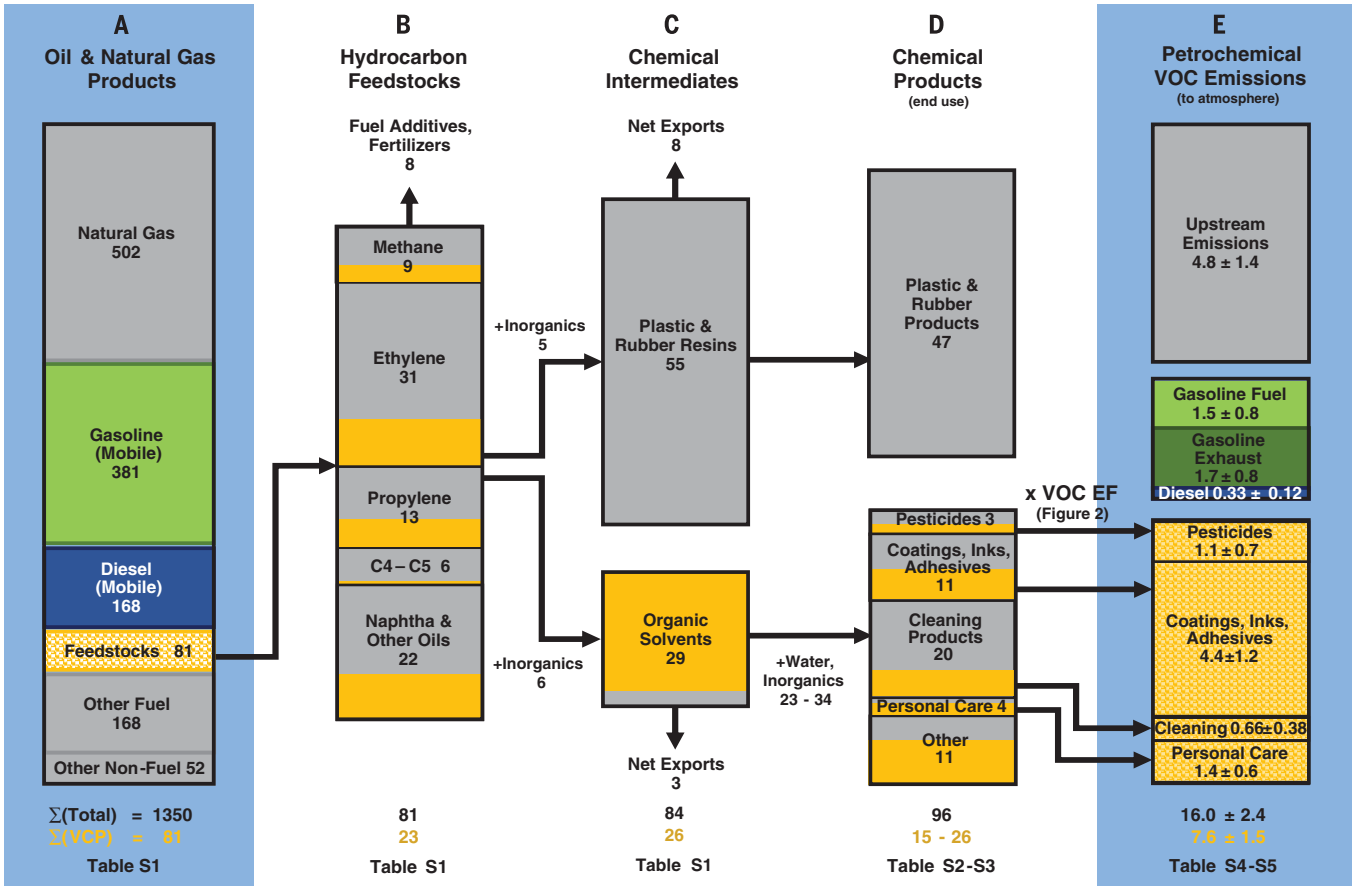

Fig. 1. Mass balance of organic compounds through the U.S. petrochemical industry in 2012, from crude oil and natural gas production to resulting VOC emissions. (**A** to **E**) Within the chemical manufacturing sector, orange sections of boxes track hydrocarbon feedstocks (A), the fraction used for production of organic solvents [(B) and (C)], organic solvents consumed domestically for chemical products (D), and resulting emissions from use of volatile chemical products (E). Emissions from plastic, rubber, and other chemical products are not considered here. All units are in Tg; boxes are sized proportionally among (B), (C), and (D) (*17*).

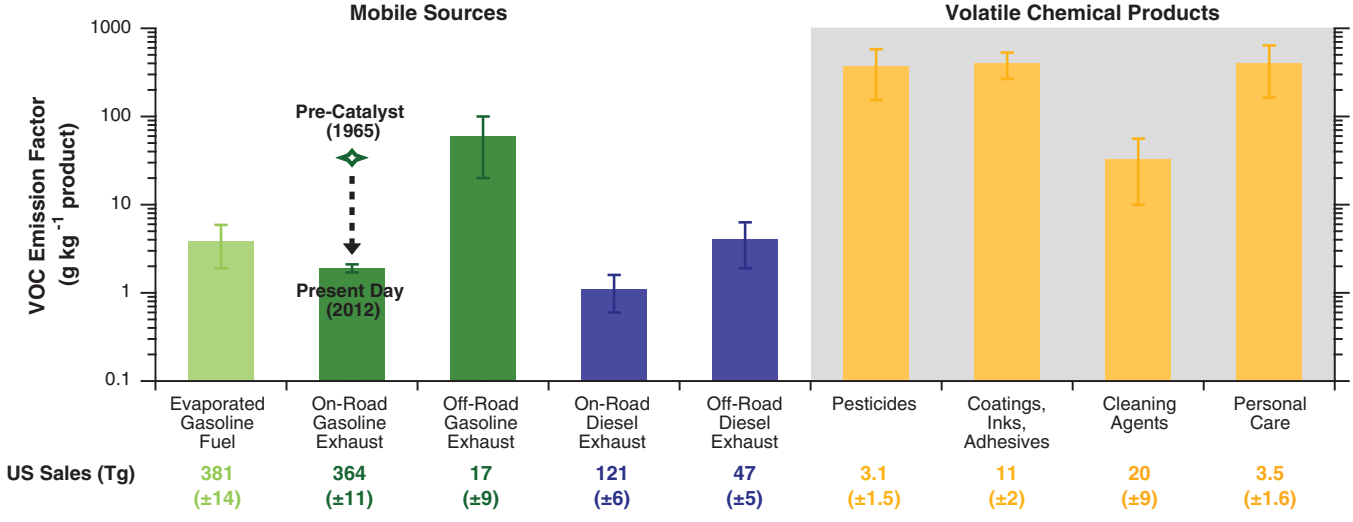

Fig. 2. Total VOC emission factors for end uses of petrochemical sources considered in this study, including from mobile sources and volatile chemical products. Shown in the bottom row are sales data of fuels for mobile sources (from Fig. 1A) and sales data of volatile chemical products (from Fig. 1D). The green symbol and dashed arrow illustrate the large reductions in tailpipe VOC emission factors as precatalyst on-road gasoline vehicles were replaced by present-day vehicle fleets. Error bars reflect the 95% confidence interval of the mean or expert judgment (*17*).

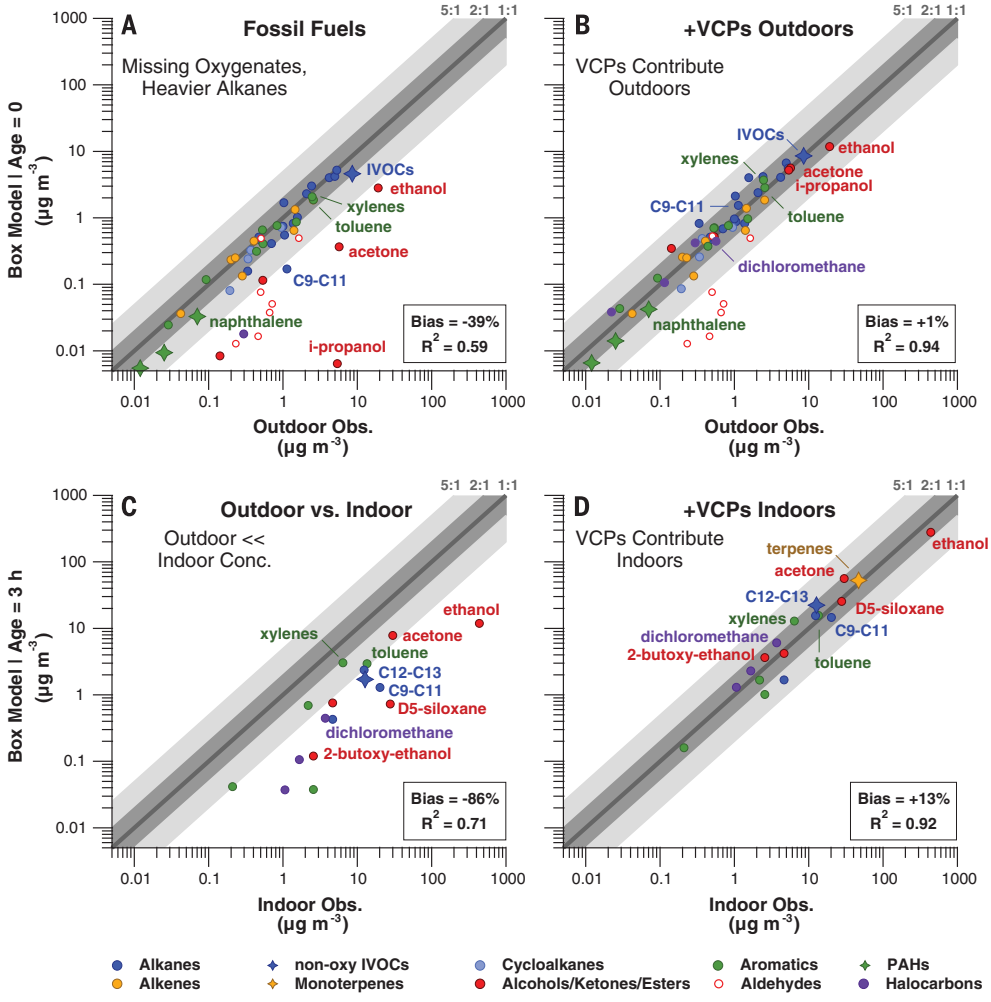

Fig. 3. Box modeling of petrochemical VOC emissions in outdoor Los Angeles air and in buildings. (**A** and **B**) Evaluations of our two-compartment box model with ambient observations of individual VOCs measured at Pasadena, CA, in 2010. In (A), we input only emissions from fossil fuels (mobile + upstream sources) into the model and evaluate against outdoor data under "no chemistry" conditions; (B) is the same as (A) but with the addition of VCP emissions. (**C** and **D**) Comparison of our box model against indoor observations of residential/commercial buildings. In (C) we allow outdoor VOCs to age by 3 hours at [OH] = 1.5×10^6 molecules cm^{-3} in the model, typical of ambient conditions at the ground site; (D) is the same as (C) but with the addition of VCP emissions indoors. For all panels, points below the 1:1 line indicate that the box model underpredicts ambient or indoor concentrations relative to observations. Shown at the lower right of each panel is the mean relative bias and R^2 of the model calculated in log space. Model statistics exclude aldehydes, which appear to be from other emission sources.

represent substantial VOC emissions (Fig. 1E, gray bar). Note that methane emissions are not shown in these estimates. Upstream processes are uncertain, and more research is needed to better constrain their emissions of VOCs (*24*–*27*).

In the United States, current inventories consistently underestimate total VOC emissions from VCPs by factors of 2 to 3 nationally (table S5) and regionally (table S6). Nationally, mobile-source emissions are overestimated by ~40%. The main effect of our analysis is to shift the relative contribution of VOC emissions from petrochemical sources, away from mobile sources and toward VCPs (fig. S2). At national and urban scales, we attribute 15 to 42% of petrochemical VOCs to mobile sources and 39 to 62% of petrochemical VOCs to VCPs. The rest is from upstream sources associated with oil and natural gas production and distribution.

European inventories also show half of VOC emissions from VCPs (*15*, *28*). This is in contrast to source apportionment studies of ambient measurements in Europe, which suggest that emissions from traffic are the largest source, with chemical product emissions substantially overestimated (*28*). However, we expect VCPs to be an important source of urban VOC emissions in both European and U.S. cities, because (i) transportation-related VOCs are similar across industrialized countries (*29*), (ii) VOCs emitted from use of VCPs (e.g., acetone) are found in ambient air on both continents (*30*, *31*), and (iii) indoor levels of VOCs from chemical products are similar (*32*, *33*). As discussed below, our emissions inventory is well constrained by a comprehensive set of ambient and indoor measurements, and is more extensive in terms of chemical speciation than measurements used in prior source apportionment studies. Previous studies typically relied on ambient VOC measurements mainly of compounds found in fossil fuels, while not including many species found in chemical products (*16*). This may explain why prior source apportionment studies have underestimated the influence of VCP emissions as sources of urban VOCs.

Chemical fingerprint of VCPs found in ambient and indoor air

If chemical products are an important source of urban air pollution, then their chemical fingerprint (fig. S3) should be consistent with ambient and indoor air quality measurements. To test our hypothesis, we used Los Angeles as a case study and modeled emissions from petrochemical sources in a two-compartment box model, where one box represents ambient air and a second box represents indoor air of buildings located within the basin (fig. S4).

California has an extensive regulatory reporting program for consumer products (*34*), including residential and commercial uses, which we used to speciate emissions. These speciation profiles provided us with target compounds to characterize in both outdoor and indoor environments. We also accounted for industrial emissions from VCPs (e.g., degreasing, adhesives, and coatings). The reporting data are in agreement with a U.S. database of chemicals (*35*) used as key constituents in chemical products (table S7). The VOC speciation profiles of VCPs (table S8) are distinguishable from those of fossil fuels (table S9), although there is some overlap in species present.

The outdoor box model predictions were evaluated against summertime ambient VOC measurements made in Pasadena during 2010 (*30*) (table S10). In ambient air, we found that fossil fuel VOCs [from mobile sources and from local oil and natural gas production and distribution (*36*)] can only account for 61% of the mass of freshly emitted VOCs measured, and 59% of their variability (Fig. 3A). The model could be underestimating emissions as a result of biases in emission inventories, chemistry, and/or transport. However, to account for the effects of

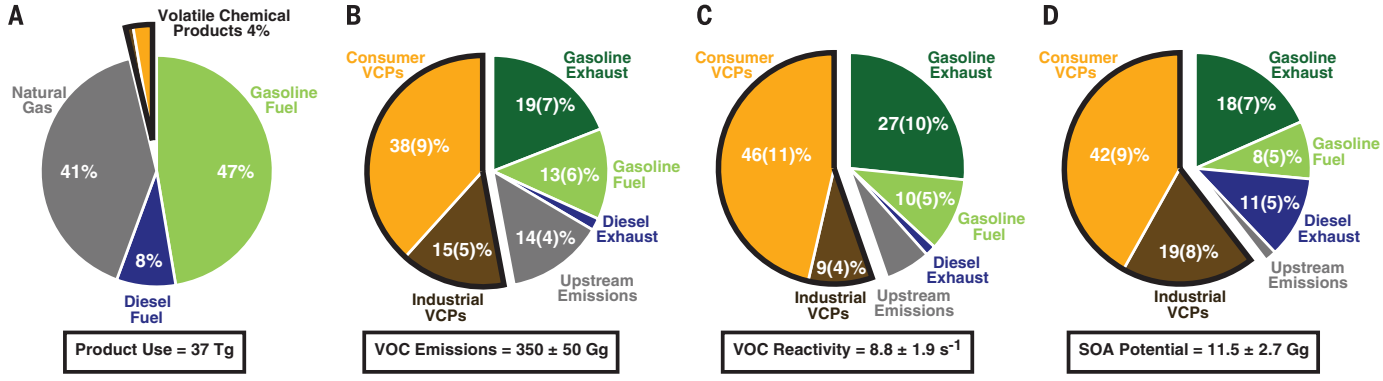

Fig. 4. Contributors to ambient air pollution in Los Angeles. (**A** to **D**) Distribution of (A) petrochemical product use, (B) VOC emissions, (C) VOC reactivity with OH, and (D) SOA formation potential across petrochemical sources only. Contributions from nonfossil sources are not shown. Uncertainties in source apportionment were determined by Monte Carlo analysis.

chemistry, we used a technique that extrapolates measured concentrations to fresh emission conditions (*30*), and the atmospheric dilution in our box model is consistent with three-dimensional chemical transport modeling of the Los Angeles basin (*37*). We therefore conclude that large underpredictions are due to missing emission sources. A surprising result is that mobile-source emissions of ethanol account for less than 20% of ambient concentrations, even though gasoline blends now routinely include at least 10% ethanol. This suggests that other sources are contributing substantially to ambient ethanol concentrations, which we attribute to VCPs.

Adding emissions from VCPs (Fig. 3B) reduces the model bias in ambient air from −39% to +1%, and the R^2 in the box model improves from 0.59 to 0.94. Emissions from key markers in VCPs are now consistent with ambient observations, including those for ethanol. Ethanol and isopropanol are in personal care products, cleaning agents, and alcoholic beverages. Acetone is a common ingredient in paint thinners (*16*) and is exempt from VOC regulations because of its low reactivity. Nonane, decane, undecane, and heavier nonoxygenated IVOCs are present in mineral spirits, a petroleum distillate common in solvent-borne coatings. Chlorinated hydrocarbons (e.g., dichloromethane) are in various VCPs, including cleaning agents and paint thinners (*38*). Except for formaldehyde, primary emissions of aldehydes do not appear to be good markers of fossil fuels (Fig. 3A) or VCPs (Fig. 3B) considered in this study, and are therefore excluded from our model bias and R^2 calculations. One possible source of aldehydes is cooking emissions (*39*).

Because a high fraction of the emissions from consumer VCPs occurs in residences and commercial buildings, their chemical fingerprint should be even stronger in indoor air. We tested our indoor model with measurements of residential (*32*) and commercial buildings (*40*) (table S11). Indoor concentrations of compounds found in VCPs were ~7 times those in ambient air (Fig. 3C). We took into account chemical removal and formation of ambient VOCs before exchange with the indoor environment (Fig. 3B versus Fig. 3C). Next, we injected consumer VCP emissions into our indoor box model, accounting for typical air exchange rates of buildings. The correspondence between our model predictions and indoor air quality measurements is high (Fig. 3D, R^2 = 0.92). The model results are now consistent with typical indoor air concentrations for key markers (e.g., acetone, C9–C11 n-alkanes, ethanol, and dichloromethane) and important classes of SOA precursors, including terpenes (e.g., limonene) (*41*), glycols and glycol ethers (e.g., 2-butoxyethanol) (*42*), volatile methyl siloxanes (e.g., D5-siloxane) (*43*), aromatics (e.g., toluene, xylenes) (*44*), and heavier alkanes (e.g., C12–C13 n-alkanes) (*45*).

Urban air quality implications

Here, we assess the importance of VCP emissions to ambient air pollution, again using Los Angeles as a test case (Fig. 4). Los Angeles currently violates the U.S. 8-hour O_3 standard, and O_3 formation remains sensitive to the reactivity of VOCs emitted and their secondary products with respect to the hydroxyl radical (OH) (*46*). We attribute half of VOC reactivity (Fig. 4C) from petrochemical sources to VCPs and the other half to mobile and upstream sources. Because the VOC reactivity of VCPs is similar to that of transportation fuels (table S12), the distribution looks similar to that of VOC emissions (Fig. 4B). The ambient and indoor air measurements shown in Fig. 3 constrain primary emissions from VCPs that contribute ~70% of the OH reactivity from VCPs. Consumer products contain reactive OVOCs and terpenes, which emit upon use, even after accounting for sewer losses (*20*).

Prior studies often report missing sinks of OH reactivity in urban atmospheres (*47*), which can degrade forecasting capabilities of regional models of O_3 (*27*). Specifically in the Los Angeles basin, a recent model (*48*) underestimated OH reactivity by a factor of ~2 relative to measurements. Here, we compare our inventory-based estimate of VOC reactivity with direct measurements made at Pasadena (*48*). In fig. S5, we show that half of measured OH reactivity (21 ± 7 s^{-1}) can be explained by fossil fuel VOC emissions (3.9 ± 1.8 s^{-1}) and other non-VCP sources of OH reactivity (7.3 ± 1.6 s^{-1}). The emissions from use of VCPs contribute an additional 4.8 ± 3.4 s^{-1}, bringing the summed OH reactivity to within ~25% of the observations (fig. S5). Although our inventory slightly underestimates OH reactivity, it is now within uncertainties of measurements. The inclusion of typically unmeasured or unreported oxygenated compounds from VCPs can help to resolve some of the missing OH reactivity observed over cities.

In the past, aerosol models substantially underestimated SOA in cities (*49*). Advances in model representations of semivolatile/intermediate-volatility organic compounds have helped to bring better closure between models and observations (*50*–*53*). However, questions remain with respect to whether the models accurately represent the mixture of emission sources and multigenerational aging schemes (*50*, *53*). In Fig. 4D, we show VCPs to be larger contributors to fossil SOA (60 ± 9%) than are mobile and upstream emission sources (40 ± 9%). This is in contrast to prior studies in the United States and Europe finding that the transportation sector is currently the leading source of SOA formation in cities (*10*, *11*). The aerosol yields used in this study (table S12) are mostly estimated from the Statistical Oxidation Model (SOM) (*54*), along with a one-dimensional volatility basis set (*51*) for OVOCs. SOM approximately accounts for multigenerational aging and can be used to estimate yields for compounds lacking laboratory measurements in the interim.

The model-observation comparison of fossil-derived SOA improves substantially when we add VCP emissions to traditionally considered transportation emissions (fig. S6). Note that nonfossil contributions to SOA, such as from wood burning, cooking, and biogenic sources, are not considered here. If we consider emissions from mobile sources and upstream emission sources alone, then the amount of fossil SOA predicted by SOM is lower than measurements at the Pasadena ground site by a factor of 3.4 ± 1.7 (*55*, *56*). The inclusion of VCP emissions is required to bring the modeled and measured SOA to agreement, within their respective uncertainties (fig. S6). Although aerosol yields are uncertain (fig. S7), the air quality measurements shown in Fig. 3 constrain primary

emissions from VCPs, which contribute ~70% of the SOA formation potential.

Straight, branched, and cyclic alkanes account for 42 ± 4% of the SOA formation potential from VCPs, followed by OVOCs (29 ± 12%), alkenes and terpenes (17 ± 5%), and aromatics (12 ± 3%). We find SOA distributed over a wide spectrum of species, and not dominated by any individual compound (table S8). The use of petroleum distillates is a major source of heavier alkanes and cycloalkanes (C_5 to C_{15}) as well as aromatics (e.g., toluene and xylenes). Fragrances are major contributors, most prominently of limonene, α-pinene, β-pinene, and 3-carene (*57*). Relatively few experiments to date have characterized aerosol formation from primary emissions of oxygenated IVOCs (*42*), especially those with six or more carbon atoms, and whose emissions are potentially important.

In the United States, O_3 regulations do not address lower-volatility compounds (vapor pressure <0.1 mm Hg at 20°C) (*21*), yet these can evaporate on atmospherically relevant time scales (*19*) and contribute to SOA (*13*). Volatile methyl siloxanes are also exempt, and their oxidation is also known to form SOA (*43*). Disclosure of ingredients used to make fragrances is not required (*57*), but terpenes are common and known aerosol precursors (*41*). Chemical manufacturers have reformulated products to reduce aromatic content, such as in cleaning agents (*33*). However, single- and multiple-ring aromatics are still present in products and in indoor air (*32*), and they contribute to SOA outdoors (*44*, *58*).

Human health implications

Although fossil fuels remain important sources of urban air pollution, exposure to ambient $PM_{2.5}$ is increasingly from chemical products as the transportation sector becomes cleaner. Additionally, because a large fraction of VCP emissions occurs in buildings, exposure to air toxics is of concern indoors (*59*). Below we summarize two implications for human health:

(1) The average fossil contribution to carbonaceous aerosols ($\sum$ = black carbon + organic aerosol) measured in ambient air at Pasadena was 3.4 ± 1.0 μg m^{-3} (*55*, *56*), which does not include nonfossil components from cooking or biogenic sources. Of the fossil total, ~40%, or ~1.3 μg m^{-3}, is attributed to directly emitted particles (*55*, *56*), mainly from diesel engines (*7*). The SOA from use of VCPs (Fig. 4D) is of similar magnitude and accounts for ~35% of the fossil total, or ~1.2 μg m^{-3}. As diesel particle filters and oxidation catalysts become more widespread, and reduce diesel contributions to $PM_{2.5}$ (*60*), the fraction of $PM_{2.5}$ from VCPs will grow because SOA precursor emissions from VCPs are not decreasing as quickly (*7*).

(2) We show that indoor emissions of aromatics and chlorinated hydrocarbons from use of VCPs are consistent with typical indoor concentrations (Fig. 3D), which are of concern because of their human toxicity (*61*). Indoor emissions of aromatic compounds have decreased by ~7% per year between 1981 and 2001 (*33*), comparable to decreases in transportation emissions of ~8% per year (*7*, *22*). Consumer uses of VCPs likely remain key sources of human exposure to air toxics relative to fossil fuels, especially because people spend most of their time indoors (*62*).

Traditional approaches to mitigating air pollution emphasize transportation and industrial sources (*63*). However, chemical products are an emerging source of urban VOCs (*22*), including SOA precursors (*7*), because VOC emissions from VCPs are not declining as fast as those from transportation. New paradigms leveraging research tools from the indoor and outdoor air quality communities could strengthen efforts to reduce human exposure to O_3, $PM_{2.5}$, and air toxics. As the composition of chemical products has evolved to remove chlorofluorocarbons to address stratospheric O_3, shifted from solvent- to water-borne formulations to mitigate tropospheric O_3, and phased out toxic components (*33*), VCPs have begun to contribute significantly to SOA formation outdoors. Given that global mortality from fine particles is significantly greater than for ambient O_3 pollution (*1*), further study is needed on whether chemical products currently designed to mitigate O_3 are also sufficient to protect humans from exposure to fine particles.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/359/6377/760/suppl/DC1
Materials and Methods
Tables S1 to S12
Figs. S1 to S7
References (*64*–*159*)

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EVOLUTIONARY ECOLOGY

Natural selection and the predictability of evolution in *Timema* stick insects

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Predicting evolution remains difficult. We studied the evolution of cryptic body coloration and pattern in a stick insect using 25 years of field data, experiments, and genomics. We found that evolution is more difficult to predict when it involves a balance between multiple selective factors and uncertainty in environmental conditions than when it involves feedback loops that cause consistent back-and-forth fluctuations. Specifically, changes in color-morph frequencies are modestly predictable through time (r^2 = 0.14) and driven by complex selective regimes and yearly fluctuations in climate. In contrast, temporal changes in pattern-morph frequencies are highly predictable due to negative frequency-dependent selection (r^2 = 0.86). For both traits, however, natural selection drives evolution around a dynamic equilibrium, providing some predictability to the process.

Evolutionary biology is often portrayed as a descriptive rather than predictive science (*1*, *2*). Nonetheless, the extent to which past evolution predicts future evolution can be quantified by investigating how well early subsets of a time series predict subsequent changes. However, predictability in the form of such temporal autocorrelation does not consider the underlying mechanisms driving evolutionary change and thus can be inherently low. Considering the mechanisms of evolution can lead to increased understanding of evolutionary change and its predictability, and we study such mechanisms here.

Evolutionary predictability is mediated by several factors. First, evolution can be unpredictable because of random processes such as genetic drift (*3*). Second, even when evolution occurs by deterministic natural selection, predictive power can be diminished if multiple, complex forms of selection act simultaneously and by uncertainties in how the ecological conditions that affect selection change through time (*1*, *2*, *4*–*7*). For example, negative frequency-dependent selection (NFDS) favoring rare alleles can enhance predictability by causing increases in allele frequency to be followed predictably by decreases (and vice versa) (*8*, *9*). However, the extent of predictability will depend on how NFDS interacts with other evolutionary processes (e.g., directional selection stemming from climate change) and on whether the ecological conditions that affect these other processes can themselves be predicted. Third, the interaction of genes within their genomic context (i.e., dominance and epistasis) and with the environment (i.e., plasticity) may affect the anticipated trajectory of evolution (*10*–*12*). For example, directional selection is expected to produce a predictable evolutionary response only if the traits affected are reasonably heritable, and even then responses can be complex and nuanced (*4*–*7*, *10*).

Studying the predictability of evolution across different time scales is particularly challenging (*1*, *2*). For example, the immediate impact of natural selection can be readily measured in short-term field studies or experiments. Such studies suggest that strong selection is not uncommon at the scale of one or a few generations (*13*, *14*), especially when new environments are colonized (*15*–*17*). However, short-term changes need not translate into long-term directional trends. Rather, evolution across geologic and phylogenetic time scales may be characterized by periods of relative stasis interspersed between occasional bursts of sustained directional change, consistent with Simpson's fossil-record–inspired model of "adaptive zones" (*18*, *19*). Indeed, strong but fluctuating selection can generate a pattern of little change when averaged over longer time periods (*14*). Field studies that measure patterns of evolution over many years or decades are somewhat intermediate between immediate and geologic time scales and thus have the potential to illuminate how short-term selection relates to longer-term patterns of evolution (*1*, *20*–*22*). Such studies are rare because they require long-term temporal monitoring that cannot be sped up with more effort. We here analyze the predictability of evolution in a long-term study of the stick insect *Timema cristinae* and bolster our inferences using manipulative experiments and genomic analyses.

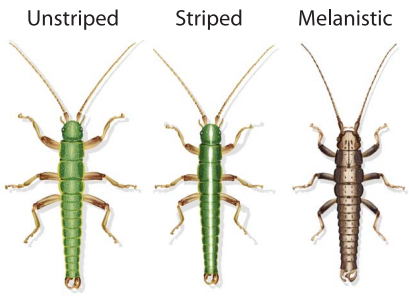

Fig. 1. Drawings of the three morphs of *T. cristinae*.

Polymorphism in stick insects

T. cristinae is a univoltine, wingless, plant-feeding stick insect that exhibits three morphs that are cryptic on different plant species or tissues (Fig. 1) (*23*–*27*). A green morph bearing a white dorsal stripe is cryptic on the leaves of *Adenostoma fasciculatum*, a green and unstriped morph is cryptic on the leaves of *Ceanothus spinosus*, and a melanistic (i.e., brownish/gray and unstriped) morph is cryptic on the stems of both hosts (but is conspicuous on leaves). Accordingly, the striped morph is common on *Adenostoma*, the unstriped morph is common on *Ceanothus*, and the melanistic morph is found at ~10% frequency on both hosts. We refer to the variation between green (striped plus unstriped) and melanistic individuals as "color polymorphism" and that between green-striped and green-unstriped individuals as "pattern polymorphism" (i.e., color and pattern are different "traits"). These polymorphisms are highly heritable, with strong genetic dominance (melanistic body coloration is recessive to green, and stripe pattern is recessive to unstriped; details below) (*23*, *24*).

Several processes maintain color and pattern polymorphism (*23*–*27*). A balance between divergent selection and gene flow between populations on *Adenostoma* versus *Ceanothus* helps maintain pattern polymorphism (*26*, *27*). However, other factors likely contribute, because even areas dominated by one host rarely fix for a single-pattern morph (*26*, *27*). The frequency of melanism does not vary markedly among populations, such that variation in color is maintained by balancing selection within populations, potentially involving heterozygote advantage and selection that varies with microhabitat (stems versus leaves) (*23*, *24*). Spatial and host-related aspects of evolution for these morphs are thus reasonably well understood. In contrast, whether and how morph frequencies change through time, and whether they do so predictably, is unknown.

We studied temporal dynamics in *T. cristinae* using 25 years of field data from the mountains around Santa Barbara, California (545 locality-by-host-by-year estimates of morph frequency on the basis of 34,383 individuals collected from 1990 to 2017; mean *n* per locality-by-host-by-year = 63; SD = 141) (data S1). We focus our autocorrelation analyses of predictability (*28*) on the locality HV (Hidden Valley), where we collected data over a continuous 18-year period, with no years of

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missing data (total n = 3470; mean yearly n = 193; SD = 268).

Results

Temporal change in allele frequencies

We tested the hypothesis that temporal change in allele frequencies at the genetic region underlying the morphs is due, in part, to natural selection. Although past studies support selection on the morphs (*23*–*27*), these results do not mean that all temporal changes are due to selection, because selection and drift are not mutually exclusive (*29*, *30*). Genomic data from different time points provide a means to test for selection, because strongly selected regions are expected to show greater change through time than the more neutral genomic background (*29*, *31*). Genomic data are further required in our specific instance because genetic dominance and heterozygote excess complicate inference of allele frequency change using phenotypic data alone (*23*, *24*).

We used de novo genome sequencing of a melanistic and green morph, with Dovetail hi-rise scaffolding of Illumina reads (N50 = ~16 and 8 megabases, respectively) (*32*), linkage mapping (*25*), and genome-wide association (GWA) mapping to explicitly delimit a single, contiguous genomic region (~10.5 megabases in size) associated with color and pattern variation (Fig. 2 and figs. S1 and S2). Consistent with a similar study with a more fragmented reference genome, this region exhibits three core haplotypes (i.e., alleles), one corresponding to each morph, designated *s*, *u*, and *m* for green-striped, green-unstriped, and melanistic, respectively (i.e., in terms of diploid genotypes and phenotypes: *uu*, *us*, and *um* are green-unstriped; *ss* and *sm* are green-striped; *mm* is melanistic) (*23*). We refer to this region as the *Mel-Stripe* locus hereafter.

We quantified allele frequency changes at *Mel-Stripe* over time within three published data sets: (i) genotyping-by-sequencing (GBS) data collected in a natural population on *Adenostoma* [FHA (locality Far Hill on *Adenostoma*] in 2011 and 2013 (*30*, *33*); (ii) resequenced whole genomes from individuals collected in FHA and used in an 8-day (i.e., within-generation) release and recapture field experiment (*30*); and (iii) GBS data in a between-year (i.e., between-generation) field transplant experiment (*25*).

In each case, we contrasted change through time at *Mel-Stripe* to that of the remainder of the genome (to all genomic scaffolds, i.e., loci, that harbored as many single-nucleotide polymorphisms as *Mel-Stripe*, which was 40, 16, and 39 loci, respectively, for the three data sets noted above). Due to our explicit interest in *Mel-Stripe*, we did not attempt to delimit other loci under selection. If such loci exist, they could upwardly bias our estimates of genome-wide change relative to a case of neutrality, making our results for *Mel-Stripe* conservative.

We found that *Mel-Stripe* showed the greatest temporal allele frequency change of all genomic regions, in all three data sets (FHA: change = 0.0273, P = 0.024; within-generation experiment: change = 0.0340, P = 0.059; between-generation experiment: change = 0.0988, P = 0.025; exact probabilities; Fisher's combined probability test across data sets: X^2 = 20.50, df = 6, P = 0.0023) (Fig. 2). Dispersal alone is unlikely to drive these observed patterns because FHA was sampled over an area that is larger (>10,000 m^2) than the dispersal capacity of *T. cristinae* (i.e., one to a few dozen meters per generation) (*30*, *33*, *34*). Furthermore, field surveys detected essentially no dispersal off experimental bushes in the recapture study (*30*), and selection on pattern has been previously observed in the presence, but not the absence, of predation (with dispersal possible in both treatments) (*35*, *36*). Thus, selection likely contributed to the genetic change we observed at the *Mel-Stripe* locus. We thus next turned to whether such selection was associated with weakly or strongly predictable patterns of evolution.

Predictability of the evolution of body color and complex selection regimes

We quantified the predictability of evolution using autoregressive moving average (ARMA) models (*28*). This analysis revealed that color morphs

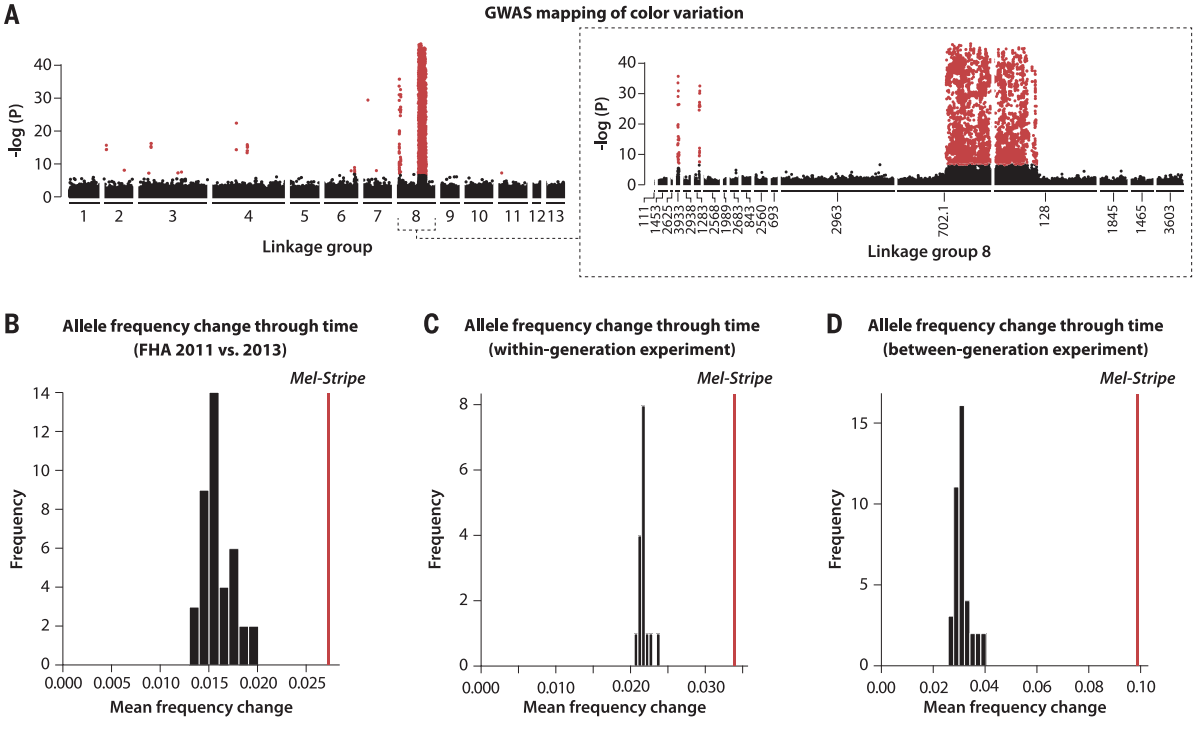

Fig. 2. Genomic change through time at the *Mel-Stripe* locus. (**A**) Manhattan plots showing results for genome-wide association mapping of color. The *y* axes show *P* values, with red denoting genome-wide significance. The left-hand plot shows results genome-wide (LG, linkage group). The right-hand plot is zoomed in on LG8, which shows the bulk of association, and here numbers below the *x* axis delimit different genomic scaffolds. The *Mel-Stripe* locus is evident by the block of strong association spanning scaffolds 702.1 and 128. (**B**) Allele frequency change through time in the natural population FHA (2011 versus 2013). (**C**) Allele-frequency change through time in the within-generation experiment. (**D**) Allele frequency change through time in the between-generation experiment. In (B) to (D), the vertical red line shows change at the *Mel-Stripe* locus and the histogram shows the distribution of change across other similar-sized scaffolds in the genome (i.e., the genomic background).

at HV exhibited subtle and only moderately predictable changes through time (median predictive r^2 = 0.14, ARMA) (Fig. 3 and table S1). This was associated with support for multiple, complex, and counteracting sources of selection (Fig. 4). Across the 25-year study period, the frequency of melanistic morphs increased in years where spring temperatures were warmer [overall effect of temperature = 0.187, 95% equal-tail probability intervals = 0.063 to 0.309; correlation between observed and predicted frequency from cross-validation = 0.16, 95% confidence interval (CI) = 0.04 to 0.28, P = 0.0102, Bayesian hierarchical linear model] (Fig. 4 and table S2). However, laboratory experiments indicate that melanistic individuals have weaker heat tolerance, relative to green individuals (B = 3.57, 95% CIs = 1.34 to 9.51, P = 0.0111, Cox proportional hazards regression model using exact likelihood). These results imply that selection for crypsis on dry, brownish plants in warmer years may favor dark colors but that thermoregulatory selection acts in an opposing direction. However, further work is required to test this hypothesis directly and to establish how well the laboratory experiments match field conditions. Notably, melanistic individuals exhibit fewer fungal infections and greater mating success than other morphs, further suggesting that selection is multifaceted (*24*).

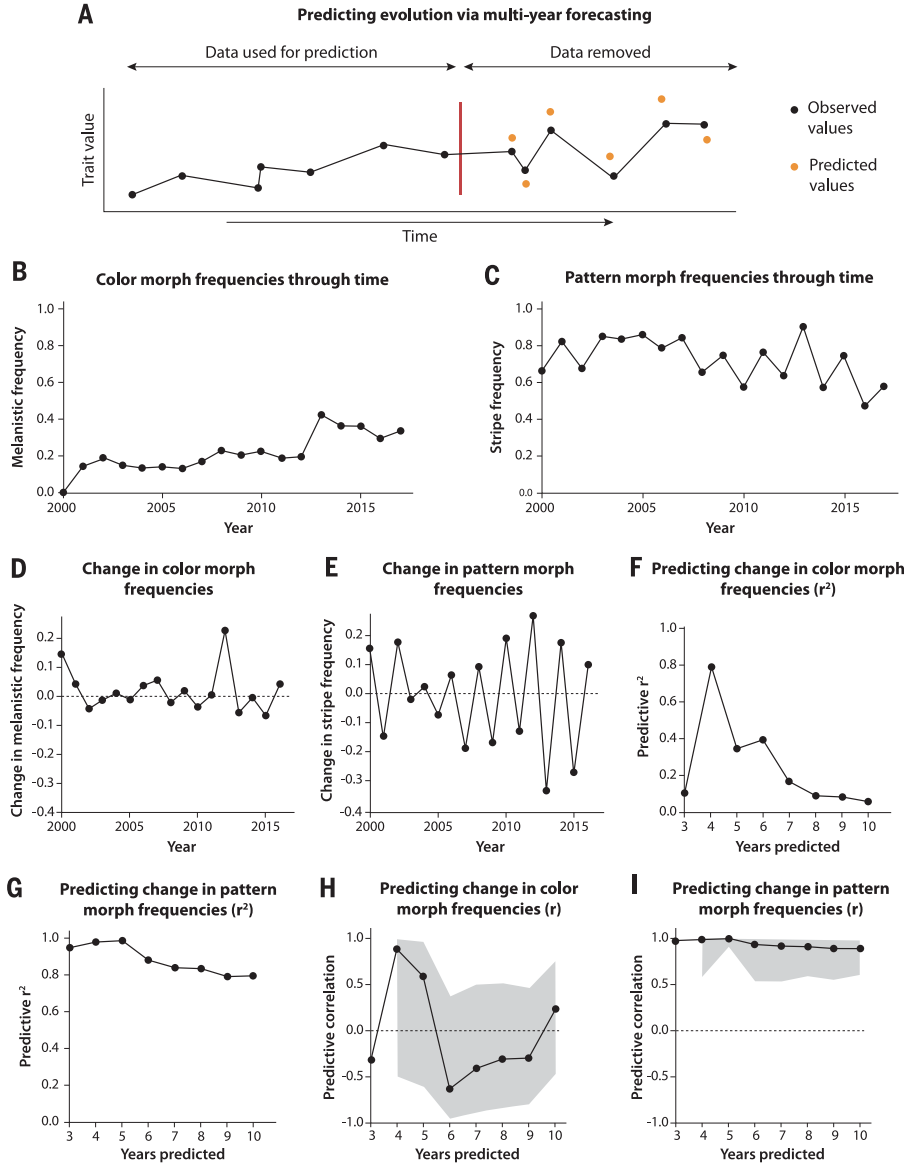

Fig. 3. Predicting evolution in *Timema cristinae* stick insects. (**A**) Schematic of analytical approach for predicting evolution using temporal autocorrelation. Black points represent observed values in a time series. Some number of these observed points are removed (in this case, the six right-hand–most points), and the missing values for them are predicted using the remainder of observed points. Predictive power is the strength of association between observed and predicted values. (**B**) Color-morph frequencies through time. (**C**) Pattern-morph frequencies through time. (**D**) Change in color-morph frequencies. (**E**) Change in pattern-morph frequencies. (**F**) Predicting change in color-morph frequencies (r^2). (**G**) Predicting change in pattern-morph frequencies (r^2). (**H**) Predicting change in color-morph frequencies (r). The difference from (F) is that r values are not squared such that their sign is evident. Shaded areas are 95% CIs. (**I**) Predicting change in pattern-morph frequencies (r). The difference from (G) is that r values are not squared such that their sign is evident. Shaded areas are 95% CIs.

Given that selection appears complex, we used our genomic data to estimate selection coefficients explicitly (for all six diploid genotypes underlying the morphs, with three alleles: *s*, *m*, and *u*). This analysis revealed that viability selection on *Adenostoma* during late life-history stages (i.e., in the within-generation experiment) favored the *s*/*s* homozygote (posterior probability that fitness of *s*/*s* > the following genotypes: *m*/*u* = 0.93, *u*/*u* = 0.81, *m*/*m* = 0.82, *m*/*s* = 0.84, *u*/*s* = 0.91). In contrast, the most-fit genotype between years at the FHA locality (also on *Adenostoma*) was the *s*/*m* heterozygote (posterior probability that fitness of *s*/*m* > the following genotypes: *m*/*u* = 0.90, *s*/*s* = 0.97, *u*/*u* = 0.81, *m*/*m* = 0.92, *u*/*s* = 0.94). Both *s*/*s* and *s*/*m* are green-striped in terms of phenotype and cryptic on *Adenostoma*. Thus, a fluctuating balance between many factors, potentially including heterozygote advantage (*23*), may explain why evolution involving the deterministic process of selection was not more highly predictable.

Predictability of the evolution of pattern

Our findings for color raise the question of whether evolution is ever highly predictable? We address this issue by reanalyzing the data from HV considering striped versus unstriped individuals (i.e., pattern, rather than color, polymorphism). This demonstrates that striped morph frequencies at HV exhibited consistent increases followed by decreases (i.e., up and down fluctuations) across 18 consecutive years (binomial sampling probability < 0.0001) (Fig. 3). Thus, the evolution of pattern was highly predictable (median predictive r^2 = 0.86, ARMA). In fact, predictive power at the scale of 3 to 5 years was near perfect (>0.95), and remained high even after a decade (>0.80). The observed pattern of predictable up and down fluctuations could reflect a case where predators have specific search images for common prey, resulting in NFDS selection favoring rare prey phenotypes.

Morph frequency and selection

To test the NFDS hypothesis, we transplanted green-striped and green-unstriped *T. cristinae* to *Adenostoma* in either 1:4 or 4:1 ratios (n = 1000 individuals, 10 replicates per treatment) (Fig. 5). The NFDS hypothesis predicts that the striped morph, cryptic on *Adenostoma*, would exhibit a stronger survival advantage when rare. Supporting this prediction, the striped morph experienced strong selection when initially rare (selection coefficient, s = 0.70) and increased in frequency in all 10 experimental replicates (posterior probability that change > 0 was >0.999). In contrast, the striped morph showed idiosyncratic changes

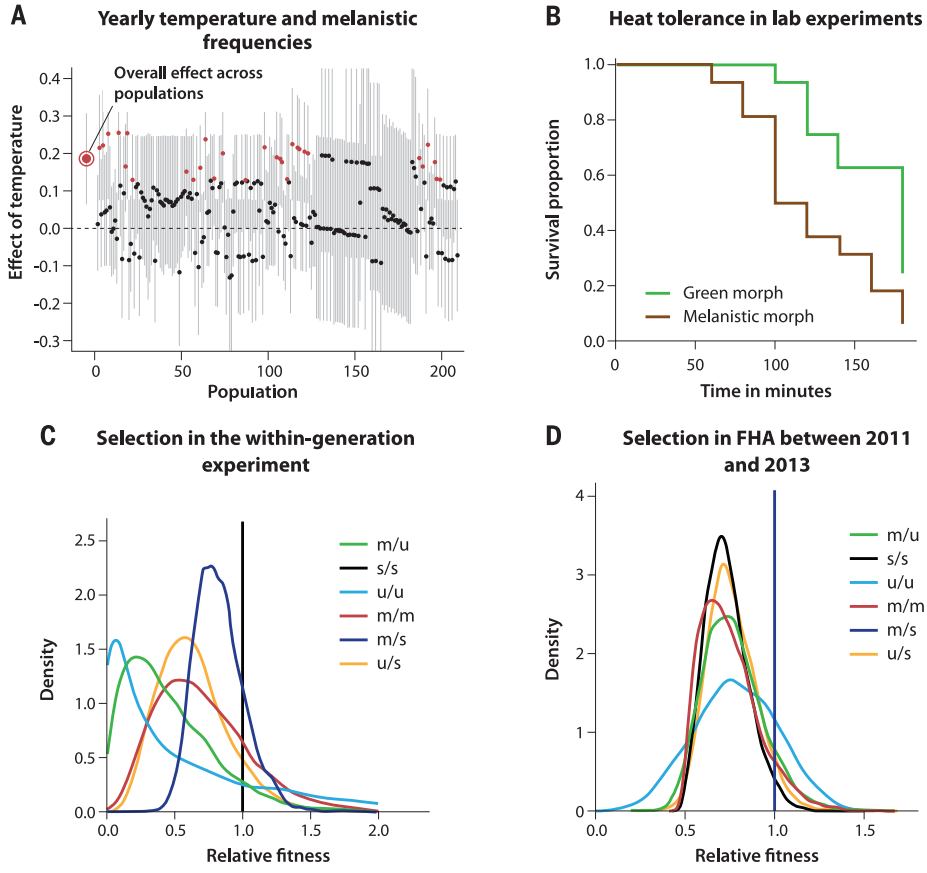

Fig. 4. Complex patterns of natural selection. (**A**) Associations between the frequency of melanistic morphs and yearly spring temperature. Positive effects indicate increases in melanistic frequency with increased temperature. Significant effects are shown in red. The left-most data point represents the average effect across populations, and the remaining points are for individual populations. Among-population variation is high, but all significant effects are positive. (**B**) Morph-specific survival time in thermoregulatory (i.e., heat tolerance) laboratory experiments. (**C**) Genotype-specific fitness in the within-generation experiment on the host *Adenostoma* (*s/s* is most fit). Shown are the posterior probabilities from estimates of genotype-specific fitness. (**D**) Genotype-specific fitness in the natural population FHA on *Adenostoma* (*s/m* is most fit). Shown are the posterior probabilities from estimates of genotype-specific fitness.

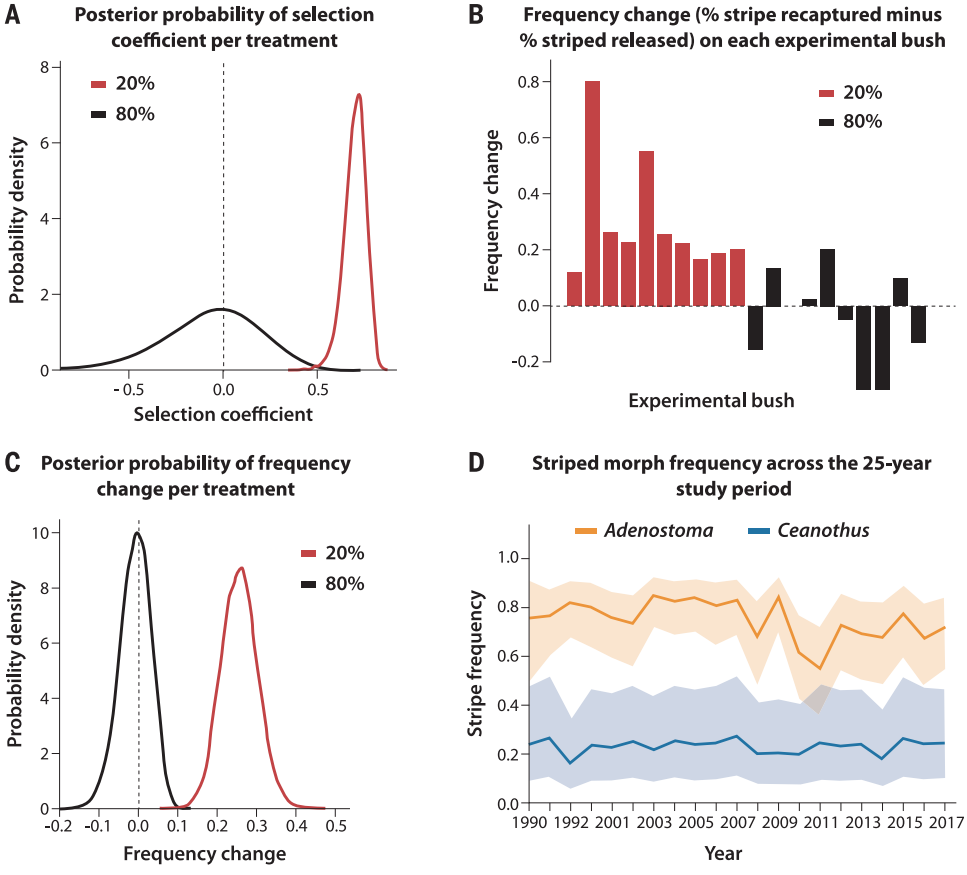

Fig. 5. Evidence for NFDS on pattern and resulting stability in morph frequency differences between hosts. (**A**) Posterior probability estimates of the selection coefficient in each treatment. Positive values on the *x* axis represent selection favoring striped individuals. (**B**) Changes in the frequency of striped morphs in releases at 20% of the population and 80% of the population during the course of the experiment. (**C**) Posterior probability distributions of change in the frequency of striped morph per treatment. (**D**) Yearly differences between host plant species in natural populations in the frequency of striped morphs (lines denote posterior medians and shaded regions, given the 95% equal-tail probability intervals).

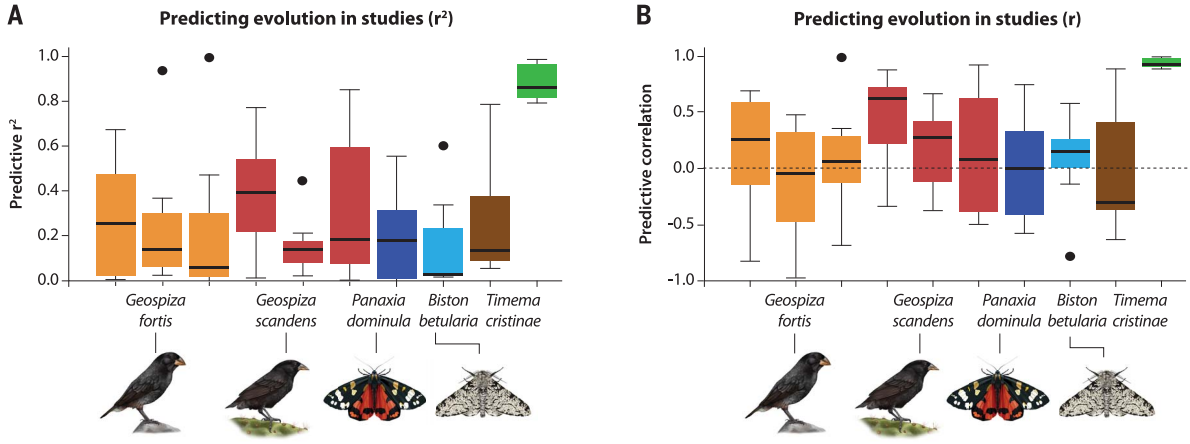

Fig. 6. Predicting evolution in different systems. (**A**) Predicting evolution for evolutionary time series in (left to right) *Geospiza fortis* body size, *Geospiza fortis* beak morphology (principal components 1 and 2), *G. scandens* body size, *G. scandens* beak morphology (principal components 1 and 2), *Panaxia dominula* and *Biston betularia* morph frequencies, and *T. cristinae* color and pattern-morph frequencies. Box plots show the distribution of r^2 between true and predicted evolutionary change across 3- to 10-year model-based forecasts. (**B**) Predicting evolution in studies (r). The difference from (A) is that r values are not squared such that their sign is evident.

when initially common (s = –0.04, posterior probability that change > 0 = 0.43). Although our results differ from NFDS, where the sign of selection reverses very strongly, they are consistent with the strength of selection being dependent on frequency (i.e., directional selection that weakens with increasing allele frequency is akin to frequency-dependent selection). It is possible that selection against the striped morph would be more strongly negative if ratios were manipulated more extremely (e.g., to 10:1).

Conclusions

We observed complex and fluctuating sources of selection. Together with gene flow (*26*), these selection pressures likely contribute to relative stability in the difference between hosts in morph frequency over the 25-year study period (Fig. 5). Complex and fluctuating selection may thus help maintain polymorphism but prevent divergence of sufficient magnitude to strongly drive speciation (*24*). NFDS in particular may cause evolutionary systems to exhibit resilience, as reported in other complex ecological, social, and physical systems (*37*–*39*). Such resilience increases predictability of short-term evolution, because a system returns to its former state following perturbation. However, it can make long-term predictions difficult because substantial evolution only happens when the system reaches a tipping point that pushes it more permanently to a very different state.

Finally, our results suggest that the predictability of evolution can depend on the nature of selection and our understanding of it. Thus, we predicted evolution more accurately for pattern, where selection appears to be strongly associated with frequency, than for color, where a myriad of factors, some poorly understood, affect fitness. As further illustration of this point, predictability in the form of temporal autocorrelation is modest to weak in other well-known studies of contemporary evolution: beak and body size changes in Darwin's finches and morph frequency changes in the scarlet tiger and peppered moth (*21*, *40*, *41*) (median predictive power per study system, r^2, in 3- to 10-year forecasting analyses 0.03 to 0.18, ARMA) (Fig. 6, figs. S3 to S6, and table S1). Adding climatic (i.e., rainfall) data to the *Geospiza* finch case, where climate is known to affect seed distributions, improves predictive power in *Geospiza fortis* (e.g., mean r^2 increase relative to a model without rainfall = 0.08, ARMA) (table S3). Nonetheless, predictive power even considering rainfall is modest and increased only in one of the two finch species examined (table S3). It is possible that predictability remains limited because seed size itself was not modeled, because the relationship between evolution and rainfall is complex such that only extreme droughts have strong effects, and because some extreme climatic events precede the 10-year period that our forecasting is based upon.

In conclusion, our constrained understanding of selection and environmental variation (i.e., limits on data and analysis), rather than inherent randomness, can thus limit ability to predict evolution. In turn, these limitations may affect our understanding of ecological processes, because to the extent that evolution can be predicted, perhaps so can its ecological consequences for population dynamics, community structure, and ecosystem functioning (*42*–*44*).

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/359/6377/765/suppl/DC1
Materials and Methods
Figs. S1 to S6
Tables S1 to S3
Data S1
References (*45*–*63*)

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A major chromatin regulator determines resistance of tumor cells to T cell–mediated killing

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Many human cancers are resistant to immunotherapy for reasons that are poorly understood. We used a genome-scale CRISPR/Cas9 screen to identify mechanisms of tumor cell resistance to killing by cytotoxic T cells, the central effectors of anti-tumor immunity. Inactivation of >100 genes sensitized mouse B16F10 melanoma cells to killing by T cells, including *Pbrm1*, *Arid2* and *Brd7*, which encode components of the PBAF form of the SWI/SNF chromatin remodeling complex. Loss of PBAF function increased tumor cell sensitivity to interferon-γ, resulting in enhanced secretion of chemokines that recruit effector T cells. Treatment-resistant tumors became responsive to immunotherapy when *Pbrm1* was inactivated. In many human cancers, expression of *PBRM1* and *ARID2* inversely correlated with expression of T cell cytotoxicity genes, and *Pbrm1*-deficient murine melanomas were more strongly infiltrated by cytotoxic T cells.

Cancer immunotherapies that target inhibitory receptors on T cells including the PD-1 receptor, can induce durable responses, but the majority of patients do not respond (*1*). The mechanisms that determine resistance to these immunotherapies remain poorly understood. Cytotoxic T cells are key effectors of tumor immunity based on their ability to detect and kill transformed cells following T cell receptor (TCR) recognition of peptide antigens bound to MHC class I proteins (*2*). T cell–mediated cytotoxicity can be remarkably efficient, but it is diminished when MHC class I expression by tumor cells is reduced. Cytotoxicity is also inhibited when tumor cells express PD-L1, the ligand for the PD-1 receptor on T cells (*3*). We hypothesized that sensitivity and resistance of tumor cells to T cell–mediated attack is dynamically regulated by multiple pathways in tumor cells that could represent novel targets for immunotherapy.

Discovery of tumor cell-intrinsic genes regulating sensitivity and resistance to T cell–mediated killing

Tumor cells transduced with a genome-scale gRNA library were subjected to selection with cytotoxic T cells to identify genes that controlled resistance to T cell–mediated killing (Fig. 1A). We selected the murine B16F10 melanoma cell line for this screen because it is resistant to checkpoint blockade with antibodies targeting the PD-1 and/or CTLA-4 receptors (*4*, *5*). Inactivation of resistance genes resulted in depletion of the corresponding gRNAs, but such depletion could only be detected with sufficient sensitivity when most tumor cells had sufficient Cas9 activity. We therefore selected a B16F10-Cas9 clone with high editing efficiency (fig. S1) and tested it with positive controls that were either more resistant (*B2m*$^{-/-}$) or sensitive (*Cd274*$^{-/-}$) to T cell–mediated cytotoxicity (fig. S2). This B16F10-Cas9 clone was then transduced with a genome-scale gRNA library in a lentiviral vector (*6*). Selection was performed either with Pmel-1 T cells which have a relatively low TCR affinity for an endogenous melanoma antigen (*7*) or high-affinity OT-I T cells (*8*). Edited tumors cells were selected by three-day co-culture with Pmel-1 CD8 T cells (or one day for OT-I T cells), and the representation of all gRNAs was quantified by Illumina sequencing of the gRNA cassette (Fig. 1A). The specificity of gRNA enrichment/depletion was demonstrated by comparing selection with tumor-specific T cells versus control T cells of irrelevant specificity (fig. S3). This comparison also controlled for potential effects of gRNAs on cell proliferation/viability.

A number of genes known to be essential for T cell–mediated tumor immunity were identified among the enriched gRNAs in both Pmel-1 and OT-1 screens (Fig. 1B, fig. S4A, tables S1-2), including key genes in the MHC class I and IFNγ signaling pathways (*9*–*11*). Mutations in both MHC and interferon pathway genes were shown to confer resistance to cancer immunotherapy (*12*, *13*). T cell-based CRISPR/Cas9 screens have been described by two other la-

boratories. One of these studies performed an in vivo screen covering 2,368 murine genes and highlighted the phosphatase Ptpn2 as a novel target for immunotherapy (*14*). The second study focused on human tumor cells and T cells and reported that mutations in *APLNR* render tumor cells resistant to T cell–mediated cytotoxicity (*15*). Our approach emphasized sensitive detection of depleted gRNAs in a genome-wide manner, which allowed us to discover additional mechanisms conferring resistance to immunotherapy.

A striking result was that gRNAs were depleted for a large number of genes (table S1-2), indicating that inactivation of these genes sensitized tumor cells to T cell–mediated killing. Top genes in this group included known negative immune regulators including *Cd274* (encoding PD-L1 (*16*, *17*)), *Ptpn2* (*18*) and *Serpinb9* (*19*) (Fig. 1C, fig. S4B). However, the vast majority of identified genes had not been previously implicated in resistance to T cell–mediated killing (tables S1-2).

Pathways regulating resistance of tumor cells to T cell–mediated cytotoxicity

We performed gene set enrichment analysis to identify known gene sets/pathways for genes corresponding to enriched or depleted gRNA (tables S3 and S4). Five negative regulators of the Ras/MAP kinase pathway were identified among enriched gRNAs including *Nf1* (*20*), *Dusp6* (*21*), *Spred1* (*22*), *Rasa2* (*23*) and *SPOP* (*24*) (Fig. 1D). Ras pathway activation is very common among human cancers and may not only promote tumor cell growth but also attenuate tumor immunity. Braf is immediately downstream of Ras, and small molecule inhibitors of mutant $BRAF^{V600E}$ elicit stronger cytotoxic T cell responses in melanoma patients and murine tumor models (*25–27*).

Analysis of depleted gRNAs revealed a number of resistance pathways to T cell–mediated killing (Fig. 1C, D and table S4). Interestingly, all three unique components of a SWI/SNF chromatin remodeling complex referred to as the PBAF complex (*28*, *29*) were strongly depleted (*Arid2*, *Pbrm1* and *Brd7*), providing strong evidence that this complex conferred resistance to T cell–mediated killing (Fig. 1D). We also identified resistance genes in the NF-kB pathway (*30*) (*Otulin*, *Rela*, *Ikbkg*, *Ikbkb, Rnf31* and *Sharpin*) and key metabolic pathways, including mTORC1 (*Rraga*, *Rragc* and *Lamtor1* which are required for mTORC1 recruitment to lysosomes (*31*)), glycolysis (including *Nsdhl*, *Gne*, *Gale*, *Ero1l* and *Cd44*) and nicotinate/nicotinamide metabolism (including *Nadk* and *Nampt*). The NF-kB pathway was also identified as a resistance mechanism by Manguso *et al.* (*14*). Control experiments demonstrated that inactivation of such genes did not merely increase sensitivity to cell death; inactivation of representative genes (*Otulin*, *Dusp6* or *Nf1*) in B16F10-Cas9 cells did not render them more sensitive to doxorubicin induced cell death (fig. S5). The majority of identified genes (253 of 313 genes) were validated in a secondary screen (fig. S6) which also confirmed the major pathways described above (fig. S7).

Clinical relevance of PBAF complex to tumor immunity

We used TCGA RNA-seq datasets and TIMER (*32*) to examine the relevance of the CRIPSR screen (fig. S8) and PBAF complex in human cancers. We found that mRNA levels of *ARID2* and *PBRM1* negatively correlated with *GZMB* and *PRF1* mRNA levels in many human cancer types (Fig. 2A, fig. S9A-B and table S5), suggesting that lower expression of *ARID2* and *PBRM1* is correlated with higher cytotoxic activity contributed by CD8 T cells (fig. S9C-D) in human cancers. This correlation was not merely explained by the degree of CD8 T cell infiltration because ARID2 and PBRM1 mRNA levels were also negatively associated with the GZMB/CD8A ratio (Fig. 2B). In addition, we found that low ARID2 mRNA levels were associated with a substantial survival benefit in melanoma patients, but only for those tumors with a higher degree of infiltration by CD8 T cells (based on CD8 expression) (Fig. 2C). These data suggest that ARID2 and PBRM1 affect tumor immunity in a variety of human cancers.

Relevance of PBAF complex to immune checkpoint blockade therapy

The SWI/SNF complex regulates chromatin accessibility for transcription factors. The BAF version of SWI/SNF induces dissociation of Polycomb repressive complex 1 and 2 (PRC1 and PRC2) (*33*), but the PBAF complex may operate through a different biochemical mechanism. The two complexes share core subunits, but unique components are ARID1A/B for the BAF (BRG1-associated factors) complex as well as ARID2, PBRM1 and BRD7 for the PBAF complex (Fig. 3A) (*28*). To validate the role of the PBAF complex in regulating sensitivity to T cell–mediated killing, we generated B16F10 tumor cell lines in which the three genes of the PBAF complex were individually mutated by CRISPR/Cas9. Western blotting experiments confirmed diminished levels of the corresponding proteins in the mutant cell lines (Fig. 3B). Inactivation of *Arid2* diminished protein levels of Brd7 and Pbrm1, consistent with a prior study (*34*), while inactivation of *Pbrm1* did not affect protein levels of Arid2 or Brd7. Partial complexes with some chromatin remodeling activity may therefore remain in some of these knockout cell lines. Co-culture of *Arid2*, *Pbrm1* or *Brd7* mutant tumor cells with cytotoxic T cells resulted in enhanced depletion of PBAF mutant cell lines compared to B16F10-Cas9 cells transduced with a control gRNA (referred to as control B16F10 tumor cells) in a three-day co-culture assay (Fig. 3C). However, inactivation of *Arid2*, *Pbrm1* or *Brd7* genes did not alter cell proliferation over a two-week period (fig. S10A).

B16F10 tumor cells are resistant to checkpoint blockade with PD-1 and/or CTLA-4 antibodies, and we therefore examined whether inactivation of *Pbrm1* would render B16F10 tumor cells sensitive to checkpoint blockade. PD-1 plus CTLA-4 antibodies conferred therapeutic benefit in mice bearing *Pbrm1* mutant B16F10 tumors but this treatment was ineffective against control B16F10 tumors (Fig. 3D-E and fig. S10B-C). Significantly increased numbers of CD45+ immune cells, CD4 and CD8 T cells, as well as granzyme B+ CD8 T cells were present in *Pbrm1* deficient compared to control B16F10 tumors treated with PD-1 plus CTLA-4 checkpoint blockade (Fig. 3F and fig. S10D). Single-cell RNA-seq analysis of sorted CD45+ immune cells showed that gene expression signatures associated with productive anti-tumor immunity (IFNγ response, IFNα response and TNFα signaling via NF-κB) were significantly enriched in *Pbrm1* deficient compared to control B16F10 tumors for both myeloid cells (dendritic cells and M1-like macrophages) as well as lymphoid cells (T cells and NK cells) (fig. S11A-C). These single cell data also identified an increased percentage of dendritic cells and a higher ratio of tumor-inhibitory M1-like macrophages to tumor-promoting M2-like macrophages in *Pbrm1* deficient compared to control B16F10 tumors (fig. S11D). Thus, inactivation of *Pbrm1* not only sensitizes tumor cells to T cell–mediated cytotoxicity but also results in a more favorable tumor microenvironment.

Regulation of IFNγ and mTORC1 pathways by the PBAF complex

To investigate the molecular mechanisms by which the PBAF complex regulates the sensitivity of B16F10 tumor cells to T cell–mediated killing, we examined the transcriptome of PBAF deficient B16F10 cells by RNA-seq. *Arid2* and *Pbrm1* deficient B16F10 cells shared similar gene expression profiles (fig. S12A-B), consistent with their critical role in the PBAF complex. The transcriptome of *Brd7* mutant B16F10 cells was more distinct, suggesting that Brd7 may also have PBAF-independent functions (fig. S12A). mRNAs for a number of metabolic pathways were concordantly downregulated in *Arid2* and *Pbrm1* mutant cells compared to control B16F10 tumor cells, in particular gene sets associated with mTORC1 activation and cholesterol homeostasis (fig. S12C-D and fig. S13). mTORC1 was also a major resistance pathway for T cell–mediated cytotoxicity in the CRISPR/Cas9 screen (Fig. 1D).

Silencing of BAF200 (Arid2) with a siRNA was shown to reduce the expression of Interferon Induced Transmembrane Protein 1 (IFITM1) by IFNα, but not other interferon-regulated genes (*34*). We systematically examined whether the PBAF complex regulates gene expression in response to IFNγ, given the importance of this T cell-derived cytokine for tumor immunity (*12*). RNA-seq analysis showed that gene sets related to IFNγ and IFNα response were significantly enriched among genes concordantly upregulated in *Arid2* and *Pbrm1* deficient cells compared to B16F10 control cells treated with IFNγ (Fig. 4A-B), suggesting that Arid2 and Pbrm1 suppressed the expression of IFNγ responsive genes. Many of the IFNγ responsive genes suppressed by Arid2 and Pbrm1 were relevant to innate immunity or encoded chemokines (*Cxcl9* and *Cxcl10*) (Fig. 4C) (*35*). *Pbrm1* deficient tumor cells also secreted substantially larger amounts of Cxcl9 and Cxcl10 compared to control B16F10 cells following IFNγ stimulation (Fig. 4D-F) which are key chemokines for recruitment of effector T cells that express the Cxcr3 chemokine receptor (*35*). *Arid2* deficient cells had significantly increased surface levels of H2-K^b over a range of IFNγ concentrations compared to control B16F10 cells. Also, all three mutants showed increased surface levels of PD-L1 in response to IFNγ (fig. S14). *Brd7* and *Pbrm1* deficient cells only showed enhanced surface expression of PD-L1 but not H2-K^b in response to IFNγ stimulation (fig. S14) which may be due to partial complexes that retain some activity. These data demonstrate that *Arid2* and *Pbrm1* attenuate the responsiveness of B16F10 tumor cells to IFNγ, a key cytokine for the interaction of tumor cells and T cells.

The PBAF complex regulates chromatin accessibility of IFNγ–induced genes

The major function of the SWI/SNF complex is to regulate chromatin accessibility for transcription factors. We therefore performed ATAC-seq to directly assess chromatin accessibility in *Pbrm1* deficient and control B16F10 tumor cells with and without IFNγ treatment for 24 hours. Following IFNγ treatment, a substantially larger number of genomic sites were accessible in *Pbrm1* deficient than control B16F10 cells, consistent with the RNA-seq data (Fig. 5A). Sites in cluster 1 (648 sites) were more accessible prior to IFNγ treatment in *Pbrm1* deficient compared to control cells, suggesting that the corresponding genes were poised to respond to IFNγ (Fig. 5B-C, fig. S15A). Also, 2,708 sites (cluster III) showed enhanced accessibility following IFNγ exposure in *Pbrm1* mutant compared to control B16F10 cells, but their accessibility was similar between the two cell lines in the absence of IFNγ (Fig. 5B-C and fig. S15B). Motif and target gene prediction analysis suggests these sites were highly enriched with IRF motifs and associated with IFN regulated genes (fig. S15C-E). Thus, inactivation of *Pbrm1* enhances chromatin accessibility for transcription factors at promoters/enhancers of many IFNγ–induced genes.

Discussion

These data demonstrate that resistance to T cell–mediated cytotoxicity is regulated by many genes and pathways in

tumor cells. The corresponding gene products represent targets for immunotherapy because inactivating mutations sensitize tumor cells to T cell–mediated attack. The interaction between T cells and tumor cells is dynamically regulated at many levels, including innate immune and metabolic pathways within tumor cells. The PBAF complex is of particular interest because it regulates chromatin accessibility for IFN$_\gamma$ pathway within tumor cells and thereby increases resistance to T cell–mediated cytotoxicity.

The PBAF complex is a tumor suppressor and inactivating mutations in any of the three unique genes of this complex (*PBRM1*, *ARID2* and *BRD7*) are known to occur in a variety of human cancers (*28*). For example, inactivating mutations in *PBRM1* are prevalent in clear cell renal cancer (~41% of patients) (*36*). A study by Miao *et al.* in this issue demonstrates that *PBRM1* mutations in metastatic renal cancers are associated with improved clinical responses to PD-1/PD-L1 blockade (*37*). Mutations in *ARID2* and *BRD7* are also observed in a variety of other human cancers, including *ARID2* mutations in melanoma (*38*). Human tumors with inactivating mutations in *PBRM1*, *ARID2* and *BRD7* may therefore be more sensitive to PD-1 blockade as well as other forms of immunotherapy in which cytotoxic T cells serve as the main effector mechanism, including cancer vaccines and adoptive T cell therapies. This study provides a mechanistic understanding for these clinical findings by demonstrating that PBAF-deficient tumor cells are more sensitive to T cell–mediated cytotoxicity. We also show that PBAF-deficient tumor cells produce higher levels of chemokines (Cxcl9 and Cxcl10) in response to IFN$_\gamma$, resulting in more efficient recruitment of effector T cells into tumors (*35*).

The immunotherapy field has thus far emphasized the targeting of inhibitory receptors expressed by immune cells. We propose that targeting of tumor cell-intrinsic resistance mechanisms to T cell–mediated cytotoxicity will be important to extend the benefit of immunotherapy to larger patient populations, including cancers that thus far are refractory to immunotherapy.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/cgi/content/full/science.aao1710/DC1
Materials and Methods
Figs. S1 to S15
Tables S1 to S5
References (*39*–*50*)

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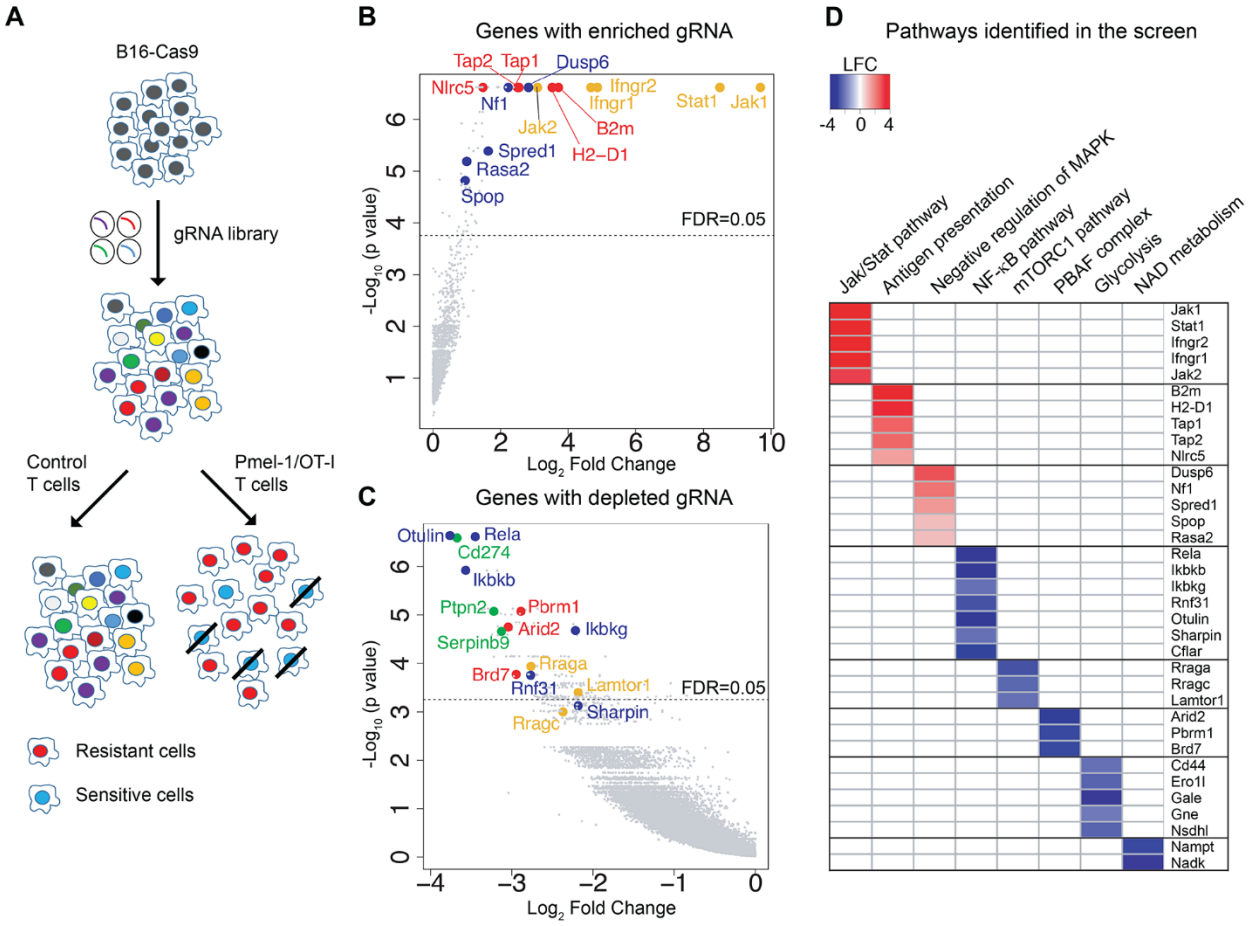

Fig. 1. Systematic discovery of genes and pathways regulating sensitivity and resistance of tumor cells to T cell–mediated killing. (**A**) Screening strategy. Cas9-expressing B16F10 cells were transduced with a genomic-scale gRNA library (4 gRNAs/gene). Edited B16F10 cells were co-cultured with activated cytotoxic T cells followed by Illumina sequencing of gRNA representation. Specific selection was performed with Pmel-1 T cells (specific for gp100 melanoma antigen) or OT-I T cells (specific for Ova peptide). Control selection was performed with T cells of irrelevant specificity. (**B**) Top genes for enriched gRNAs from Pmel-1 screen. Candidate genes were plotted based on mean $\log_2$ fold change of gRNA counts compared to control selection and p-values computed by MaGeCK. Dashed line indicates a FDR (False Discovery Rate) = 0.05. Annotated genes represent MHC class I (red), interferon (yellow) and Ras/MAPK (blue) pathways. (**C**) Top genes for depleted gRNAs from Pmel-1 screen. Genes related to PBAF form of SWI/SNF complex (red), NF-κB pathway (blue), mTORC1 pathway (yellow), and known negative immune regulators (green) were annotated. (**D**) Selected pathways and corresponding genes identified in the Pmel-1 screen. Color scale represents $\log_2$ fold change of average gRNA representation.

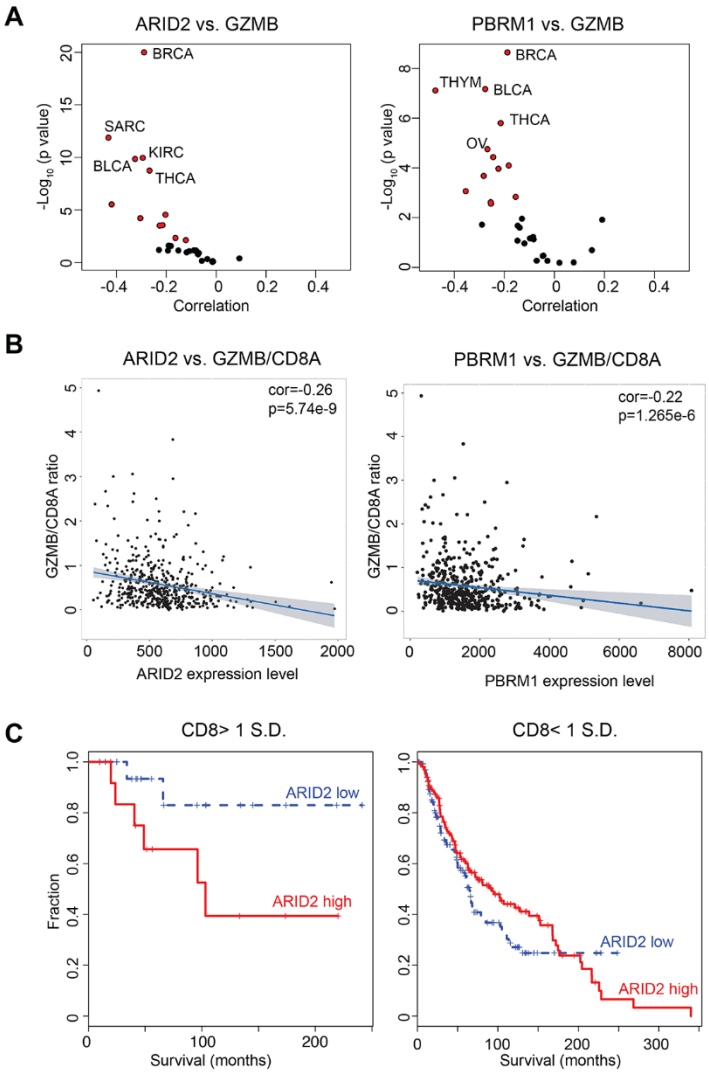

Fig. 2. Expression of ARID2 and PBRM1 is negatively correlated with T cell cytotoxicity markers in TCGA datasets. (**A**) Correlation of ARID2 and PBRM1 mRNA levels with GZMB mRNA levels in indicated cancers. Volcano plot showing the Spearman's correlation and estimated significance of ARID2 (left) or PBRM1 (right) with GZMB mRNA levels from RNA-seq data across TCGA cancer types calculated by TIMER (Tumor Immune Estimation Resource) and adjusted for tumor purity (*32*). Each dot represents a cancer type in TCGA; red dots indicate significant correlations ($p<0.01$). (**B**) Analysis of ARID2 and PBRM1 mRNA levels in relationship to GZMB and CD8A as cytotoxicity and CD8 T cell infiltration markers, respectively. Spearman's correlation of ARID2 (left) and PBRM1 (right) mRNA levels to GZMB/CD8A mRNA ratio in TCGA melanoma dataset. (**C**) Correlation of ARID2 expression level with survival of melanoma patients depending on calculated level of CD8 T cell infiltration. All patients in TCGA melanoma study were divided according to the expression level of ARID2 (higher or lower than mean expression value of all patients). The impact of ARID2 expression level on survival is shown for patients whose tumors had higher (greater than one standard deviation) or lower (less than one standard deviation) expression of CD8 [(CD8A+CD8B)/2].

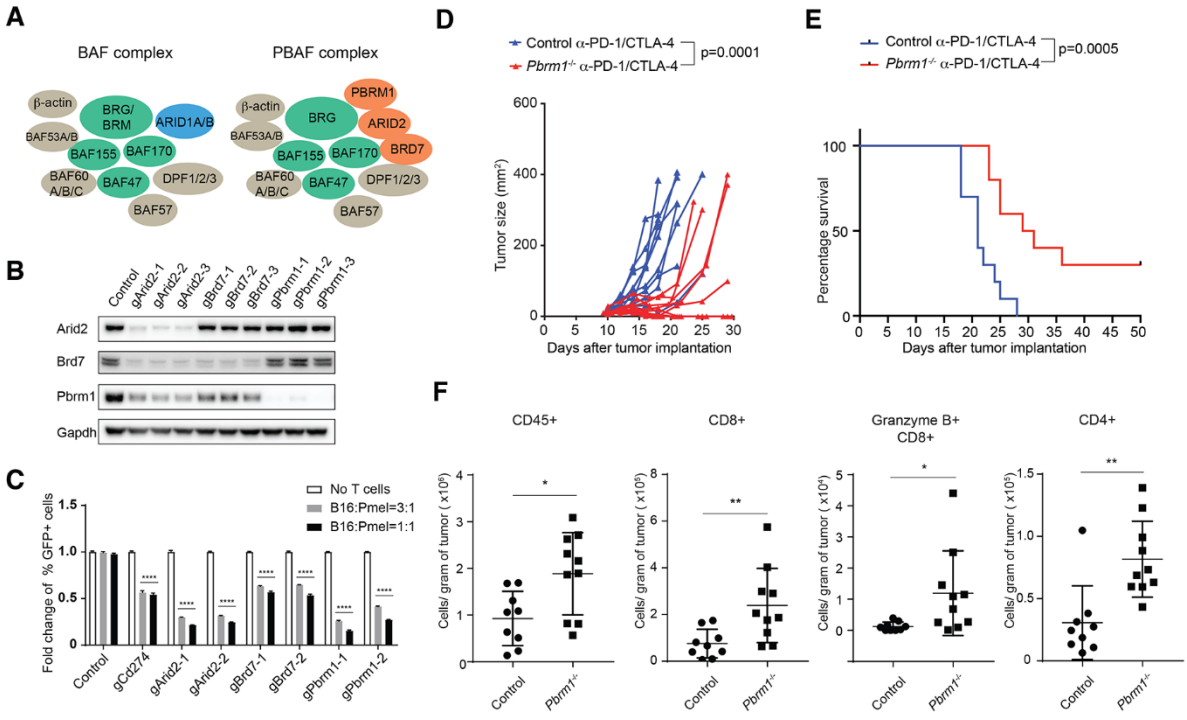

Fig. 3. Inactivation of PBAF complex sensitizes tumor cells to T cell–mediated killing and synergizes with checkpoint blockade therapy. (**A**) Cartoon illustrating the composition of BAF and PBAF versions of SWI/SNF complex. (**B**) Western blot showing protein levels of Arid2, Brd7, Pbrm1 and Gapdh in control and indicated knockout cell lines. (**C**) GFP-positive *Arid2*, *Pbrm1* or *Brd7* deficient B16F10 cells were mixed with GFP-negative control B16F10 cells at approximately 1:1 ratio. Tumor cells were co-cultured with Pmel-1 T cells at indicated effector to target ratios for 3 days in triplicates; the fold change of % GFP+ tumor cells was determined by FACS. Two-way ANOVA was used to determine statistical significance (**** $p<0.0001$). Values represents mean +/− SD. (**D**) Mice bearing control (n=10) or *Pbrm1*-deficient B16F10 tumors (n=10) were treated with α-PD-1 (200μg/mouse) plus α-CTLA-4 antibodies (100μg/mouse) and tumor size was measured. Two-way ANOVA was used to determine statistical significance for time points when all mice were viable for tumor measurement. (**E**) Survival of mice inoculated with control (n=10) or *Pbrm1*-deficient B16F10 cells (n=10) and treated with α-PD-1 plus α-CTLA-4 antibodies. Log-rank (Mantel-Cox) test was used to determine statistical significance. (**F**) Flow cytometric analysis of immune cell infiltration in *Pbrm1*-deficient and control B16F10 tumors. The number of CD45+, CD4+, CD8+ and Granzyme B+ CD8+ T cells was determined per gram of tumor. Mann-Whitney test was used to determine significance (* $p<0.05$, ** $p<0.01$). Values represents mean +/− SD. Data in (C-F) are representative of two independent experiments.

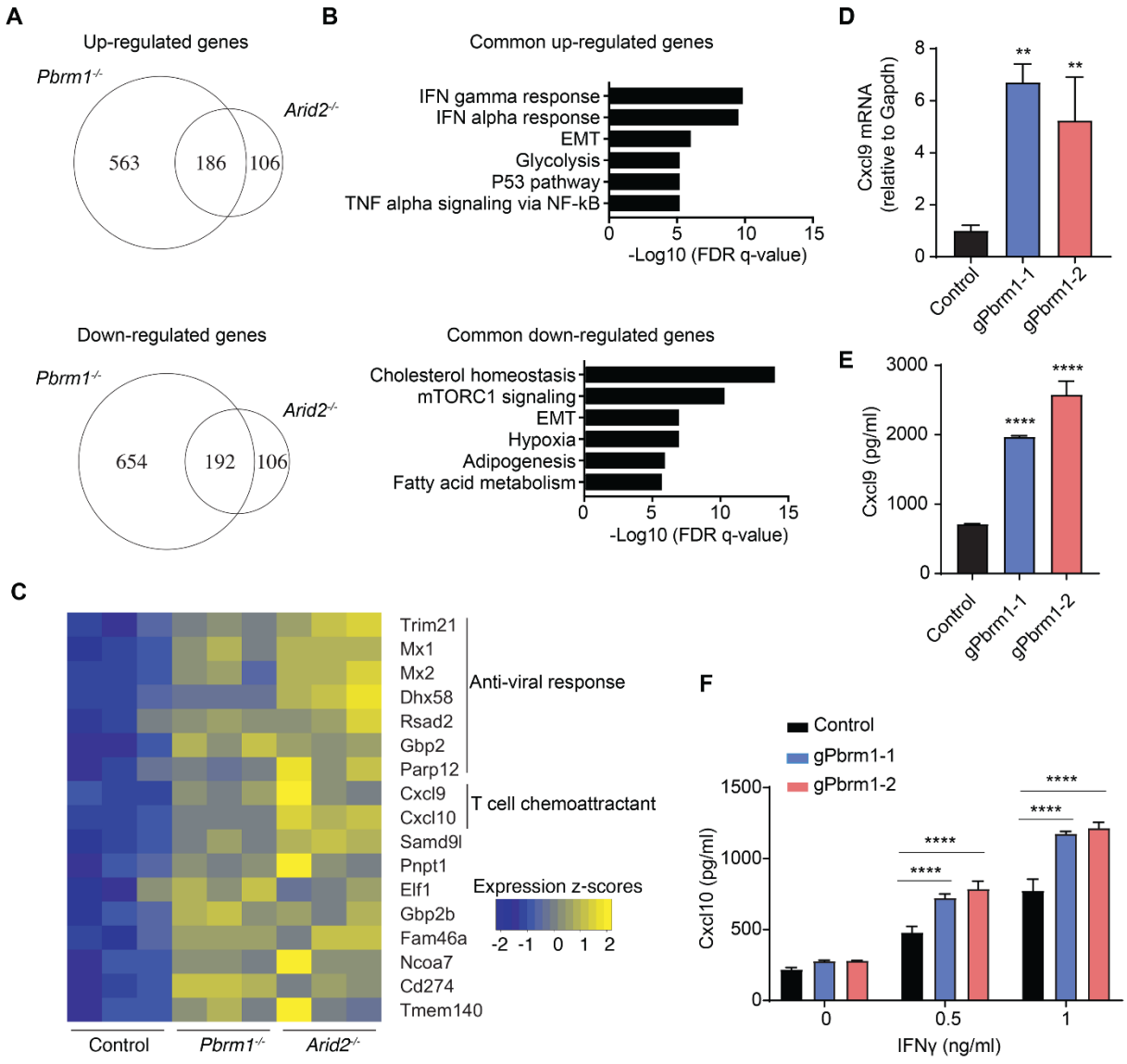

Fig. 4. Enhanced responsiveness to IFNγ stimulation by *Arid2* and *Pbrm1* deficient tumor cells. (**A-C**) RNA-seq analysis of *Arid2* or *Pbrm1* deficient cells and control B16F10 cells treated with IFNγ (10ng/ml) for 24 hours. (**A**) Venn diagram showing differentially regulated mRNAs in the presence of IFNγ. (**B**) Hallmark gene sets enriched for commonly up- or down-regulated mRNAs in both *Arid2* and *Pbrm1* deficient cells compared to control B16F10 cells in the presence of IFNγ treatment (as shown in A). (**C**) Heat map showing expression value (z-score based on cufflink count) of interferon-responsive genes in control, *Arid2* and *Pbrm1* deficient B16F10 cells following IFNγ treatment. (**D-E**) Cxcl9 mRNA level (**D**) and Cxcl9 protein secretion (**E**) comparing *Pbrm1*-deficient and control B16F10 tumor cells stimulated with IFNγ (10ng/ml) for 24 hours. Values represents mean +/− SD. (**F**) Cxcl10 secretion by *Pbrm1*-deficient and control B16F10 tumor cells stimulated with IFNγ (0, 0.5 and 1 ng/ml) for 24 hours. Values represents mean +/− SD. One-way ANOVA (D-E) and two-way ANOVA were used to determine significance (F). ** p<0.01, **** p<0.0001. Data in (D-F) are representative of two independent experiments.

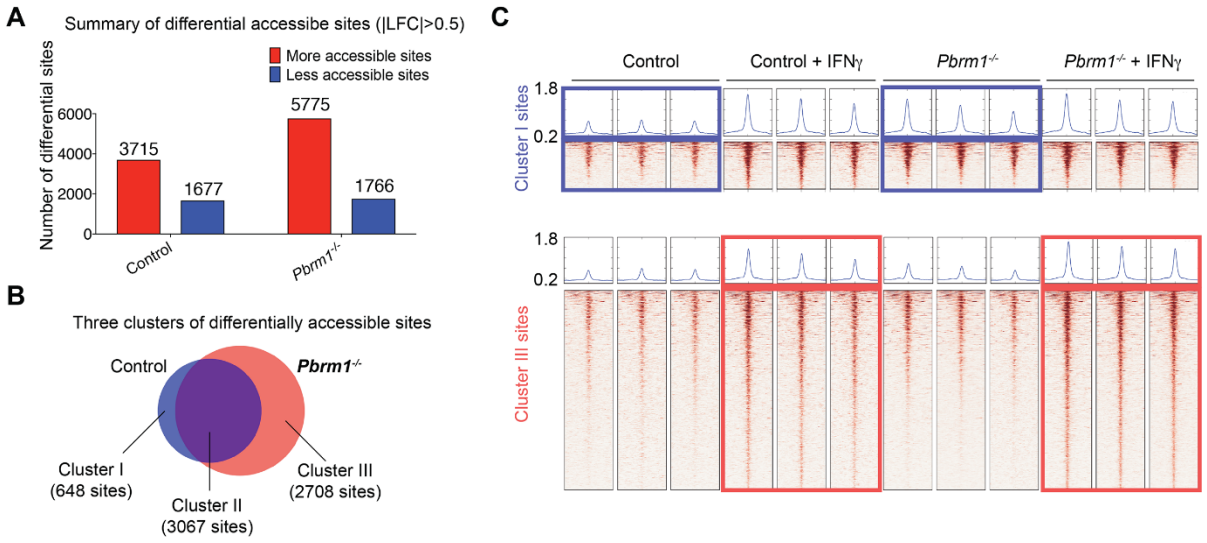

Fig. 5. Enhanced chromatin accessibility for IFNγ responsive genes in *Pbrm1*-deficient tumor cells. ATAC-seq was performed on *Pbrm1*-deficient and control B16F10 cells +/− IFNγ stimulation (10ng/ml) for 24 hours. (**A**) Genome-wide analysis of differentially accessible chromatin sites ($|\log_2$ fold change$|$ >0.5) following IFNγ stimulation in control versus *Pbrm1*-deficient B16F10 tumor cells. (**B**) Venn diagram illustrating accessible sites gained following IFNγ treatment in control (blue) and *Pbrm1*-deficient (red) cells. (**C**) Chromatin accessibility heat maps for all sites in clusters I (top panel) and III (bottom panel). Aggregated reads within 2kb of center of differentially accessible regions are shown above heat maps.

REPORT

APPLIED PHYSICS

Wrapping with a splash: High-speed encapsulation with ultrathin sheets

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Many complex fluids rely on surfactants to contain, protect, or isolate liquid drops in an immiscible continuous phase. Thin elastic sheets can wrap liquid drops in a spontaneous process driven by capillary forces. For encapsulation by sheets to be practically viable, a rapid, continuous, and scalable process is essential. We exploit the fast dynamics of droplet impact to achieve wrapping of oil droplets by ultrathin polymer films in a water phase. Despite the violence of splashing events, the process robustly yields wrappings that are optimally shaped to maximize the enclosed fluid volume and have near-perfect seams. We achieve wrappings of targeted three-dimensional (3D) shapes by tailoring the 2D boundary of the films and show the generality of the technique by producing both oil-in-water and water-in-oil wrappings.

Many liquid-phase technologies require the encapsulation of one liquid in another. In the stabilization of emulsions, drug delivery, and remediation of oil spills, liquid droplets are separated from the surrounding liquid by a fluid monolayer of molecular or particulate surfactants (*1*–*3*). By contrast, we typically wrap solid contents, such as chocolates or the filling in a dumpling, with solid elastic sheets. Solid wrappings of liquids would allow new possibilities, such as drops with nonspherical shapes, designed permeability, and mechanical shear rigidity. Sufficiently thin planar sheets will spontaneously wrap liquid droplets by balancing the elastic energy of curving the sheet with the reduction in interfacial surface energies. Elastomer films of thickness $t \sim 100$ μm were shown to bend around a water droplet by this mechanism (*4*, *5*). For much thinner films, the energetic cost of bending becomes negligible compared with the surface energies (*6*). Paulsen *et al.* (*7*) found that in this regime of highly bendable sheets (*8*), the wrappings are optimal in the sense that they enclose the maximum volume within a fixed area of sheet. However, those experiments changed the volume of the liquid quasistatically and required controlled initial conditions that are not scalable for the rapid production of wrapped drops.

Here, we establish a fast, dynamic route to wrapping in the high-bendability regime, exploiting the dynamics generated by the impact of a drop of oil on an ultrathin polymer sheet floating on a pool of water. Polystyrene films of thickness t from 46 to 372 nm are cut into circular discs of radius W = 1.6 to 3.2 mm and placed on the water surface in a cuvette (*9*) as shown in Fig. 1. A drop of fluorinated oil of radius R = 0.6 to 1.2 mm, density ρ_{oil} = 1800 kg/m^3, and surface tension γ_{oil} = 16 mN/m is released from a height h = 10 to 300 mm above the surface. The drop hits the surface with a kinetic energy proportional to h. Immediately after the impact, a crater begins to form, which reaches a maximum depth and then retracts back toward a flat interface. During the retraction, the drop separates from the water-air interface while the sheet wraps around the drop. Despite the uncontrolled dynamics of the splash, the drop achieves optimal wrapping, both in terms of the three-dimensional (3D) shape of the wrapped drop (*7*) and in the near-perfect closure achieved along the seam. This sequence of events takes tens of milliseconds to complete (movie S1). Once the wrapped oil separates from the water surface, it sinks under gravity.

The static 3D shape is optimal when the exposed area of the fluid interface is minimized, as in Eq. 1 (*7*)

$$U = \gamma A_{free} \quad (1)$$

where the only dimensionless control parameter is W/R, the ratio of the sheet radius to the droplet radius. In the dynamical splashing process, the energies of the initial and final state involve the surface energy of the partially or fully wrapped drop, as well as the energies of all other interfaces between the air, oil, water, and sheet. The final energy is higher, which implies that an energy barrier (*9*) must be overcome by the kinetic energy of the drop. As is typically done in splashing problems (*10*), we take the ratio of the kinetic energy at impact to the initial surface energy of the drop to form the dimensionless Weber number, $We = \frac{\rho_{oil} v^2 R}{\gamma_{oil}}$. If the oil drop does not carry sufficient kinetic energy to overcome all the relevant interfacial energies, it fails to separate from the water-air interface, and both oil and sheet spread out over the water surface.

In Fig. 2A, we show a phase diagram that summarizes the outcomes of experiments with circular sheets of thickness t = 47 nm and varying We and W/R. The threshold We for successful wrapping (red line) increases with W/R. (Occasionally, even above the threshold We, the drop pinches off and separates from the interface but is pulled back onto the surface by transient fluid flows.) The final configurations above the threshold We, obtained for various values of W/R, are shown in Fig. 2B. As W/R increases, the sheet covers a larger portion of the drop's surface. For all the experiments shown in Fig. 2, we reproducibly

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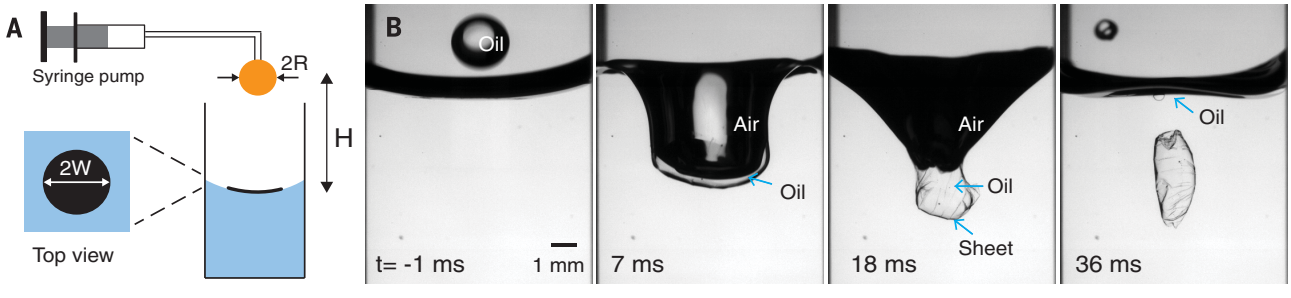

Fig. 1. Process of wrapping a splashing drop with a thin sheet. (**A**) Schematic of the experiment. (**B**) Sequence of events observed in a typical experiment where a fluorocarbon oil drop is wrapped with a polystyrene sheet. Here, W/R = 2.4, We = 400, and thickness t = 47 nm.

obtain the optimal 2-fold shape (reminiscent of an empanada) near complete wrapping ($W/R \cong 2.26$). This process rarely gets stuck in competing, near-optimal states (such as the 3-fold state) found in the quasistatic experiments (*7*). For larger W/R, the sheet has more area than is required to cover the droplet and forms crumpled, but closed, wrappings.

Bending energies of the wrapped state are expected to be negligible compared with interfacial energies; this competition may be quantified by the bendability, a dimensionless number, given by (*8*): $\gamma W^2/B$, for a sheet of size W, Young's modulus E, Poisson ratio Λ, and bending stiffness $B\left(=\frac{Et^3}{12(1-\Lambda^2)}\right)$. Our experiments are conducted at high bendability (~10^4 to 10^7) (*6*, *8*, *11*). The assumption that bending energy can be neglected is confirmed by experiments on films with a range of thicknesses (t = 46 to 372 nm) keeping W/R constant (Fig. 2C). There is no measured thickness dependence in the outcome. Neglecting bending energies in the sheet, we estimate a threshold *We* by considering the difference in surface energies of the initial and final configurations (see the supplementary text). This estimate is an order of magnitude lower than the observed threshold (see Fig. 2A).

This estimate fails because it only considers the energies of the initial and final states and neglects the barrier presented by intermediate states as the oil drop pierces the water surface [unlike (*5*, *7*)] to create a topologically distinct final state with a new set of interfaces. The sequence of images in Fig. 1 (see also movie S1) shows that the impact sets the water surface in motion, forming a crater that grows in size, reaches a maximum, and then collapses back to a flat interface. When the interface begins to rapidly relax back from the highly deformed shape, the oil at the interface collects into a drop, forms a neck, and pinches off to detach from the interface. This motivates the hypothesis that successful wrapping events can be understood as the pinch-off of a pendant drop. Moreover, in successful penetration events, a part of the oil drop is left behind at the interface, which is another characteristic of pinch-off.

To understand wrapping as a pinch-off of a pendant drop, we study droplet impact in the absence of a sheet. Although many studies have looked at the impact of a drop of liquid on a bath of identical or miscible liquid (*12*–*15*), few have considered immiscible liquids (*10*).

The oil in our experiments is denser than water, but a drop of small enough radius R placed gently at the surface will float because the force of surface tension ($F_\gamma \sim 2\pi R\gamma$, ignoring the geometry of the Neumann contact) exceeds the force of gravity ($F_g = \frac{4}{3}\pi R^3 \Delta\rho g$, where $\Delta\rho = \rho_{oil} - \rho_w$). Above a threshold size $R_0 = \sqrt{\frac{3}{2}}\, l_c$ set by the capillary length $\left(l_c = \sqrt{\frac{\gamma}{\Delta\rho g}}\right)$, gravity dominates the oil-water surface tension ($F_g > F_\gamma$), and the drop sinks and pinches off. However, a smaller drop can penetrate the surface if it has sufficient initial velocity (see Fig. 2A, W/R = 0). Figure 3A shows the time evolution of the height (y) of the lowest point on the interface after the impact of a drop of radius $R < R_0$. The water-air interface accelerates upward against gravity in the moments leading up to the detachment of the drop (indicated by the hourglass marker). In this dynamic version of pinch-off, the effective downward force on the drop is boosted by a factor $\alpha = \frac{a+g}{g}$, where a is the upward acceleration of the interface measured in the lab frame. Our hypothesis is that the threshold size for pinch-off is simply modified to $R_0 = \sqrt{\frac{3}{2\alpha}}\, l_c$.

To test this idea, we show in Fig. 3B the nondimensional acceleration α computed from the $y(t)$ curves (see the supplementary text), in the absence of a sheet, as a function of release height (h) and *We*. The value of α initially increases with *We* but then saturates at approximately the threshold *We* required for successful penetration of the

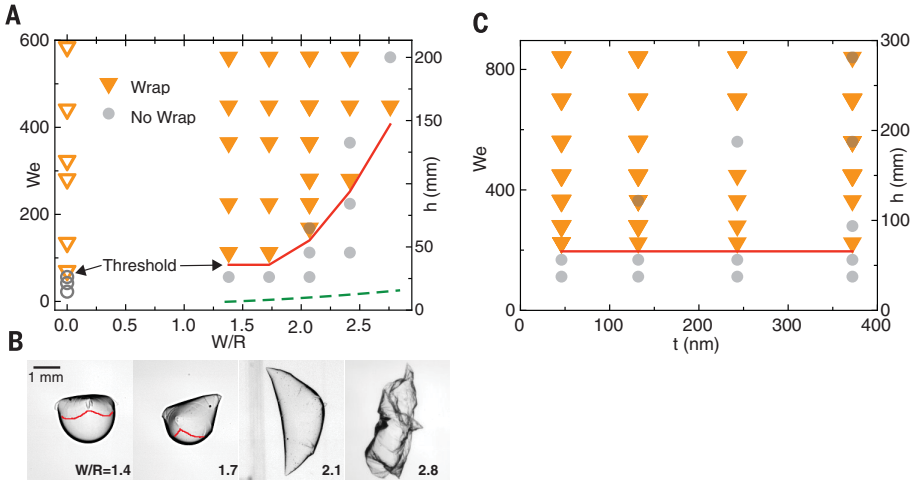

Fig. 2. Threshold for successful wrapping. (**A**) Data points indicate the outcome of the experiment as a function of *We* and *W/R*. The red curve shows the observed threshold for successful wrapping. The dashed green curve shows a naive threshold computed from the difference in the surface energies between the initial and the final states, assuming no loss of energy to the fluid. The open symbols represent experiments on a bare water surface without any sheets. (**B**) Examples of structures obtained for various *W/R* values. For clarity, boundaries of sheets (red curves) have been drawn by hand for *W/R* = 1.4 and 1.7. (**C**) The threshold *We* for successful wrapping shows no dependence on the thickness t. Here, *W/R* = 2.4. In some cases (gray circles above the threshold), a wrapping forms, but fluid recirculation in the cell brings it to the surface, causing it to unwrap.

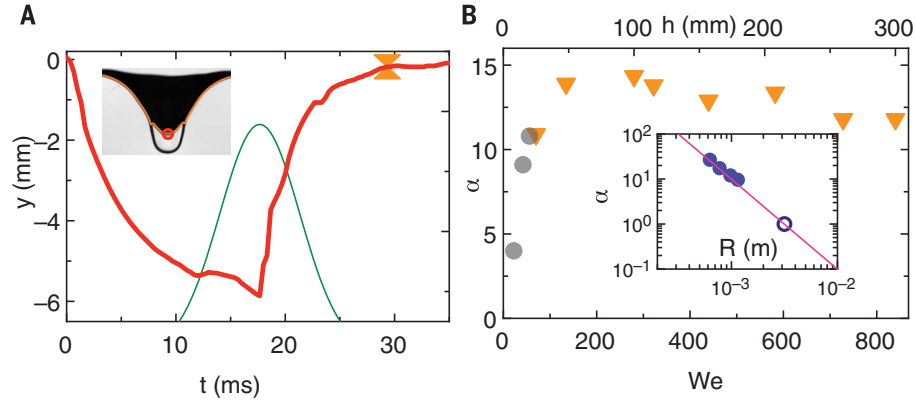

Fig. 3. Pinch-off dynamics in the absence of a sheet. (**A**) Time evolution (red curve) of the lowest point (red circle) of the air surface (orange curve in the inset) for *We* = 320 in the absence of a sheet. The hourglass marker shows the instant when the pinch-off of the oil drop is complete. The oil-water interface (dark-light contrast) is also clearly visible. The acceleration α is computed with a Gaussian derivative filter (green curve). (**B**) The values of $\alpha\left(=\frac{a+g}{g}\right)$ obtained as a function of *We* (or h) for R = 1.15 mm. Circles mark no penetration, triangles successful penetration. (Inset) The value of α at threshold for different drop sizes R. Filled circles represent splashing experiments, whereas the open circle represents a quasistatic experiment. The red line is the function $\alpha = \frac{3}{2}\left(\frac{l_c}{R}\right)^2 = \left(\frac{3}{2}\right)\left(\frac{\gamma}{g(\rho_o - \rho_w)}\right)R^{-2}$.

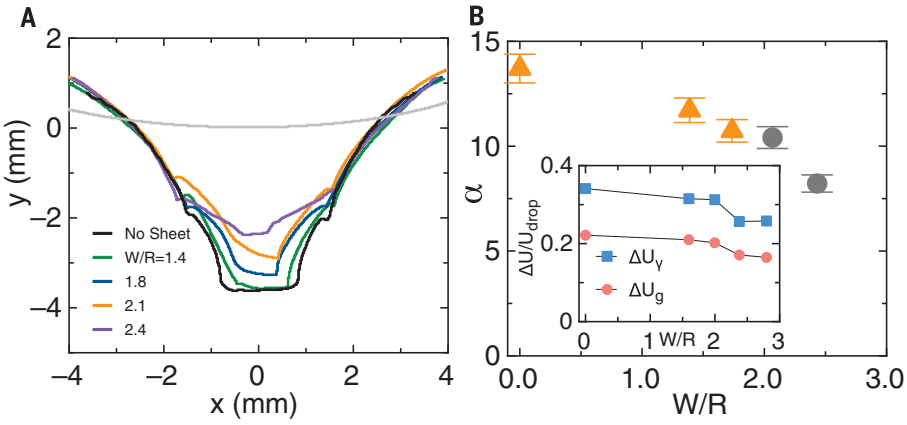

Fig. 4. Effect of the sheet on pinch-off dynamics. (**A**) Profiles of the air cavity 10 ms after impact for *We* = 112 and different *W/R*. The oil and sheet lie under the rough, central part of the profile and join the smooth air-water interface at the kink. The gray curve shows the air-water interface before the impact. (**B**) The nondimensional acceleration α as a function of *W/R* for *We* = 112. Triangles and circles represent wrap and no-wrap situations, respectively. The inset shows the change in surface and gravitational energies (see the supplementary text and fig. S3) computed at the parameter values of (A).

drop (orange triangles). The threshold depends on the size of the drop (*R*), because the two forces scale differently with the radius of the drop (~R^3 and ~*R*, respectively). The inset shows the measured value of α at the threshold as a function of *R*. We also plot the result from the quasistatic experiment (i.e., α = 0), where a drop is gently placed at the water surface and its volume gradually increased until it becomes unstable and sinks. The predicted relationship $\left(\alpha = \frac{3}{2}\left(\frac{l_c}{R}\right)^2\right)$ describes all the data with no adjustable parameters (red curve in Fig. 3B). We emphasize, however, that this is far from a complete predictive understanding: α is a measured quantity that is controlled by the hydrodynamics of the impact, and its functional dependence on *We* is unknown.

The energy transfer from the drop during the impact is further modified by the elastic sheet (*5*, *16*); the threshold *We* increases upon increasing the size of the sheet. For a given *We*, the interface deforms less for larger sheets, as shown by profiles of the air-water interface displayed in Fig. 4A and fig. S4. Correspondingly, the acceleration α decreases with increasing *W/R* as shown in Fig. 4B for *We* = 112. Thus, at this fixed value of *We*, wrapping occurs for small *W/R* but fails at larger *W/R* (circles). Although the sheet is extremely flexible, it affects fluid dissipation, presumably by changing the boundary condition for fluid flow at the interface from being free in the case of an air-water interface to a no-slip condition when covered with the sheet. We notice from Fig. 2, A and C, that the threshold *We* as $t \to 0$ is different from the limit as $W/R \to 0$; that is, even an arbitrarily thin sheet modifies the dynamics of splashing.

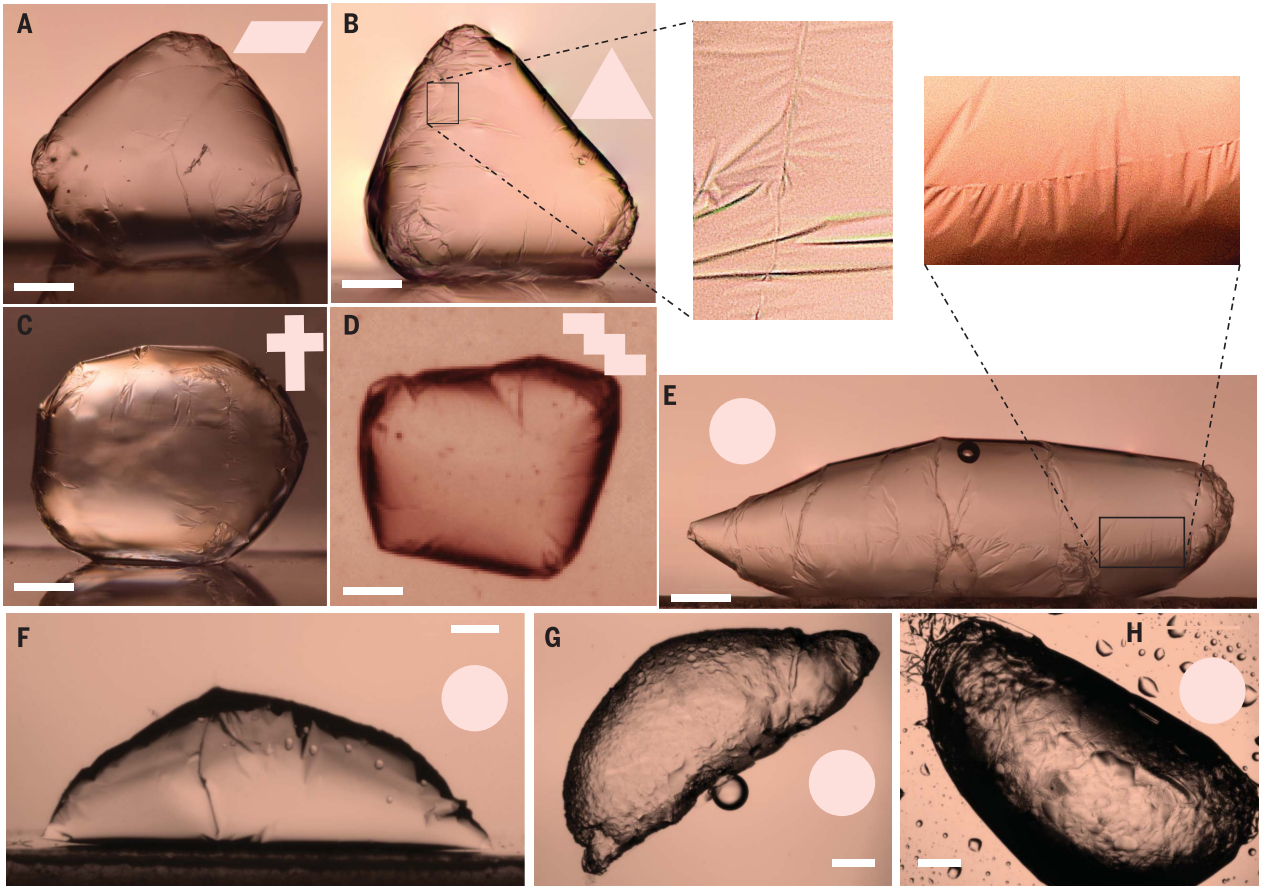

Fig. 5. Versatility of wrapping technique. (**A** to **E**) Different 3D shapes obtained from wrapping a drop of fluorinated oil inside water using sheets whose shapes are sketched in the insets. The quality of the seam is highlighted by the magnified sections of the images. (**F**) Mineral oil wrapped in an ethanol environment. (**G**) Water drop wrapped in a hexadecane environment. (**H**) Water drop extracted out in air from hexadecane. Scale bar, 0.5 mm.

Using the profiles shown in Fig. 4A and assuming axial symmetry, we compute the interfacial areas and, hence, the total surface and gravitational energies (see the supplementary text and fig. S3) 10 ms after impact for different values of W/R. The surface and gravitational energies decrease modestly with increasing W/R. Taken together, these account for a substantial fraction of the incoming kinetic energy of the drop.

We thus validate a picture of the underlying physics of droplet penetration as a pinch-off process driven by the large acceleration of the interface resulting from impact: We are able to correctly predict acceleration as a function of radius (Fig. 2B) and understand qualitatively the effect of the sheet in the splash. A solid sheet can profoundly affect the transfer of energy to the fluid, even if it is too thin to store elastic energy. Our data (Fig. 4B) more sharply pose a central question in the hydrodynamics of an immiscible splash; droplet penetration can be understood if the retraction acceleration α is determined in terms of initial kinetic energy We.

We illustrate the potential of impact wrapping by showing that the 3D shape of the wrapped drop can be tailored by designing the planar shape of the sheet. We have studied wrappings with sheets cut in 2D shapes inspired by the geometry of folding polyhedra (*17*). A tetrahedron can be cut open into a planar sheet in many different ways (*18*), known as the nets or unfoldings. Two of the simplest polygonal unfoldings of a tetrahedron (*18*) indeed yield a 3D shape close to a tetrahedron (Fig. 5, A and B). We also examined two different possible nets of a cube. The resulting wrappings are shown in Fig. 5, C and D. We emphasize that unlike in origami, no features need be scribed along the intended folds of the planar net (*19*, *20*); the 3D shape is guided purely by a 2D contour. This is remarkable, as a planar shape like an equilateral triangle can be folded into many different closed 3D shapes (*21*), but a high-symmetry wrapping is selected during splashing. The wrappings are also robust under mechanical perturbations; a wrapped object can be deformed substantially and reform into the optimal shape, with the free edges having realigned (movie S4).

The quality of encapsulation achieved in wrapping 3D objects with 2D sheets depends crucially on how well the free edges are aligned together. Close examination of the seam achieved in these wrappings (Fig. 5, B and E) reveals that the edges of the sheet avoid both an overlap and an opening. The absence of an overlap suggests that there is no self-adhesion. Thus, this method of encapsulation is also reversible and can be opened to release the encapsulated liquid or can spontaneously reform after being distorted (see movie S4). This near-perfect seam is also an efficient barrier to diffusion and evaporation (as shown in figs. S5 and S6 and movie S5) and in this respect can be superior to particulate encapsulants.

In Fig. 5, F and G, we demonstrate the generality of the process with examples of hydrocarbon oil wrapped in an ethanol phase and of a water drop encapsulated in a hydrocarbon environment. In these situations, the sheet can also be functionalized to accommodate any chemical incompatibility of the fluid with the sheet. In Fig. 5G, for example, we use a bilayer sheet with an amorphous fluorocarbon polymer (Cytop) on the oil side of the interface and polystyrene on the aqueous side, because polystyrene is degraded by prolonged contact with the hydrocarbon oil. Finally, in Fig. 5H, we demonstrate that the wrapped object may be extracted out of the liquid-liquid interface where it was created, provided that the surface energy of this interface is relatively low. Thus, the versatility and robustness of impact wrapping indicates the possibility of application in many settings for many pairs of liquids—e.g., as containers for chemical reactions, targeted delivery of tiny liquid cargo, or separation and isolation of unwanted liquid phases. Here, we use bilayer films to achieve chemical compatibility, but a large class of scalable techniques can be exploited to make polymer films with designed chemical functionality, optical qualities, or controlled permeability.

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SUPPLEMENTARY MATERIALS

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PEPTIDE MODIFICATION

Natural noncanonical protein splicing yields products with diverse β-amino acid residues

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Current textbook knowledge holds that the structural scope of ribosomal biosynthesis is based exclusively on α-amino acid backbone topology. Here we report the genome-guided discovery of bacterial pathways that posttranslationally create β-amino acid–containing products. The transformation is widespread in bacteria and is catalyzed by an enzyme belonging to a previously uncharacterized radical *S*-adenosylmethionine family. We show that the β-amino acids result from an unusual protein splicing process involving backbone carbon-carbon bond cleavage and net excision of tyramine. The reaction can be used to incorporate diverse and multiple β-amino acids into genetically encoded precursors in *Escherichia coli*. In addition to enlarging the set of basic amino acid components, the excision generates keto functions that are useful as orthogonal reaction sites for chemical diversification.

Overcoming the structural limitations of ribosomal biosynthesis, which is based on a restricted set of amino acids, is important in biology and applied life sciences (*1*–*4*). Natural proteins and ribosomally produced peptides are diversified through posttranslational modifications that equip them with a wide range of added structural and functional features (*1*). All known ribosomally generated biomolecules are based on α-amino acid backbone topologies. In synthetic biology, efforts have been made to incorporate non–α-amino acid residues into proteins by ribosome engineering or by tRNA misacylation. Although in vitro strategies have resulted in products containing α-hydroxy or β-amino acids (*5*–*9*), we know of only a single in vivo case, which used mutated ribosomes to incorporate β^3-Phe–based units (*10*).

We recently reported the discovery of radical *S*-adenosylmethionine (rSAM) enzymes that irreversibly introduce multiple D-amino acids into ribosomally synthesized and posttranslationally modified peptides (RiPPs) (*11*–*14*). These enzymes act on small precursor proteins containing either a nitrile hydratase–like (also termed proteusin) or a Nif11-like N-terminal leader and a variable C-terminal core region. During biosynthesis, the core is modified and proteolytically released from the leader. Although the encoding biosynthetic gene clusters are widespread in bacteria (*15*), the only proteusins that have been characterized to date are the cytotoxic, pore-forming polytheonamides (*11*, *16*–*18*), which are the most extensively modified known peptides and contain numerous D-amino acids introduced by a rSAM epimerase (*11*, *14*).

In a broader analysis of such RiPP clusters, genes encoding an orphan rSAM family (TIGR04103, rSAM_nif11_3) attracted our attention owing to their consistent colocalization with Nif11 precursor genes. These rSAMs contain a C-terminal region with homology to SPASM domains present in various peptide-modifying rSAM enzymes (*19*). One homolog, here termed PlpX, is encoded in the orphan *plp* locus from *Pleurocapsa* sp. PCC 7319. The locus contains one proteusin and two Nif11 precursor genes, as well as the previously characterized rSAM epimerase PlpD (Fig. 1A) (*12*, *13*). To assign function to the remaining genes in the *plp* cluster, we studied the activity of PlpX. We coexpressed the gene with either of the two Nif11 precursor genes *plpA2* and *plpA3*, which are located directly upstream and encode precursors with predicted cores of 25 and 23 amino acids, respectively (Fig. 1B). Both precursor genes were modified to produce N-terminally His_6-tagged proteins carrying a factor Xa (Fx) cleavage site at the leader-core interface. After coexpression with *plpX* in *Escherichia coli* BL21(DE3), Ni-affinity purification, and cleavage with trypsin, the core peptides **1** and **2** of His_6-PlpA2-Fx and His_6-PlpA3-Fx, respectively, lacked detectable modifications (Fig. 2A). Closer analysis of the *plp* locus (Fig. 1A), however, revealed an unannotated small open reading frame, named *plpY*, located downstream of *plpX*, an architecture that we also detected in other clusters encoding PlpX homologs (figs. S1 and S2 and table S1). PlpY has weak similarity to PqqD from pyrroloquinoline quinone biosynthesis (*20*) and to the RiPP recognition element domains that occur in various modifying enzymes and mediate precursor binding (*21*) (fig. S3). When *plpY* was coexpressed with *plpX* and *plpA2* or *plpA3*, the liquid chromatography–mass spectrometry (LC-MS) chromatograms contained two additional broad peaks (Fig. 2A) that partially overlapped with unmodified **1** (products **3** and **4**) and **2** (products **5** and **6**). Tandem mass spectrometry (MS/MS) experiments (Fig. 2B) revealed a mass difference consistent with C_8H_9NO loss in PlpA2 (diastereomers **3** and **4**) and PlpA3 (diastereomers **5** and **6**), which was mapped to core regions carrying tyrosine residues (Tyr^{21} and Tyr^{6}, respectively; numbering relates to core position). For detailed product characterization, simultaneous digestion of the His_6-PlpA3-Fx product with trypsin and chymotrypsin cleanly provided a core fragment (Ala^1 to Trp^{12}) composed of two diastereomers (**7** and **8**; Fig. 2C), which were separated by means of high-performance LC. Nuclear magnetic resonance (NMR) analysis (figs. S4 to S15 and tables S3 and S4) revealed heteronuclear two- and three-bond correlations that suggest an α-keto-β^3-Met moiety present in both diastereomers. Specifically, we observed cross peaks to the newly formed ketone and amide carbonyls with characteristic chemical shifts of δ = 196 and 165 parts per million (figs. S9 and S15), respectively, similar to those of other α-keto-β^3-Met–containing peptides (*22*). Attempts to obtain an enzymatic product enriched in one

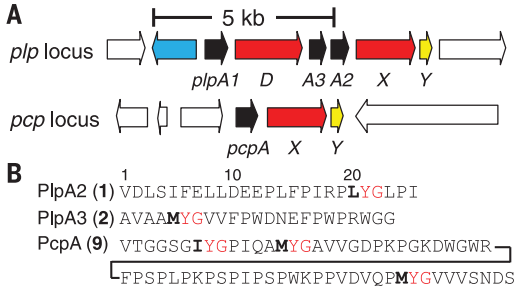

Fig. 1. The *plp* and *pcp* loci from *Pleurocapsa* spp. PCC 7319 and 7327 and the investigated core peptides. (**A**) Map of the *plp* and *pcp* loci. Black, precursor genes (*plpA1*, *A2*, *A3*, and *pcpA*); red, rSAM genes (*plpX* and *pcpX*, examined in this study, and epimerase gene *plpD*); yellow, *plpY* and *pcpY* encoding the PlpY and PcpY accessory proteins; blue, putative hydroxylase gene; white, unknown function. (**B**) Core peptide sequences from Nif11-type precursors (PlpA2, PlpA3, and PcpA) studied in this work. YG motifs and their preceding amino acids are shown in red and bold, respectively. The PlpA1 proteusin core does not contain a YG motif. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

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diastereomer were unsuccessful, in line with the tendency of α-ketoamides to tautomerize at physiological pH (*23*).

Using His_6-PlpA3-Fx, we next investigated the origin of the β-amino acid moiety by feeding various ^{13}C-labeled amino acids to expression cultures. For individual feeding experiments, labels of [1-^{13}C]Met, [U-^{13}C]Met, [1-^{13}C]Tyr, and [U-^{13}C]Tyr were detected by MS in the peptide products (figs. S16 to S19). NMR-based characterization of the purified core fragment **8** (PlpA3, residues 1 to 12) revealed enhancements of ^{13}C signals, indicating a fully intact Met unit with only C1 of Tyr retained, accounting for the amide carbonyl in the product (figs. S16 to S19). These

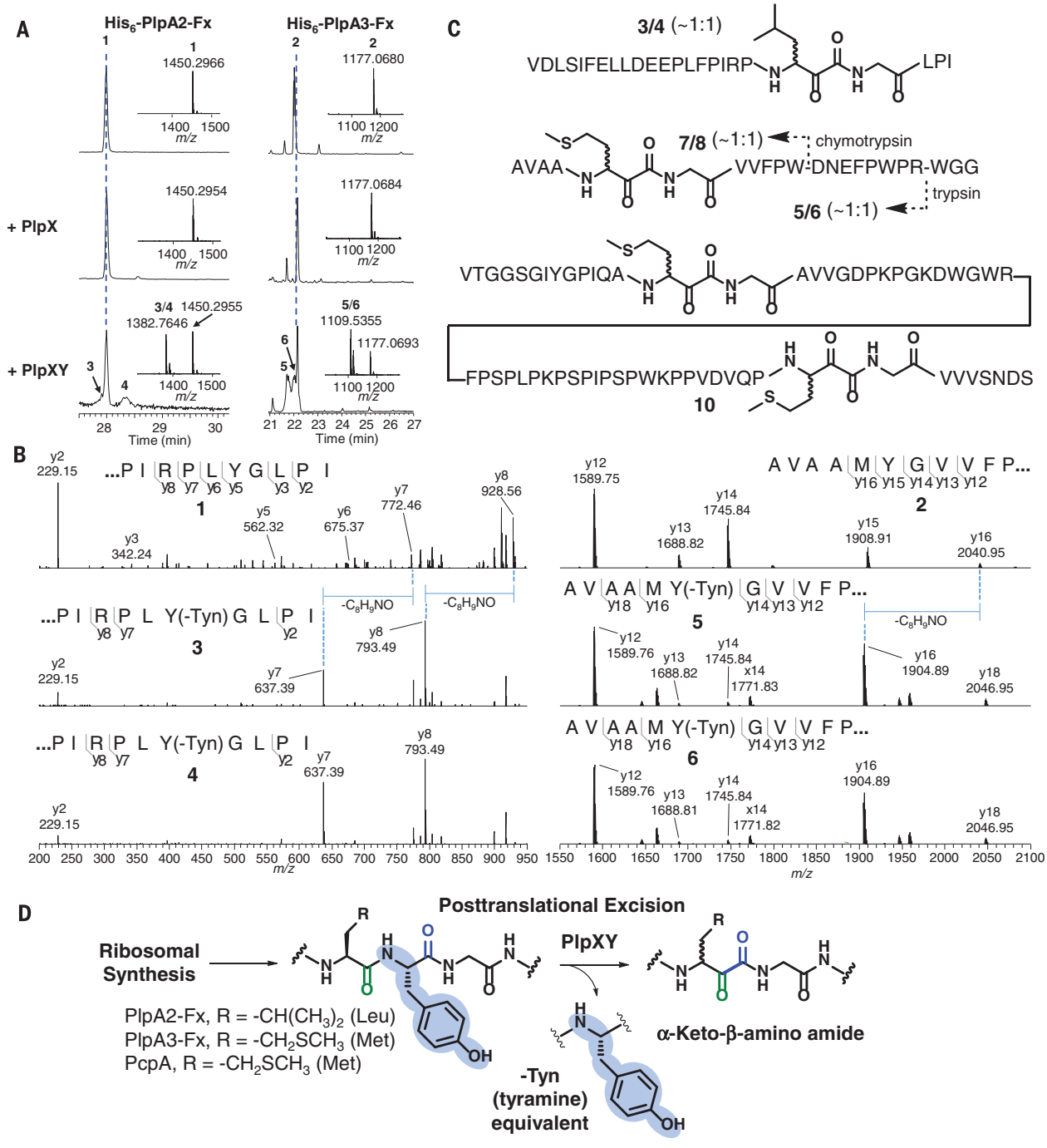

Fig. 2. Detection of PlpX activity by coexpression in *E. coli*. (**A**) Total ion chromatograms from trypsin digests of His_6-PlpA2-Fx and His_6-PlpA3-Fx, indicating the starting material (**1** and **2**) in all runs. New products **3** to **6** are only detected in coexpression experiments with PlpX and PlpY. The inlays are extracted mass spectra (retention time = 27.6 to 28.6 min for PlpA2-Fx and 21.3 to 22.5 min for PlpA3-Fx). (**B**) MS/MS spectra for **1** to **6** derived from LC-MS/MS to localize the modification. -Tyn indicates loss of C_8H_9NO. *m/z*, mass/charge ratio. (**C**) Peptide fragments (**3** to **6**) detected in (A). Products **5** and **6** were obtained from trypsin digest and **7** and **8** from combined trypsin and chymotrypsin digest. Products **3** and **4**, **5** and **6**, and **7** and **8** are pairs of epimers differing at the newly formed stereochemically labile β position. (**D**) Net reaction catalyzed by PlpX. The products lack one equivalent of tyramine formally excised from the backbone. The keto carbonyl group shown in green was selectively labeled with [1-^{13}C]Met and [U-^{13}C]Met, whereas the amide carbonyl shown in blue was selectively labeled with [1-^{13}C]Tyr and [U-^{13}C]Tyr (figs. S16 to S19).

data confirm that PlpX catalyzes an unusual reaction involving tyramine excision from the backbone and reconnection of the remaining protein sections to generate β-amino acids (Fig. 2, C and D). β-Amino acids with or without α-keto groups are only known for nonribosomal and polyketide pathways (fig. S20), where they are integrated by direct incorporation of β-residues, amination of polyketide moieties (*24*), or by as-yet uncharacterized net C1 extension mechanisms (*25*, *26*).

C–C bond cleavage is known for various rSAM enzymes acting on free amino acids (*27*–*33*)—for example, the hydrogenase maturation protein HydG cleaving Tyr to *p*-cresol, CO, and CN^- (*30*). These lyases are only distantly related (<15% amino acid identity) to PlpX and do not contain a SPASM domain. We hypothesized that the PlpXY mechanism may involve formation of *p*-cresol, as for HydG. However, many attempts to detect *p*-cresol or structural variants with or without nitrogen in in vivo coexpressions were unsuccessful. In RiPP biosynthesis, rSAM and SPASM domain–containing proteins catalyze diverse reactions (*34*). In protein alignment and network analyses of PlpX and other SPASM domain proteins, MftC, catalyzing a C-terminal oxidative decarboxylation and Tyr-Val C–C cross-link event (*35*), was the closest characterized homolog (figs. S21 and S22).

To obtain insights into the prevalence and distribution of this modification, we analyzed bacterial (meta)genomes deposited in GenBank, as well as 93 newly sequenced cyanobacteria from the Pasteur Culture Collection, for genes that associate with the same TIGRFAM family as the splicase PlpX. We detected 53 positives in 436 phylogenetically diverse cyanobacteria, almost all of them neighboring *nif11*- and *plpY*-type genes (figs. S23 and S24 and table S5). All precursors comprise between one and three Tyr residues that are part of conserved "XYG" motifs also present in the splice sites of PlpA2 and PlpA3. Additional members of TIGRFAM rSAM_nif11_3 also occur in various proteobacteria and *Frankia* spp. actinomycetes (table S5). Each splicase gene was consistently flanked by a small gene encoding YG peptides. Notable examples are genes from *Thiothrix* spp. for proteins with up to five YG copies. Neither Nif11-type leaders nor PlpY homologs were identified in these noncyanobacterial systems. We detected 27 further rSAM gene candidates in the TARA Ocean metagenomic data set (*36*), for which six contigs were long enough to reveal adjacent genes for YG peptides (table S5). These data suggest that various prokaryotes are able to generate β-amino acid–containing products. To test whether multiple YG sites direct several splicing events in one precursor, we coproduced His_6-PcpA bearing three YG motifs (**9**; Fig. 1B) from the thermophile *Pleurocapsa* sp. PCC 7327 (Fig. 1A and fig. S24) with its splicase gene partners *pcpX* and *pcpY*. Proteolysis and LC-MS analysis (figs. S25 and S26) revealed two modifications at the C-terminal YG motifs (Tyr^{15} and Tyr^{56}) to give product **10** (Fig. 2C and figs. S27 to S29), demonstrating that a single splicase can catalyze excisions at multiple sites in one protein. The fate of this moiety and the structure of the natural products from these gene clusters remain cryptic and are under investigation in our laboratory.

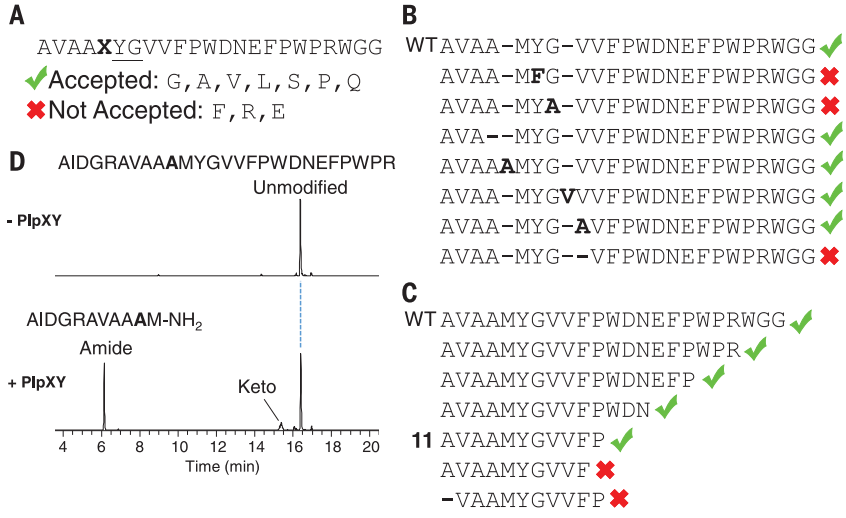

Fig. 3. Mutational analysis and detection of amide intermediate. (**A**) Mutations at **X** to install a variety of β-amino acids. (**B**) Mutations within and around the YG motif. Bold indicates mutated residues; dashes at conserved sites show deletions. (**C**) Truncations to yield a minimal core motif that is excised. (**D**) Detection of amide intermediate from His_6-PlpA3-Fx-4A5 insertion mutant. Green check marks indicate sequence conversion. Red X's indicate minimal or no conversion. WT, wild-type core sequence.

The introduction of α-keto-β-amino acids into gene-encoded precursors has considerable potential for applications in drug discovery, chemical biology, and synthetic biology, which we started to explore in a series of experiments. Eight different residues (where X is Ala, Met, His, Leu, Ile, Cys, Phe, or Lys) are part of the currently known cyanobacterial XYG motifs, and six further residues (where X is Gly, Val, Ser, Asp, Glu, or Arg) occur in other bacteria (table S5). To evaluate the potential of PlpX to generate diverse β-residues, we constructed ten Met substitution mutants at the MYG site of His_6-PlpA3-Fx (Fig. 3A). Of these, seven (Gly, Val, Leu, Ser, Ala, and the not yet naturally observed Pro and Gln) were converted, whereas Phe, Glu, and Arg mutants were not at all or only poorly accepted (figs. S30 to S39 and table S6). Various insertion, deletion, or substitution mutations surrounding the XYG motif were generally tolerated (Fig. 3B and figs. S40 to S44), but mutations within YG abolished splicing (Fig. 3B, figs. S45 and S46, and table S6). We also generated His_6-PlpA3-Fx truncation variants (Fig. 3C, figs. S47 to S52, and table S6) to identify a minimal core sequence converted by PlpXY. These studies defined an 11-residue sequence (**11**) that is accepted, suggesting opportunities to introduce α-ketoamides into peptides and proteins in a motif-based fashion. During these mutational analyses, we also gained initial insights into the nature of the excision reaction. We noticed that one of the point mutant coexpressions (His_6-PlpA3-Fx-4A5 plus PlpXY) yielded truncated C-terminal Met5-amide as by-product (Fig. 3D and fig. S53), which was not observed from a wild-type precursor. This shunt product might arises from inefficient conversion of an imine intermediate (e.g., a dehydroglycine moiety) that might form after initial radical cleavage of the tyrosine side chain, analogous to HydG catalysis (fig. S54) (*30*).

Two strategies to genetically incorporate reactive carbonyls use evolved tRNA–aminoacyl tRNA synthetase pairs (*37*) and the aldehyde chemical tag (*38*). To test the potential of PlpX for orthogonal labeling, the His_6-PlpA3-Fx ketoamide was converted in vitro to the corresponding oxime in the presence of methoxyamine (fig. S55). In addition, the ketoamide was conjugated to fluorescein-5-thiosemicarbazide (**12**) under mild conditions to give the corresponding fluorescent product **13** (Fig. 4A and fig. S56).

Natural (nonribosomal; fig. S20) and synthetic products containing α-ketoamide moieties show diverse bioactivities (*39*). Of particular medical importance is the inhibition of cysteine and serine proteases by reversible binding to the keto group. Industrial screening of synthetic ketoamide peptide libraries identified CVS 4453 (**14**) as a hepatitis C virus protease inhibitor lead. Further optimization provided boceprevir **15** (Fig. 4B), an approved drug for the treatment of chronic hepatitis C infections (*40*–*42*). We generated a core related to **14** by replacing the first five residues within His_6-PlpA3-Fx to give engineered precursor **16**. This precursor contains six non-native residues N-terminally flanking the YG motif. Coproduction with PlpXY provided the corresponding ketoamide **17** with a conversion comparable to that of His_6-PlpA3-Fx (fig. S57). This result suggests the potential of using synthetic biology platforms to access and screen genetically encoded ketoamide pharmacophore libraries for drug discovery.

We demonstrate a naturally occurring splicing reaction that introduces diverse and multiple α-keto-β-amino acids into proteins. This work opens multiple avenues for applications in chemistry

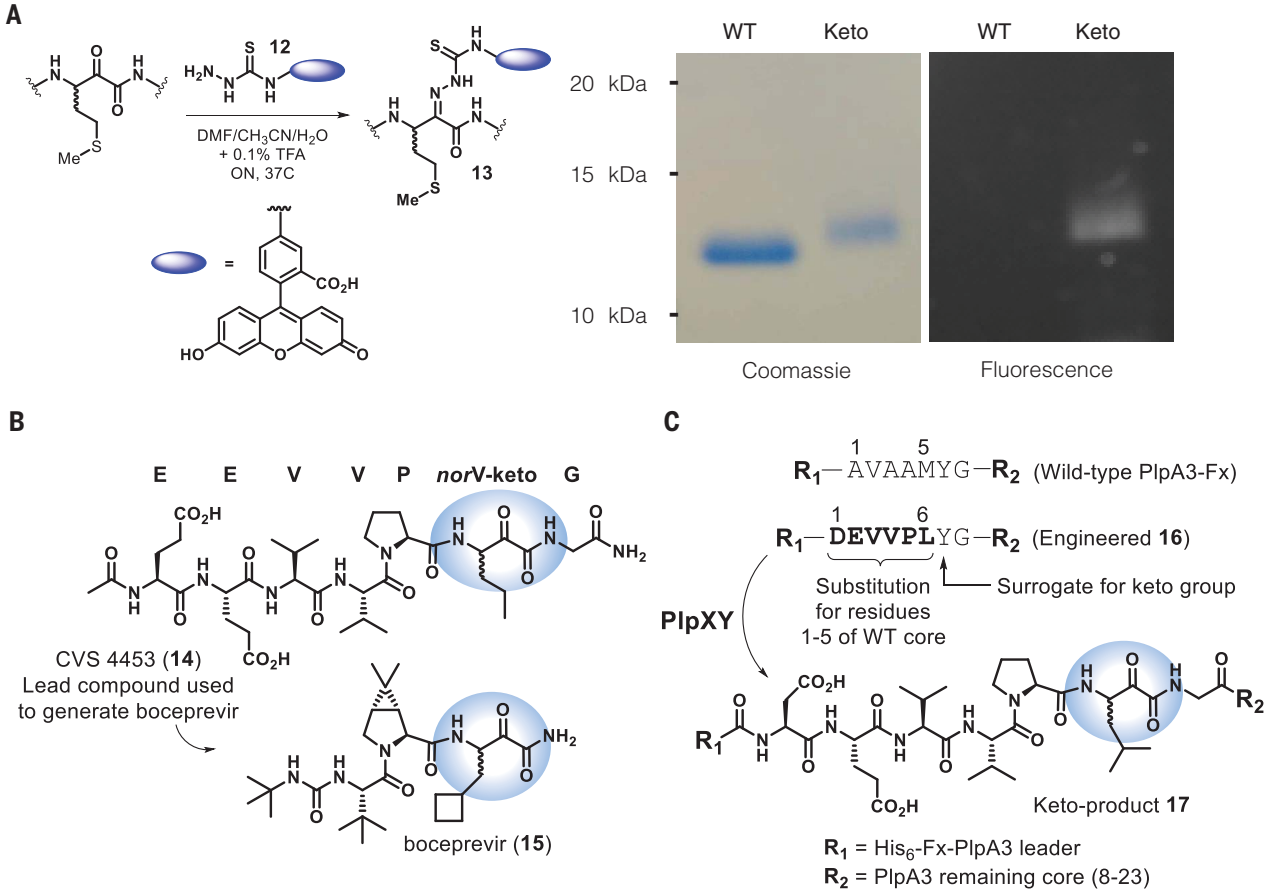

Fig. 4. Applications for tyramine splicing. (**A**) Conjugate formation to a fluorogenic probe (fluorescein thiosemicarbazide **12**) to give thiosemicarbazone **13**. WT, unmodified His_6-PlpA3-Fx; Keto, same precursor modified by PlpXY. DMF, *N*,*N*′-dimethylformamide; TFA, trifluoroacetic acid. (**B**) Synthetic hepatitis C virus protease inhibitors. CVS 4453 **14** was a lead compound used to generate boceprevir **15**. (**C**) Introduction of a genetically encoded protease inhibitor sequence into His_6-PlpA3-Fx. Tyr is located at the position of the keto group to be introduced. Coproduction of precursor **16** with PlpXY gave the corresponding ketoamide **17** (fig. S57).

and biology and highlights how bioinformatic analyses can streamline experiments to discover pathways and transformations that change the way we view fundamental biology.

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SUPPLEMENTARY MATERIALS

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QUANTUM OPTICS

Observation of three-photon bound states in a quantum nonlinear medium

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Bound states of massive particles, such as nuclei, atoms, or molecules, constitute the bulk of the visible world around us. By contrast, photons typically only interact weakly. We report the observation of traveling three-photon bound states in a quantum nonlinear medium where the interactions between photons are mediated by atomic Rydberg states. Photon correlation and conditional phase measurements reveal the distinct bunching and phase features associated with three-photon and two-photon bound states. Such photonic trimers and dimers possess shape-preserving wave functions that depend on the constituent photon number. The observed bunching and strongly nonlinear optical phase are described by an effective field theory of Rydberg-induced photon-photon interactions. These observations demonstrate the ability to realize and control strongly interacting quantum many-body states of light.

Bound states of light quanta have been proposed to exist in specifically engineered media with strong optical nonlinearities (*1*–*5*). In recent times, photonic dimers have been observed experimentally (*6*). Such bound states of photons can be viewed as quantum solitons (*7*, *8*), which are shape-preserving wave packets enabled by the cancellation of nonlinear and dispersive effects. In contrast to classical solitons, where the self-consistent shape varies smoothly with total pulse energy, quantum solitons have optical nonlinearity that is strong enough for the wave packet shape to depend on the constituent number of photons in a quantized manner (*7*, *8*). The creation of quantum solitons not only represents an important step in fundamental studies of photonic quantum matter (*6*, *9*, *10*) but also may enable new applications in areas ranging from quantum communication to quantum metrology (*11*, *12*).

We use an ultracold atomic gas as a quantum nonlinear medium to search for a photonic trimer. This medium is experimentally realized by coupling photons to highly excited atomic Rydberg states by means of electromagnetically induced transparency (EIT). The resulting hybrid excitations of light and matter—Rydberg polaritons—inherit strong interactions from their Rydberg components and can propagate with very low loss at slow group velocity v_g (*13*–*15*). The nonlinearity arises when photons are within a Rydberg blockade radius r_B of one another, where strong interactions between atoms in the Rydberg state (*16*) shift the Rydberg level out of the EIT resonance, blocking the excitation of more than one Rydberg atom within r_B. In the dissipative regime (on atomic resonance), the blockade results in photon loss and antibunching (*17*–*19*). In the dispersive, off-resonant regime, the index of refraction varies with the separation between photons, resulting in an attractive force (*6*).

Our experimental setup (*20*) (Fig. 1, A and B) consists of a weak quantum probe field at wavelength λ = 780 nm and waist w = 4.5 μm coupled to the $100S_{1/2}$ Rydberg state via a strong 479-nm control field in the EIT configuration (Fig. 1B). The interactions occurred in a cloud of laser-cooled ^{87}Rb atoms in a far-detuned optical dipole trap. Measurements are conducted at a peak optical depth $OD_B \simeq 5$ per blockade radius r_B = 20 μm. To suppress dissipative effects, we work at a large detuning $\Delta \geq 3\Gamma$ from atomic resonance (Γ is the population decay rate of the $5P_{3/2}$ state; see Fig. 1B) and at a control laser Rabi frequency where the transmission through the medium is the same with and without EIT, but the phase differs appreciably (Fig. 1C). Consequently, the transmission hardly varies with probe photon rate (Fig. 1D, top), whereas a strongly rate-dependent phase with a slope of 0.40(±0.07) rad·μs is observed (Fig. 1D, bottom).

The quantum dynamics of interacting photons are investigated by measuring the three-photon correlation function and phase. Because dispersion outside of the atomic medium is negligible, any amplitude and phase features formed inside the nonlinear medium are preserved outside and can be detected in the form of photon number and phase correlations. The third-order photon correlation function has been measured previously in coupled atom-cavity and quantum dot–cavity systems, as well as in nonclassical states of three photons such as the Greenberger-Horne-Zeilinger and N00N states (*12*). In our approach, we split the light onto three single-photon counting modules. Furthermore, by mixing a detuned local oscillator into the final beam splitter, we can also perform a heterodyne measurement in one of the detection arms (Fig. 1A). To connect the observed correlations to the physics of interacting Rydberg polaritons, we consider a state containing up to three photons

$$|\psi\rangle = |0\rangle + \int dt_1\, \psi_1(t_1)|t_1\rangle + \int dt_1 dt_2\, \psi_2(t_1,t_2)|t_1,t_2\rangle + \int dt_1 dt_2 dt_3\, \psi_3(t_1,t_2,t_3)|t_1,t_2,t_3\rangle \quad (1)$$

where $|t_1,\cdots,t_N\rangle = \frac{1}{N!}a^\dagger(t_1)\cdots a^\dagger(t_N)|0\rangle$, $a^\dagger(t)$ is the photon creation operator of the time bin mode t, and N is the number of photons. The correlation functions (Fig. 2) can be related to the wave functions as $g^{(2)}(t_1,t_2) = \frac{|\psi_2(t_1,t_2)|^3}{|\psi_1(t_1)|^2|\psi_1(t_2)|^2}$ and $g^{(3)}(t_1,t_2,t_3) = \frac{|\psi_3(t_1,t_2,t_3)|^2}{|\psi_1(t_1)|^2|\psi_1(t_2)|^2|\psi_1(t_3)|^2}$. We refer to the phase $\tilde{\phi}^{(N)}$ of the N-photon wave function ψ_N as the N-photon phase—namely, $\tilde{\phi}^{(1)}(t_1) = \mathrm{Arg}[\psi_1(t_1)]$, $\tilde{\phi}^{(2)}(t_1,t_2) = \mathrm{Arg}[\psi_2(t_1,t_2)]$, and $\tilde{\phi}^{(3)}(t_1,t_2,t_3) = \mathrm{Arg}[\psi_3(t_1,t_2,t_3)]$. The N-photon phase is obtained from the phase of the beat note signal on the third detector, conditioned on having observed $N-1$ photons in the other two detectors. The conditional phase relative to N uncorrelated photons (i.e., the nonlinear part of the phase) is denoted as $\phi^{(N)}$ (Fig. 3).

The experimentally measured $g^{(3)}$ function (Fig. 2, A and B) displays a clear bunching feature: The probability to detect three photons within a short time (≲25 ns) of one another is six times higher than for noninteracting photons in a laser beam. The increase at $t_1 = t_2 = t_3$ is accompanied by a depletion region for photons arriving within ~0.7 μs of one another, particularly visible along the lines of two-photon correlations ($t_i = t_j \neq t_k$, where t_i, t_j, and t_k are the photon detection times at detectors D_i, D_j, and D_k, respectively, and i, j, and k are permutations of 1, 2, and 3) (Fig. 2A): This depletion region is caused by the inflow of probability current toward the center $t_1 = t_2 = t_3$. Figure 2B compares the two-photon correlation function $g^{(2)}(t, t+|\tau|)$ with that for three photons, of which two were detected in the same time bin, $g^{(3)}(t, t, t+|\tau|)$. The trimer feature is approximately a factor of 2 narrower than the dimer feature, showing that a photon is attracted more strongly to two other photons than to one. Figure 2C illustrates the binding of a third photon to two photons that are detected with a time separation T. If T exceeds the dimer time scale τ_2, then the third photon binds independently to either

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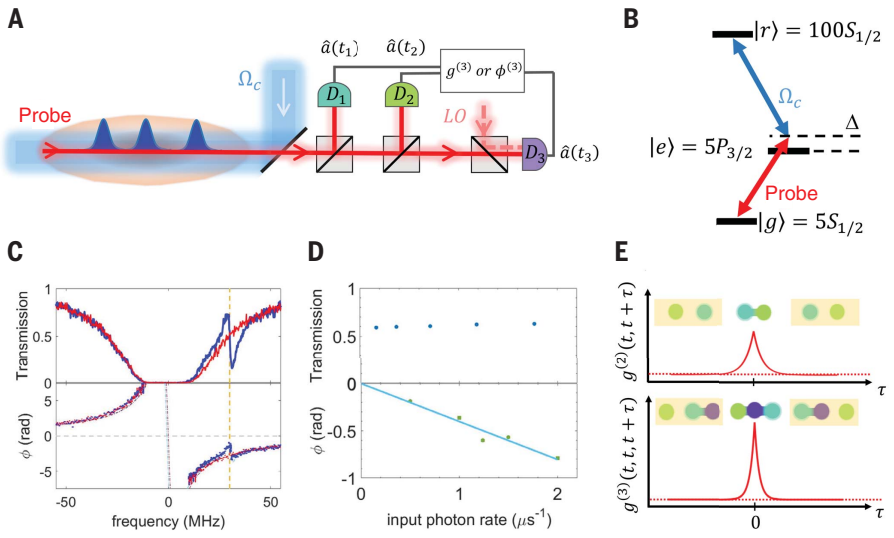

Fig. 1. Qualitative descriptions of the experiment. (**A** and **B**) Setup and atomic-level scheme. The atoms are optically pumped into the hyperfine (F) and magnetic (m_F) sublevel $|g\rangle = |5S_{1/2}, F = 2, m_F = 2\rangle$. The weak coherent probe light is coupled to the Rydberg state $|r\rangle = |100S_{1/2}, m_J = 1/2\rangle$ (m_J, projection of the total electron angular momentum along the quantization axis) via an intermediate state $|e\rangle = |5P_{3/2}, F = 3, m_F = 3\rangle$, with linewidth $\Gamma/2\pi$ = 6.1 MHz, by means of a counterpropagating control field that is detuned by fj below the resonance frequency of the upper transition, $|e\rangle \rightarrow |r\rangle$. Strong interactions between probe photons are detected via photon correlations of the transmitted light, which is split onto three single-photon detectors with equal intensities. To perform phase measurements, a local oscillator is mixed into detector D_3. $\hat{a}(t)$, photon annihilation operator of the time bin mode t; Ω_c, control laser Rabi frequency; g, correlation function; ϕ, phase; LO, local oscillator. (**C**) Transmission (top) and phase ϕ (bottom) as a function of probe frequency measured at a low input photon rate (0.5 μs^{-1}). ϕ is measured without conditioning on the detection of other photons. The control laser is set at $\Delta/2\pi$ = 30 MHz below the $|e\rangle \rightarrow |r\rangle$transition, with Rabi frequency $\Omega_c/2\pi$ = 10 MHz. The blue and red traces are from measurements with and without a control beam, respectively. The blue and red dashed lines in the bottom graph are theoretical expectations. The vertical yellow dashed line marks electromagnetically induced transparency (EIT) resonance. (**D**) Rate dependence of transmission (top) and unconditional phase (bottom) on the two-photon resonance $|g\rangle \rightarrow |r\rangle$, with a one-photon detuning of $\Delta/2\pi$ = 30 MHz and a control Rabi frequency $\Omega_c/2\pi$ = 10 MHz. Whereas the transmission is rate-independent, the phase is strongly rate-dependent (slope is 0.4 rad·μs). (**E**) Schematic correlation functions for two (top) and three (bottom) photons as a function of their time separation τ. The attractive interaction leads to photon bunching, with three photons being more tightly bound together than two photons.

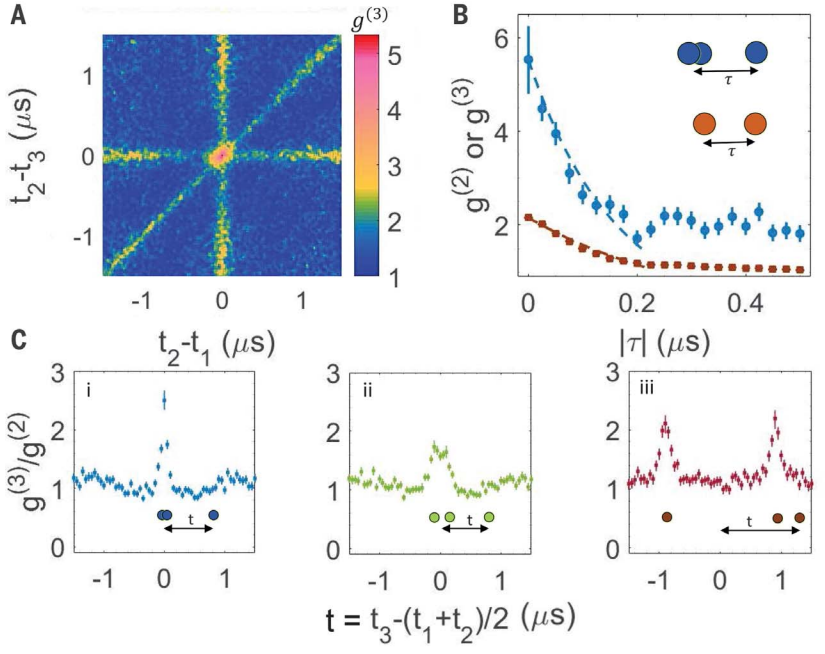

Fig. 2. Photon correlation functions with tighter bunching due to the three-photon bound state. Photon correlation functions were measured on EIT resonance and at one-photon detuning $\Delta/2\pi$ = 30 MHz, control Rabi frequency $\Omega_c/2\pi$ = 10 MHz, an input photon rate of 1 μs^{-1}. (**A**) 2D representation of the three-photon correlation function $g^{(3)}(t_1, t_2, t_3)$, with t_i being the photon detection time at detector D_i. Three-photon bunching corresponds to the central region, two-photon bunching to the stripes. (**B**) $g^{(3)}(t, t, t + |\tau|)$ (blue data points) and $g^{(2)}(t, t + |\tau|)$ (brown data points), with the decay constants calculated from the exact solution for the bound states τ_3^c = 0.16 μs and τ_2^c = 0.32 μs, respectively (dashed lines). The calculated exponential decay is scaled to match the initial point of the measured intensity correlation functions. The approximately twofold smaller decay length of the three-photon correlation function shows that a photon is more strongly bound to two photons than to one. The fitted exponential decay constants with zero offset for $g^{(3)}$ and $g^{(2)}$ are τ_3 = 0.14(2) μs and τ_2 = 0.31(6) μs, respectively, in agreement with the calculated values. (**C**) Three representative plots of $g^{(3)}(t_1, t_2, t_3)/g^{(2)}(t_1, t_2)$ for fixed time separation $T \equiv |t_1 - t_2|$ = 0 μs (i), T = 0.2 μs (ii), and T = 1.8 μs (iii), within a 50-ns window. As the two photons get farther and farther away from each other, the sharply decaying $g^{(3)}$ function transitions to a slower decaying $g^{(2)}$ function. For intermediate time separations (ii), interference occurs between all states, including the dimer and trimer. All permutations of the detectors are used to generate the data in (B) and (C). Error bars indicate 1 SD.

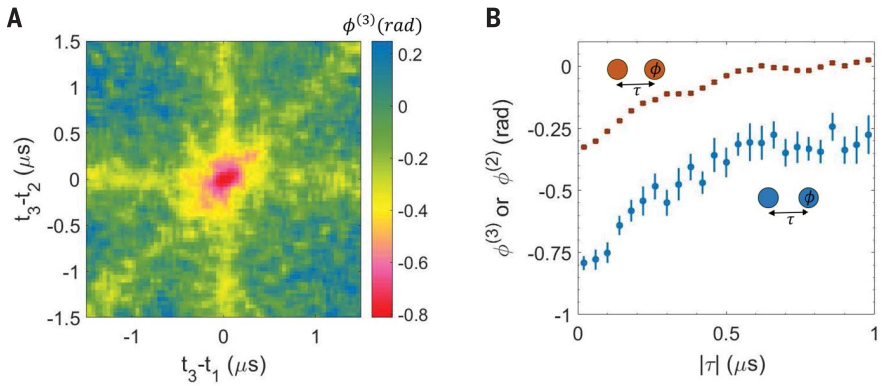

Fig. 3. Larger nonlinear phase for three photons. Nonlinear phase was measured under identical conditions as the data in Fig. 2. (**A**) Conditional phase $\phi^{(3)}(t_1,t_2,t_3)$, where t_1 and t_2 correspond to photon detection events at detectors D_1 and D_2, and a heterodyne measurement is performed on detector D_3 at time t_3. (**B**) Diagonal cut $\phi^{(3)}(t,t,t+|\tau|)$ (blue), with the two conditioning probe photons within 40 ns of each other, and $\phi^{(2)}(t,t+|\tau|)$ (brown), showing a larger phase when conditioning on two other near-simultaneous photons [$\phi^{(3)}$] than on one near-simultaneous photon [$\phi^{(2)}$]. $\phi^{(N)}$ is referenced to its own average value when all N photons are too far apart to be correlated. Specifically, $\phi^{(2)}(t_1,t_2)\equiv\tilde{\phi}^{(2)}(t_1,t_2)-\left(\tilde{\phi}^{(1)}(t_1)+\tilde{\phi}^{(1)}(t_2)\right)\xrightarrow{|t_1-t_2|\to\infty}0$ and $\phi^{(3)}(t_1,t_2,t_3)\equiv\tilde{\phi}^{(3)}(t_1,t_2,t_3)-\left(\tilde{\phi}^{(1)}(t_1)+\tilde{\phi}^{(1)}(t_2)+\tilde{\phi}^{(1)}(t_3)\right)\xrightarrow{|t_i-t_j|\to\infty,\forall i\neq j}0$. At large $|\tau|$, $\phi^{(3)}$ asymptotically goes to $\phi^{(2)}(t,t)$ because $\phi^{(3)}(t,t,t+|\tau|)\xrightarrow{|\tau|\to\infty}\tilde{\phi}^{(2)}(t,t)+\tilde{\phi}^{(1)}(t+|\tau|)-\left(\tilde{\phi}^{(1)}(t)+\tilde{\phi}^{(1)}(t+|\tau|)\right)=\phi^{(2)}(t,t)$. Error bars indicate 1 SD.

photon, whereas for $T<\tau_2$ the two peaks merge into a single, more tightly bound trimer. This is analogous to the binding of a particle to a double-well potential as the distance between the wells is varied, because the polaritons can be approximately described as interacting massive particles moving at a finite group velocity (*6*).

The dispersive and distance-dependent photon-photon interaction also manifests itself in a large conditional phase shift that depends on the time interval τ between the detection of the conditioning photons (at times $t_1=t_2=t$) and the phase measurement on detector D_3 at time t_3. We observe a conditional phase shift $\phi^{(3)}(t,t,t+|\tau|)$ for the trimer near $\tau=0$ (Fig. 3A) that is substantially larger than the dimer phase shift $\phi^{(2)}(t,t+|\tau|)$ (Fig. 3B). This confirms that the interaction between a photon and a dimer is stronger than that between two photons.

To understand these results quantitatively, we apply an effective field theory (EFT) (*21*) that describes the low-energy scattering of Rydberg polaritons. This EFT gives us a one-dimensional (1D) slow-light Hamiltonian density with a contact interaction

$$\mathcal{H}=-\hat{\psi}^{\dagger}\left(i\hbar v_g\frac{\partial}{\partial_z}+\frac{\hbar^2}{2m}\frac{\partial^2}{\partial_z^2}\right)\hat{\psi}-\frac{\hbar^2}{ma}\hat{\psi}^{\dagger 2}\hat{\psi}^2 \quad (2)$$

where v_g is the group velocity inside the medium, $m=-\hbar\Omega_c^2/(8\Delta v_g^2)$ is the effective photon mass, $\hbar$ is Planck's constant h divided by 2π, a is the scattering length, Ω_c is the control laser Rabi frequency, and Δ is the one-photon detuning. For weak interactions, $a\approx 15.28\left(\frac{1}{OD_B}\frac{\Delta}{\Gamma}\right)^2 r_B$ (*21*, *22*). The single-mode, 1D approximation is justified by the small size of the probe waist compared with the blockade radius (r_B), whereas the corresponding Rayleigh range is similar to the atomic cloud size (with both being much larger than r_B). The latter condition implies that the incoming light has small transverse momenta components, whereas the former condition ensures that the dominant scattering occurs colinearly with the probe beam. Combined with the large effective transverse mass in this system (*23*), the residual transverse dynamics arising from interactions are effectively frozen out on the time scale of the experiment (*6*, *15*, *18*, *24*). In the limit where the average longitudinal distance between photons is larger than r_B, such that the low-momentum approximation underlying the EFT is valid, the 1D contact model provides an accurate description whenever $a\gg r_B$, the microscopic range of the two-body potential. For our parameters, we find that this condition is well satisfied as $a\gtrsim 10r_B$. $\hat{\psi}$ is a quantum field annihilation operator, which corresponds to a photon outside the medium and a Rydberg polariton inside. For our blue-detuned probe, the effective mass is negative and the interaction is repulsive. This situation maps onto a system with a positive mass and attractive interaction. The bound states can be determined from the exact solution of this model for finite particle numbers (*25*, *26*), resulting in the correlation functions $g^{(3)}(t_1,t_2,t_3)\propto e^{-\frac{|t_1-t_2|}{a/(2v_g)}}e^{-\frac{|t_2-t_3|}{a/(2v_g)}}e^{-\frac{|t_1-t_3|}{a/(2v_g)}}$ and $g^{(2)}(t_1,t_2)\propto e^{-\frac{|t_1-t_2|}{a/(2v_g)}}$.

In the case $t_1=t_2=t$, we find that $g^{(3)}(t,t,t+|\tau|)\propto e^{-2\frac{|\tau|}{a/(2v_g)}}$, implying that the width of three-photon wave packet [corresponding to $g^{(3)}$] is half that of $g^{(2)}$ for the same experimental conditions, in agreement with experimental observations. We calculate $a/(2v_g)=0.32\,\mu$s for our measured experimental parameters (*27*) and find it to be consistent with data (Fig. 2B, dashed lines). Following the quantum quench at the entry of the medium, the initial state is decomposed into the bound state and the continuum of scattering states (*6*). Near $\tau=0$, the scattering states dephase with each other, whereas the bound state propagates without distortion (*27*). This leads to a small contribution of scattering states in this region, with the bound state dominating the $g^{(3)}$ function. The observed value of $g^{(3)}(0)$ is not universal, as it is affected by the contributions from long-wavelength scattering states and nonlinear losses in the system and therefore depends on the atomic density profile of the medium. The dimer and trimer binding energies can be estimated as $E_2=-\frac{\hbar^2}{ma^2}=h\times 0.2\,\mathrm{MHz}$ and $E_3=4E_2$, respectively. This binding energy is ~10^{10} times smaller than in diatomic molecules such as NaCl and H_2 but is comparable to Feshbach (*28*) and Efimov (*29*) bound states of atoms with similar mass m and scattering length a. To further characterize the three-photon bound state, we consider the phase ratio $\phi^{(3)}/\phi^{(2)}$. For the bound-state contribution to the conditional phase $\phi^{(3)}(t,t,t)\left(\phi^{(2)}(t,t)\right)$, the Hamiltonian of Eq. 2 predicts a phase that equals the trimer binding energy multiplied by the propagation time in the medium. Thus, from the bound-state contributions, one would expect a ratio $\phi^{(3)}/\phi^{(2)}=4$, independent of the atom-light detuning Δ. Although the observed ratio (Fig. 4B) is approximately constant, it is smaller than 4.

The observed deviation is probably due to the two contributions of comparable magnitude. One correction arises from the scattering states, or equivalently, from the fact that our Rydberg medium (~130 μm) is comparable in size to the two-photon bound state (~280 μm). For a medium that is short compared with the bound state, one expects the ratio to be 3, consistent with a dispersionless Kerr medium (*30*). The other, more fundamental, correction may be due to a contribution that does not arise from pairwise interactions, effectively representing a three-photon force. Specifically, when all three photons are within one blockade radius of one another, there can be only one Rydberg excitation, and the potential cannot exceed the value corresponding to that of two photons (*21*, *31*). This saturation effect manifests itself as a short-range repulsive effective three-photon force that, according to our theoretical analysis (*27*), results in a reduction of $\phi^{(3)}/\phi^{(2)}$ below 3. The corresponding correction to the bound state is smaller in the weakly interacting regime relevant to these experiments (*31*). This explains why the effective three-photon force has a relatively weak effect on the bunching of $g^{(3)}(|\tau|<0.2\,\mu\mathrm{s})$, which is dominated by the bound state. Both the scaling arguments and numerical evidence indicate that the effective three-photon force contributes to the three-body scattering amplitudes more strongly than two-body finite range effects in this regime (*21*).

To quantitatively understand these effects, the EFT is modified to include the estimated

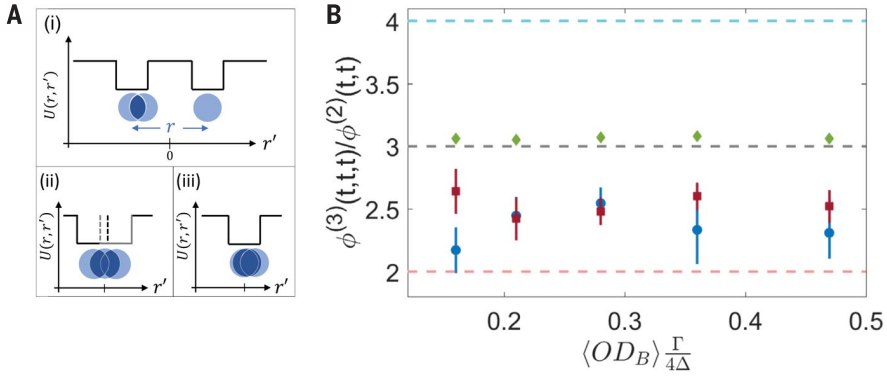

Fig. 4. Comparison of the phase ratio with the effective field theory (EFT) predictions. (**A**) Potential (solid black and gray lines) that the third photon, at position r', experiences because of the other two photons, at positions $\pm r/2$. (i) When the two photons are separated by more than twice the blockade radius ($r > 2r_B$), each of them creates its own square potential with a width of $2r_B$. (ii) When the two photons overlap ($r_B < r < 2r_B$), the potential is partially saturated. Dashed lines denote the overlap of the two interaction potentials. (iii) When the two photons are within one blockade radius ($r < r_B$), because there can be no more than one Rydberg excitation within r_B, the potential is not deeper than that created by one photon. Therefore, we overestimate the attractive potential by considering pairwise interaction only, and a repulsive effective three-photon force is required to correctly account for the saturation of the Rydberg blockade. U, interaction potential between two photons. (**B**) Measured phase ratio $\phi^{(3)}(t,t,t)/\phi^{(2)}(t,t)$ (blue) and EFT predictions (with the effective three-photon force in red; without in green) as a function of $\langle OD_B \rangle \frac{\Gamma}{4\Delta}$ where $\langle\rangle$ refers to the average over the Gaussian profile of the atomic density, and OD_B is optical depth per blockade radius. The quantity $\langle OD_B \rangle \frac{\Gamma}{4\Delta}$ is a quantitative measure of the interaction strength in this system. The control Rabi frequency $\Omega_c/2\pi$ = {22, 18, 10, 10, 8} MHz for $\Delta/2\pi$ = {54, 42, 30, 24, 18} MHz is chosen such that the transmission is insensitive to the input photon rate (Fig. 1C). We also change the input photon rate to {0.7, 1, 1, 1.3, 2.5} photons/μs to achieve similar data-acquisition rates, because the losses are larger at smaller detunings. For a fully saturated medium, one expects $\phi^{(3)}/\phi^{(2)} = 2$, as indicated by the pink dashed line. For bound states in a long medium and no effective three-photon force, one expects $\phi^{(3)}/\phi^{(2)} = 4$, as indicated by the light blue dashed line (see text). For a dispersionless Kerr medium, one expects $\phi^{(3)}/\phi^{(2)} = 3$, as indicated by the gray dashed line. EFT results are calculated with parameters from independent measurements, and the two-photon detuning from the EIT resonance is the only parameter varied within the experimental uncertainty to fit the two-photon phase. Error bars in the EFT with the effective three-photon force arise from the variations with the choice of matching conditions for the three-body scattering amplitudes (*27*). Error bars in the experimental data indicate 1 SD.

effective three-photon force (*27*). Using the modified EFT, we compare the results with and without the repulsive effective three-photon force while also taking into account the effects due to finite medium (Fig. 4B). Including this three-photon saturation force allows the phase ratio $\phi^{(3)}/\phi^{(2)}$ to go below 3, in a reasonable agreement with the experimental observations. For fully saturated interactions between the polaritons, the interaction potential does not increase with photon number, and the phase ratio should approach 2.

The observation of the three-photon bound state, which can be viewed as photonic solitons in the quantum regime (*7*, *8*), can be extended along several different directions. First, increasing the length of the medium at constant atomic density would remove the effect of the scattering states through destructive quantum interference to larger τ and would retain only the solitonic bound-state component. Additionally, the strong observed rate dependence of $\phi^{(3)}$ may indicate that larger photonic molecules and photonic clusters could be observed with improved detection efficiency and data-acquisition rate. Furthermore, with the use of an elliptical or larger round probe beam and careful engineering of the mass along different directions, the system can be extended to two and three dimensions, possibly permitting the observation of photonic Efimov states (*32*, *33*). Finally, our medium supports only one two- or three-photon bound state, corresponding to a nonlinear phase less than π. A threefold increase in the atomic density would render the interaction potential sufficiently deep for a second bound state to appear near zero energy, which should result in resonant photon-photon scattering and a tunable scattering length (*22*). The presence of large effective N-body forces in this system opens avenues to study exotic many-body phases of light and matter, including self-organization in open quantum systems (*34*, *35*) and quantum materials that cannot be realized with conventional systems.

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SUPPLEMENTARY MATERIALS

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NEUROSCIENCE

Dentate gyrus mossy cells control spontaneous convulsive seizures and spatial memory

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Temporal lobe epilepsy (TLE) is characterized by debilitating, recurring seizures and an increased risk for cognitive deficits. Mossy cells (MCs) are key neurons in the hippocampal excitatory circuit, and the partial loss of MCs is a major hallmark of TLE. We investigated how MCs contribute to spontaneous ictal activity and to spatial contextual memory in a mouse model of TLE with hippocampal sclerosis, using a combination of optogenetic, electrophysiological, and behavioral approaches. In chronically epileptic mice, real-time optogenetic modulation of MCs during spontaneous hippocampal seizures controlled the progression of activity from an electrographic to convulsive seizure. Decreased MC activity is sufficient to impede encoding of spatial context, recapitulating observed cognitive deficits in chronically epileptic mice.

Temporal lobe epilepsy (TLE) is characterized by spontaneous seizures and an increased risk for cognitive impairments; it is the most common form of epilepsy in adults. Antiepileptic drugs are ineffective in one-third of patients (*1*), indicating the need for a more complete understanding of the mechanisms underlying seizure activity and comorbid cognitive deficits. Mossy cells (MCs) are a glutamatergic cell population in the hilus of the dentate gyrus (DG) of the hippocampus, and their partial loss is a major hallmark of TLE (*2*). However, the implications of MC loss on seizure dynamics and TLE comorbidities remain poorly understood (*3*). MCs drive both network excitation through their direct granule cell (GC) connections and network inhibition via their synapses onto interneurons (INs), but it remains unclear which of these projections dominate, particularly during seizures (*4*, *5*). We used electrophysiological recordings, closed-loop optogenetics, and behavioral tests to investigate the functional role of MCs in seizure dynamics and cognition.

To modulate MC activity, we expressed the inhibitory archaerhodopsin (ArchT) or the excitatory channelrhodopsin (ChR2) selectively in MCs in mice. For ArchT expression, we topologically targeted MCs using the wheat germ agglutinin (WGA)–Cre system (Fig. 1, A to C, and fig. S1) (*6*). For MC excitation, we injected a virus for ChR2 expression into the hilus of Crlr-Cre mice (Fig. 1, E and F) (*7*). For both strategies, opsin expression was highly specific for MCs (Fig. 1H) (*4*). We verified that the opsins responded appropriately to light (Fig. 1, D and G) and that MC functional properties were similar in mice with or without opsin expression (table S1).

To characterize the effect of MC optogenetic manipulation on DG activity, we performed in vivo juxtacellular recordings of individual DG neurons (Fig. 1I). MC activation modulated IN and GC firing (Fig. 1, J and K; figs. S2 to S7; and table S2), consistent with known MC network connectivity (*3*). We also found that MC photostimulation in the ventral hippocampus elicited a response in INs and GCs recorded in the dorsal hippocampus, confirming the ability of MCs to modulate network activity distally (figs. S2 and S3) (*3*).

We first tested how MC activity affects spontaneous electrographic, nonconvulsive seizures in a well-established model of TLE with kainic acid (KA) injected unilaterally into the left dorsal hippocampus (*8*, *9*). We used a closed-loop seizure detection and intervention method in chronically epileptic mice (*10*) to deliver a 15-s light pulse at the onset of 50% of detected seizures (Fig. 2, A and B). Which seizures received light was decided randomly, and the remaining 50% of seizures received no light (sham pulse), allowing seizures with and without optogenetic perturbation to be directly compared within each animal. For MC inhibition, we delivered light to both hemispheres to target MC somata and their projections (fig. S8), confirming beforehand that illumination of ArchT-expressing MC axon terminals reduces the amplitude of synaptically evoked excitatory postsynaptic currents in GCs (fig. S9). MC inhibition and light delivery to opsin-negative controls had no effect on electrographic seizure dynamics (Fig. 2, C and D; fig. S10; and table S3). We next examined whether optogenetic MC excitation alters electrographic seizures. To excite MCs, we delivered light to the hemisphere contralateral to the KA injection site. We found that MC activation in the dorsal hippocampus, which is directly contralateral to the KA injection site, but not MC excitation in the ventral hippocampus, reduced electrographic seizure duration (Fig. 2, E and F). This location-dependent effect is consistent with the spatial distribution of dorsal MC contralateral projections, which are denser at the septotemporal level of the parent MC soma (*3*), such that dorsal stimulation can better target cells with projections directly onto the hippocampal lamella containing the focal seizure site. Although MC stimulation in the dorsal DG is capable of controlling electrographic seizures, the effect is much weaker than with inhibition of GCs (fig. S11A and table S3), the only other excitatory cell population in the DG (*11*).

A characteristic feature of MCs is their extensive projections connecting multiple lamellae and both hippocampi (*12*). This property could endow MCs with the capability to influence seizure generalization. A prediction is that MC perturbation during electrographic seizures may be sufficient to alter the progression into more severe, widespread seizures (fig. S12) exhibiting behavioral manifestations [e.g., rearing or tonic-clonic activity, Racine scale 4 to 5 (*13*)].

We tested this hypothesis by focusing on the seizures that began as electrographic seizures, then evolved into convulsive seizures, and quantified the proportion of such seizures that occurred after MC inhibition (Fig. 3). Because these seizures are much rarer than the electrographic-only seizures (*8*), animals were recorded for ~1 to 6 months (fig. S13) to accumulate a number of electrographic-to-convulsive seizures sufficient for statistical analysis. MC inhibition during the electrographic stage significantly increased the probability of seizure generalization into overt behavioral seizures (Fig. 3, C and D). Behavioral seizures were similar in duration with or without light (Fig. 3E), indicating that MC inhibition does not alter ictal activity once it has generalized. Rather, MCs affect solely the transition between electrographic and behavioral seizures. These effects were not due to a sampling bias or light artifact, as seizure frequency was not changed when we inhibited MCs after the end of the convulsive seizures (fig. S14) or when we delivered light in opsin-negative controls (Fig. 3, C and D). The effects were not influenced by the circadian rhythm as MC modulation similarly affected seizure frequency during the daytime and nighttime (fig. S13).

To determine whether convulsive seizures could be prevented by increasing MC activity, we next stimulated ChR2-expressing MCs at the onset of electrographic seizures. Exciting MCs prevented electrographic seizures from generalizing into behavioral seizures (Fig. 3, C and D). Because DG microcircuit alterations are different in the hemispheres ipsilateral and contralateral to the KA injection site (*8*, *9*), we also targeted MCs ipsilateral to the KA injection site. We found that MC excitation in the ipsilateral hemisphere also prevented seizure generalization (Fig. 3, C and D), despite the greater degree of hippocampal sclerosis ipsilaterally, where we observed a 77% MC loss compared with a 55% MC loss contralaterally, consistent with previous studies (*9*) (fig. S15).

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We next reasoned that to control convulsive seizures, MCs likely modulate activity downstream of the DG. Because the DG extrinsic projections arise from GCs (*3*), and GCs are MC postsynaptic targets (*14*), we examined whether direct GC modulation could control generalized seizures. We found that GC inhibition had no effect on convulsive seizure occurrence (fig. S11, B and C). Conversely, GC excitation robustly induced behavioral seizures (*11*). Together, our data demonstrate that MCs and GCs, the two excitatory populations in the DG, had antithetical effects on seizure dynamics and that surviving MCs have an anticonvulsive potential even after severe MC loss.

To investigate the consequences of MC loss on cognition, we examined learning and memory processes in chronically epileptic mice and in nonepileptic mice, where we inhibited MCs. We used two well-validated assays of spatial and object memory: the object location memory (OLM) and object recognition memory (ORM) tasks (*15*). Chronically epileptic mice had significant deficits in OLM compared with nonepileptic controls and were unable to distinguish the moved object from the unmoved object, as reflected in the low discrimination index (DI) (Fig. 4A and table S4). In contrast, ORM was not impaired in epileptic mice, and their DI was similar to that of nonepileptic mice (Fig. 4B). The OLM deficits are consistent with previous studies showing that repeated generalized seizures lead to decreased accuracy in spatial discrimination performance (*16*). The poor performance of epileptic mice was not due to disinterest, because both groups explored the objects at similar levels during training (fig. S16), or to increased anxiety, as assessed using the elevated plus maze test (EPM) (fig. S17).

To determine whether MC loss alone is sufficient to impair spatial cognitive abilities, we silenced MCs in nonepileptic mice during specific stages of OLM and ORM. This approach allowed us to examine how decreased MC activity affects cognition independently of other network reorganizations observed in epilepsy (*17*). Because ArchT has excitatory effects when illuminated for long periods (*18*), we switched to halorhodopsin (eNpHR) (fig. S18) for longer MC photoinhibition.

When MCs were inhibited in eNpHR mice solely during the learning phase of the OLM task, we observed a significant reduction in later performance during testing compared with enhanced yellow fluorescent protein (eYFP) controls (Fig. 4C and fig. S19). We ruled out the possibility that this impairment was related to an effect on anxiety by assessing mouse exploration in the EPM (fig. S17). The impairment was also not due to a lack of motivation for object exploration nor to an object side preference during training (fig. S20). Therefore, MC activity is necessary during spatial memory encoding. In contrast, silencing MCs during the testing phase of the OLM task did not impair performance, indicating that MC activity is not required during spatial memory retrieval (Fig. 4D). Finally, we assessed whether MCs are involved in nonspatial ORM. MC inhibition during learning or testing of ORM did not interfere with ORM task performance (Fig. 4, E and F). Together,

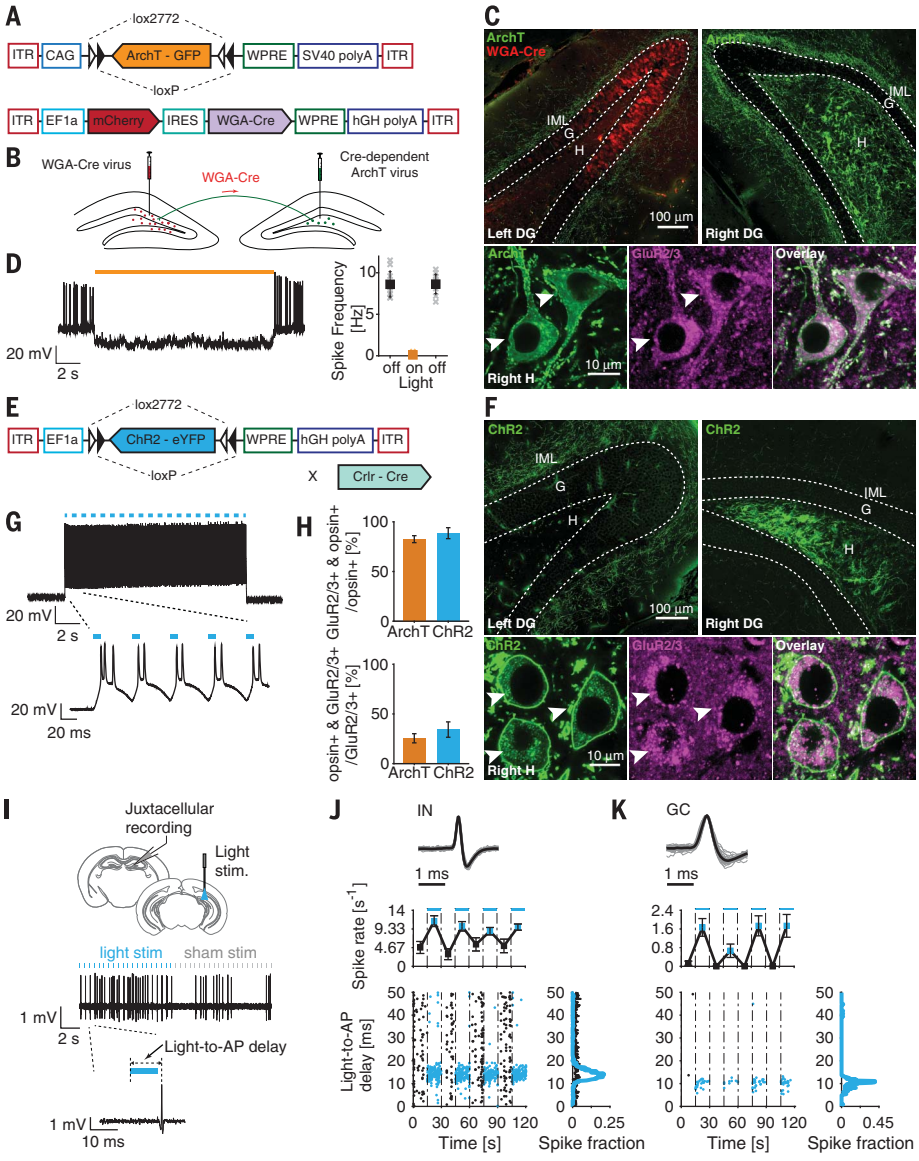

Fig. 1. Selective optogenetic control of DG MCs. (**A**) ArchT expression system. (**B**) Topological targeting of MCs with a WGA-Cre fusion protein expressed in the left DG (red) that is transsynaptically and retrogradely trafficked by neurons with projections at the injection site. WGA-Cre activates ArchT expression in the right DG MCs (green). (**C**) (Top) Confocal images of WGA-Cre and ArchT expression. (Bottom) High-magnification images of the right hilus. ArchT-expressing MCs are identified via green fluorescent protein expression and GluR2/3+ immunostaining (arrowheads). (**D**) Illumination (15 s of 589-nm light) blocks current-induced spiking in ArchT-expressing MCs, quantified on the right (N = 10 recordings; n = 3 mice). (**E**) ChR2 expression system. (**F**) (Top) Confocal images of ChR2 expression. (Bottom) High-magnification images of the right hilus. ChR2-expressing MCs are identified via eYFP expression and GluR2/3+ immunostaining (arrowheads). (**G**) Illumination (473 nm, 15 s of a 20-Hz train of 10-ms pulses) induces ChR2-expressing MC firing (N = 5 recordings; n = 3 mice). (**H**) (Top) Opsin expression specificity (N = 103|24 slices; n = 3|5 mice for ArchT+|ChR2+). ArchT+ neurons were labeled using the WGA-Cre system, and ChR2+ neurons were labeled using the Crlr-Cre transgenic mouse system. (Bottom) Extent of opsin expression (N = 20|18 slices; n = 3|3 mice for ArchT+|ChR2+). (**I** to **K**) In vivo juxtacellular recordings of DG cells in MC ChR2-expressing mice. (I) (Top) Experimental schematic. (Bottom) Single-unit activity of an IN. [(J) and (K)] Neuronal activity of an IN (J) and a GC (K) in response to MC stimulation. (Top) Normalized spike (gray lines) and unit average (black line) waveforms. (Middle) Firing rate during alternating light-off (black) and light-on (blue) epochs. (Bottom) Scatter plot (left) and distribution plot (right) of the delay between the AP and the onset of the laser (blue) or sham pulse (black). All data are presented as mean ± SEM. G, granule cell layer; H, hilus; IML, inner molecular layer; AP, action potential.

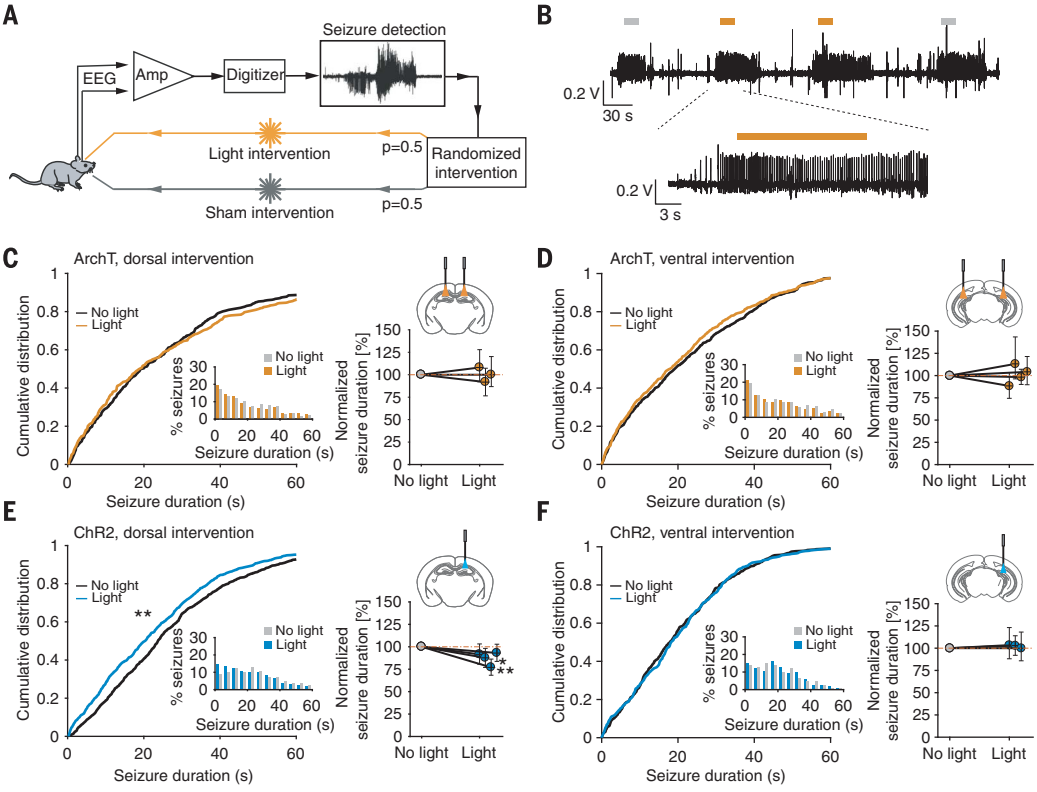

Fig. 2. Modulation of MC activity on electrographic seizure dynamics. (**A**) Closed-loop approach for in vivo real-time detection and optogenetic intervention of spontaneous seizures in epileptic mice. (**B**) Electrographic seizures, where no light (gray bar) or light (orange bar) is delivered upon seizure detection. (**C** to **F**) Light delivery to the dorsal or ventral DG of ArchT-expressing mice [(C) and (D)] and to the dorsal or ventral DG of ChR2-expressing mice [(E) and (F)]. (Left) Cumulative distribution and probability density (inset) of the seizure duration after the start of light or no-light delivery (N = 917|1194|2161|903 seizures, n = 3|4|4|3 animals for ArchT dorsal|ArchT ventral|ChR2 dorsal|ChR2 ventral). (Right) Normalized difference in seizure duration ± 95% confidence interval (CI) (*P < 0.05; **P < 0.01; Mann-Whitney U test).

these data show that MC inhibition in healthy mice during learning reduces their OLM task performance to a level similar to that observed in epileptic mice (Fig. 4, A and C). MC loss by itself, even partial, is sufficient to degrade cognitive abilities independently of other network changes in epilepsy (*17*).

In summary, selective MC inhibition allows for electrographic seizure generalization and precludes spatial memory encoding. These findings indicate that the MC loss often observed in TLE patients (*2*) is likely to be directly implicated in both seizures and comorbid cognitive deficits. Earlier studies have led to conflicting models for the role of MCs in hippocampal network dynamics. Widespread chronic MC deletion led to transient GC disinhibition (*7*), and stimulation of commissural fibers, including MC axons, inhibited GCs (*19*, *20*), indicating that MCs may exert a primarily inhibitory effect on the network. Others reported a decrease in DG activity in slices after partial MC ablation (*4*) or an increase in perforant path–induced afterdischarges with MC optogenetic excitation (*21*), suggesting that MCs exert a net excitatory effect. Our study addresses how surviving MCs affect the dynamics of spontaneously occurring electrographic and convulsive seizures in TLE, a critical question from a clinical perspective. By leveraging closed-loop optogenetics, we established unambiguously that surviving MCs have a net inhibitory role on the hippocampal network and play a protective role in preventing spontaneous seizure progression.

The progression of electrographic seizures initially restricted to the hippocampus into convulsive seizures is characterized by a spread of

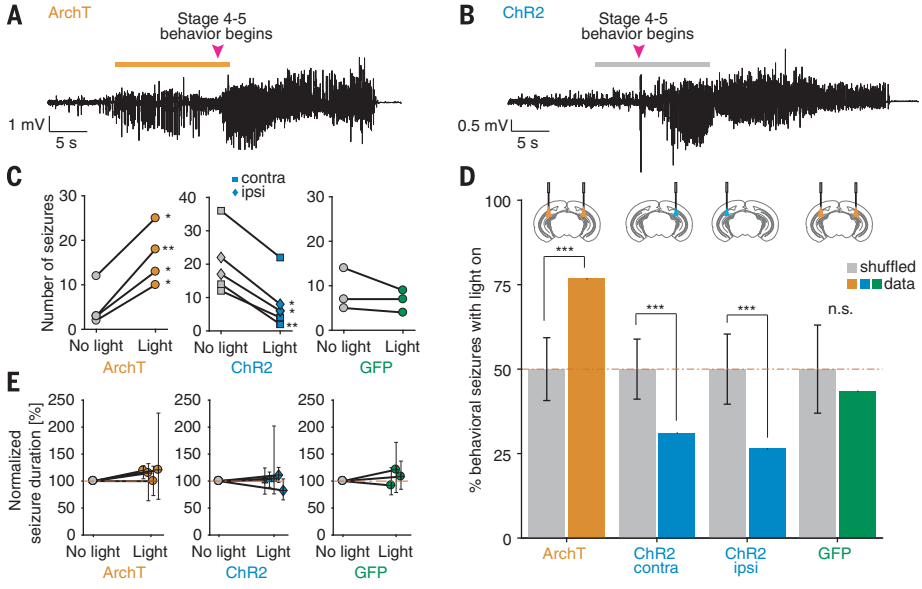

Fig. 3. MC optogenetic modulation during spontaneous seizures controls the progression of electrographic seizures into convulsive seizures. (**A** and **B**) Electroencephalogram recordings of electrographic-to-convulsive seizures in (A) an ArchT- and (B) a ChR2-expressing mouse with light (orange bar) or no light (gray bar) delivery after seizure detection. (**C**) MC photoinhibition increases (left), MC photostimulation reduces (middle), and light delivery to opsin-negative controls does not affect (right) the occurrence of convulsive seizures. *P < 0.05; **P < 0.01; two-tailed binomial test. (**D**) Control of seizure progression by MC modulation. Data are shown as the fraction of convulsive seizures occurring after light delivery (colored bars) compared with the fraction one would observe under the null hypothesis that light delivery has no effect (gray bars; expected fraction ± 95% CI). n.s., P > 0.05; **P < 0.01; ***P < 0.001; two-tailed binomial test. (**E**) MC activity modulation does not affect convulsive seizure duration. Data shown as normalized difference in seizure duration ± 95% CI (P > 0.05; Mann-Whitney U test). Contra, opsin expression contralateral to the KA injection site; ipsi, opsin expression ipsilateral to the KA injection site.

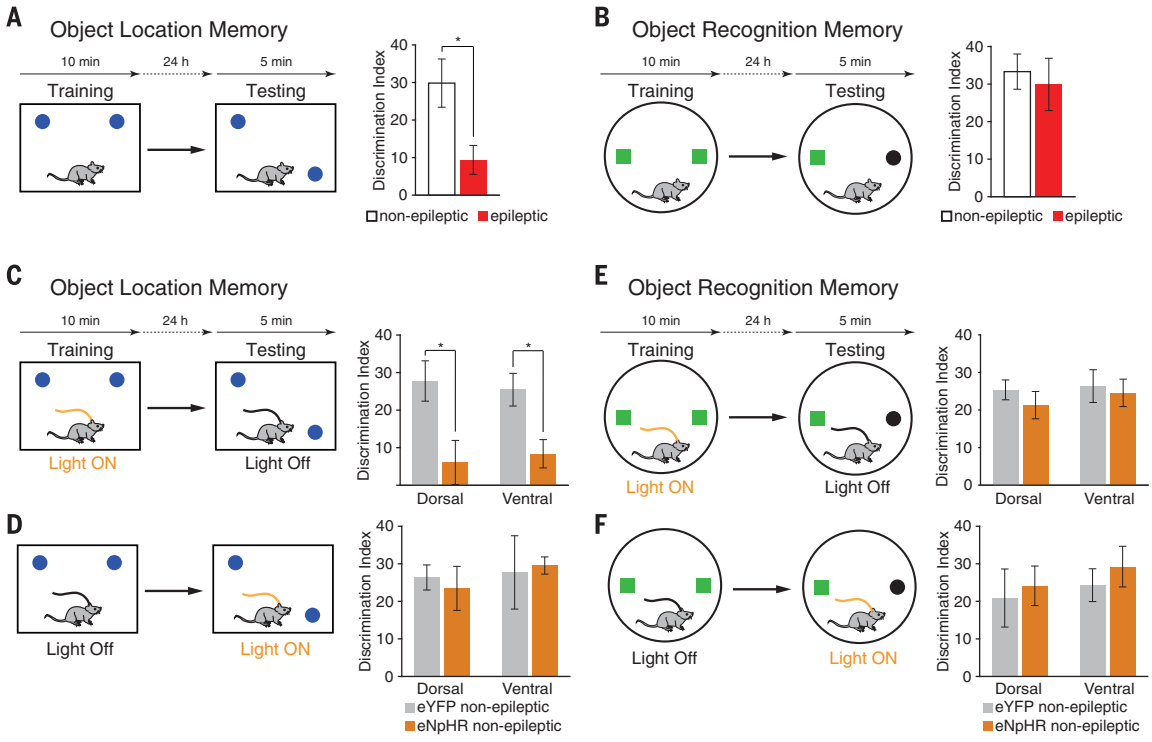

Fig. 4. Chronically epileptic mice have impaired OLM but not ORM, and MC inhibition impairs learning but not retrieval of OLM. (**A**) OLM test schematic and timeline. Epileptic mice (n = 17) exhibit significantly impaired OLM, compared with nonepileptic controls (n = 13). (**B**) ORM test schematic and timeline. Nonepileptic (n = 10) and epileptic (n = 14) mice show no significant difference in ORM. (**C**) MC photoinhibition during learning interferes with OLM (dorsal: n = 9|10; ventral: n = 8|5 for eYFP|eNpHR). (**D**) MC photoinhibition during testing does not interfere with OLM (dorsal: n = 9|8; ventral: n = 6|7 for eYFP|eNpHR). (**E** and **F**) MC photoinhibition during ORM learning does not impair task performance (dorsal: n = 10|9; ventral: n = 9|10 for eYFP|eNpHR). (F) MC photoinhibition during ORM testing does not affect task performance (dorsal: n = 10|10; ventral: n = 7|9 for eYFP|eNpHR). Data are presented as mean ± SEM. *P < 0.05; two-tailed Welch's t test.

hyperactivity to other brain regions (fig. S12). Because MCs project exclusively within the DG, and the main DG efferent projections are GC axons, it is likely that the MC anticonvulsive role involves the regulation of GC activity. We found, however, that neither GC stimulation nor inhibition could prevent convulsive seizure occurrence. Our data thus imply that the control of convulsive seizures requires coordinated modulation of spatially distributed downstream MC targets. MCs have widespread projections that contact more than 30,000 GCs and INs (*3*, *14*). This property enables MCs to coordinate the activity of spatially distributed microcircuits and may be key in blocking runaway excitation. In contrast, GCs have strong, but lamellar, projections, restricted to a few hundred micrometers along the longitudinal axis. These dense projections likely underlie the ability of GC inhibition to shorten electrographic seizures (*11*) but may be too locally restricted to prevent seizure generalization.

Our learning and memory results are consistent with the emerging model that MCs have an important role in spatial memory encoding. MCs have multiple place fields and exhibit stronger place-field remapping than GCs in response to changes in environmental cues (*22*–*24*). We demonstrated that MCs are critical in encoding, but not in retrieval, of spatially relevant information. Because GCs have been implicated in learning contextually relevant information (*25*, *26*), it is possible that MCs control information encoding by regulating GC excitability in separate lamellae through their widespread, divergent projections (*7*, *27*). Our work suggests that strategies to limit MC loss or to directly excite surviving MCs may provide powerful treatment options for seizure control.

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SUPPLEMENTARY MATERIALS

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ECOSYSTEM SERVICES

Species turnover promotes the importance of bee diversity for crop pollination at regional scales

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Ecologists have shown through hundreds of experiments that ecological communities with more species produce higher levels of essential ecosystem functions such as biomass production, nutrient cycling, and pollination, but whether this finding holds in nature (that is, in large-scale and unmanipulated systems) is controversial. This knowledge gap is troubling because ecosystem services have been widely adopted as a justification for global biodiversity conservation. Here we show that, to provide crop pollination in natural systems, the number of bee species must increase by at least one order of magnitude compared with that in field experiments. This increase is driven by species turnover and its interaction with functional dominance, mechanisms that emerge only at large scales. Our results show that maintaining ecosystem services in nature requires many species, including relatively rare ones.

We are living in an age of catastrophic species loss but have little understanding of how species loss will affect the delivery of ecosystem services—that is, those ecosystem functions that are essential to human life (*1*, *2*). The role of species richness (i.e., the number of species present in an area) in facilitating ecosystem functions has been a focus of ecological research for decades. Field and laboratory experiments clearly show that many ecosystem functions diminish with declining species richness (*1*, *3*). Whether this observation holds for ecosystem services in natural systems, however, is poorly known (*1*, *4*). The transition from smaller-scale experiments to natural systems has been predicted to both increase (*3*, *5*) and decrease (*6*) the importance of biodiversity to function, and large-scale studies attempted thus far found varying results (*1*, *7*).

For several reasons, species richness may have different effects on ecosystem function in natural landscapes compared with experiments. First, there is the difference in scale: The typical biodiversity–ecosystem functioning experiment covers an area of 3 m^2 (*8*), whereas ecosystem services operate across thousands of square kilometers and therefore include large-scale phenomena such as species distributions and spatial patterns of environmental variation. Second, manipulative experiments control or randomize aspects of community structure other than species richness, whereas natural communities vary not only in richness but also in species composition, relative abundance of each species (dominance), and the total number of individuals (abundance). Variation in these factors, as well as natural environmental variation, could modify or overwhelm the importance of species richness to ecosystem services. Third, the mechanisms that drive the biodiversity-functioning relationship in experiments operate at the within-community scale and are based on interactions among species or differences in their functional traits (*3*, *8*). By contrast, in natural landscapes the among-community scale is also relevant and will likely be governed by different mechanisms (*9*). The different questions investigated by biodiversity–ecosystem function research at the experimental versus the landscape scale are portrayed in Fig. 1, A and B.

Two well-known aspects of species' distributions lead to opposing predictions about how many species are needed to sustain ecosystem services at large scales. First, species turnover, or beta diversity [in its broad sense of changes in species identity and abundance across ecological communities (*10*)], should cause the number of species needed to increase with increasing spatial scale (*3*, *8*, *11*). Specifically, because different species are needed to provide the same function in different places, the cumulative number of species required is predicted to increase monotonically with increasing scale, analogous to the species-area relationship (*3*). The second, and contrasting, prediction stems from the fact that all natural ecological communities have high numerical dominance, with a few abundant species and many rare ones (*12*). Evidence suggests that the numerically dominant species provide most of the ecosystem services as well (*13*, *14*), raising the possibility that in nature ecosystem services might be provided by a small number of functionally dominant species.

We measured the number of species needed to provide a target level of ecosystem services as the number of sites at which the target must be met increases. We studied crop pollination by wild (unmanaged) bees, a globally important ecosystem service (*15*), at 48 commercial crop fields (hereafter "sites") in the Mid-Atlantic region of the United States. Parallel study designs and methods were used for each of three crop systems (watermelon, blueberry, and cranberry) (Fig. 1C). Within each site, we net-collected bee pollinators visiting crop flowers within a 50- to 200-m^2 transect, an area on par with that of many biodiversity-function experiments. Our sites were distributed throughout an ~3700-km^2 area, such that the spatial scale of our analysis, as it increased from 1 to 48 sites, varied across five orders of magnitude. We also measured the pollination provided by each type of bee by counting pollen grains deposited on experimental flowers. We then found the minimum set of bee species that could meet various pollination thresholds (25, 50, and 75% of the observed mean) at each site in a set of 1:48 sites (*16*). We plotted the cumulative number of bee species needed against the number of sites, as in Fig. 1B. To estimate the effect of dominance, we compared our observations with the results of a null model that removed dominance.

Our findings provide empirical support for the often proposed but rarely tested hypothesis that ecological research has underestimated the importance of biodiversity to ecosystem services in nature. At our smallest spatial scale, achieving the 50% pollination threshold required 5.5 bee species (95% confidence interval: 4.5 to 6.6 species). This is on par with findings from biodiversity-function experiments, which have indicated that fruit and seed set reach an asymptote with pollination by only three to five bee species (*17*, *18*). As spatial extent expanded from the site to the landscape (16 sites arrayed across hundreds of square kilometers) (Fig. 1C), however, the number of bee species required to achieve the 50% threshold level of pollination increased by a factor of 4.4 (mean; range: 3.9 to 4.7) (Fig. 1D). When all three crop systems were considered together, achieving the 50% threshold at 48 sites required 55 bee species, and achieving a 75% threshold required 79 species, or most of the bee species we observed (Fig. 1D and fig. S1). Lastly, although with only three crop systems we cannot make any inferences about the spatial scale at which all of the important pollinator species are known, in two of our three systems the species accumulation curves do not reach an asymptote. This suggests that considering additional sites would reveal even more species to be important (Fig. 1D).

The patterns we observed result from the combined effects of species turnover and dominance, which act simultaneously and are difficult to disentangle (*10*). We solved this problem by developing a graphical model that partitions the increases in species required into these two effects (Fig. 2A). We used a null model (Fig. 2, A and B,

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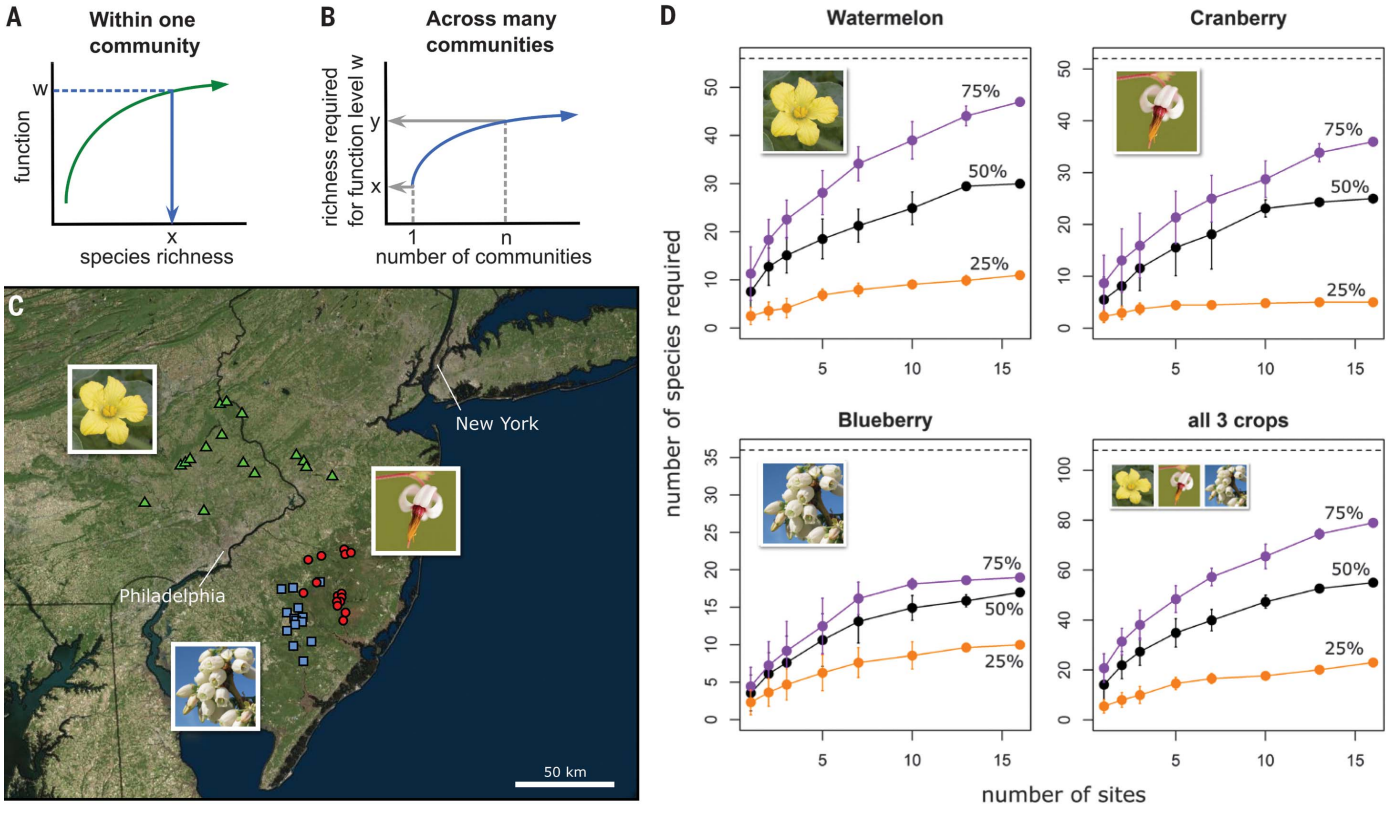

Fig. 1. How the number of bee species needed to provide pollination changes with increasing spatial extent. (**A**) A typical graph from a biodiversity-function experiment shows that a certain number of species (*x*) is needed to achieve a given level of function (*w*) within one community. (**B**) By contrast, studying ecosystem services at large scales requires analyses across communities. The threshold level of function *w* is now implicit, and the cumulative number of species required to achieve function level *w* at all *n* communities is plotted as a function of increasing spatial extent. In this example, *x* species are needed to provide function level *w* in one community, and *y* species are needed to provide function level *w* in each of *n* communities across an entire landscape. (**C**) Commercial crop fields of watermelon (green triangles), cranberry (red circles), and blueberry (blue squares) in New Jersey and Pennsylvania, USA, where bee biodiversity and crop pollination were measured. (**D**) Cumulative number of bee species required to maintain thresholds of 25% (orange), 50% (black), and 75% (purple) of the mean observed level of pollination, at each of *n* sites (*16*). Horizontal dashed lines indicate the total number of bee species observed in each study. Error bars represent 1 SD over all possible starting sites for expanding the spatial extent. For all three crops combined, each *x*-axis increment represents the addition of one site per crop.

red line) to remove dominance from the data by redistributing the total pollination delivered to each site equally among all of the bee species at the site while maintaining the observed species richness, species identity, and total pollination at each site. This approach removes the effects of dominance across communities [i.e., the larger-scale effect of dominance that arises because locally abundant species also tend to be widespread (*19*)] as well as within communities, because when no species are dominant within sites, dominant species cannot be shared across sites. Results of this null model show how many species would have been required to meet the pollen delivery threshold in the absence of dominance. Graphically, the difference between the null model and our observations is the effect of dominance (Fig. 2B, green arrows), whereas the difference between the first and *n*th site is the effect of species turnover (Fig. 2B, blue arrows).

Without dominance, more bee species would have been needed to meet the pollination threshold, which is not surprising given that functional dominance was strong in all three study systems (fig. S2). However, turnover had stronger effects than dominance at most spatial scales, and the relative strength of turnover increased with the scale of analysis (Fig. 2C). At the largest spatial extent, the number of species added because of turnover effects was 14 times (mean; range: 0.3 to 58.2) the number subtracted from it because of dominance (compare green and blue arrows in Fig. 2C and figs. S3 and S4). How the effect of dominance might change with scale, and the relative magnitude of the effects of dominance and turnover, was not previously known for any ecosystem service. Our finding that, even when present, strong functional dominance has relatively weak effects on the number of species needed does not support the hypothesis that dominance typical of natural communities will necessarily limit the importance of diversity in nature (*6*, *20*–*22*).

Previously, the effect of spatial scale on biodiversity-function relationships has been explored by aggregating experiments (*11*) but without investigation of species turnover and dominance. Most experimental communities are artificially assembled by researchers, which precludes measuring turnover in a meaningful way because any turnover observed would result from the researchers' decisions about what species to use in their experimental communities. Likewise, most experiments have excluded dominance as part of the experimental design at the within-community (plot) scale and have randomized species composition across plots, which prevents larger-scale dominance from occurring (*23*). By contrast, previous work done at large spatial scales in natural systems has shown that ecosystem services rely heavily on a few dominant species (*14*, *20*, *21*, *24*). These studies have combined data across many sites or an entire region (e.g., Amazonia) and found that a small proportion of species (often <5%) provides 50% or more of the ecosystem services (*14*, *20*, *24*). Similarly, in our own previous work, we concluded that a few dominant species were important because they explained a large proportion of the variation in pollination between sites (*21*).

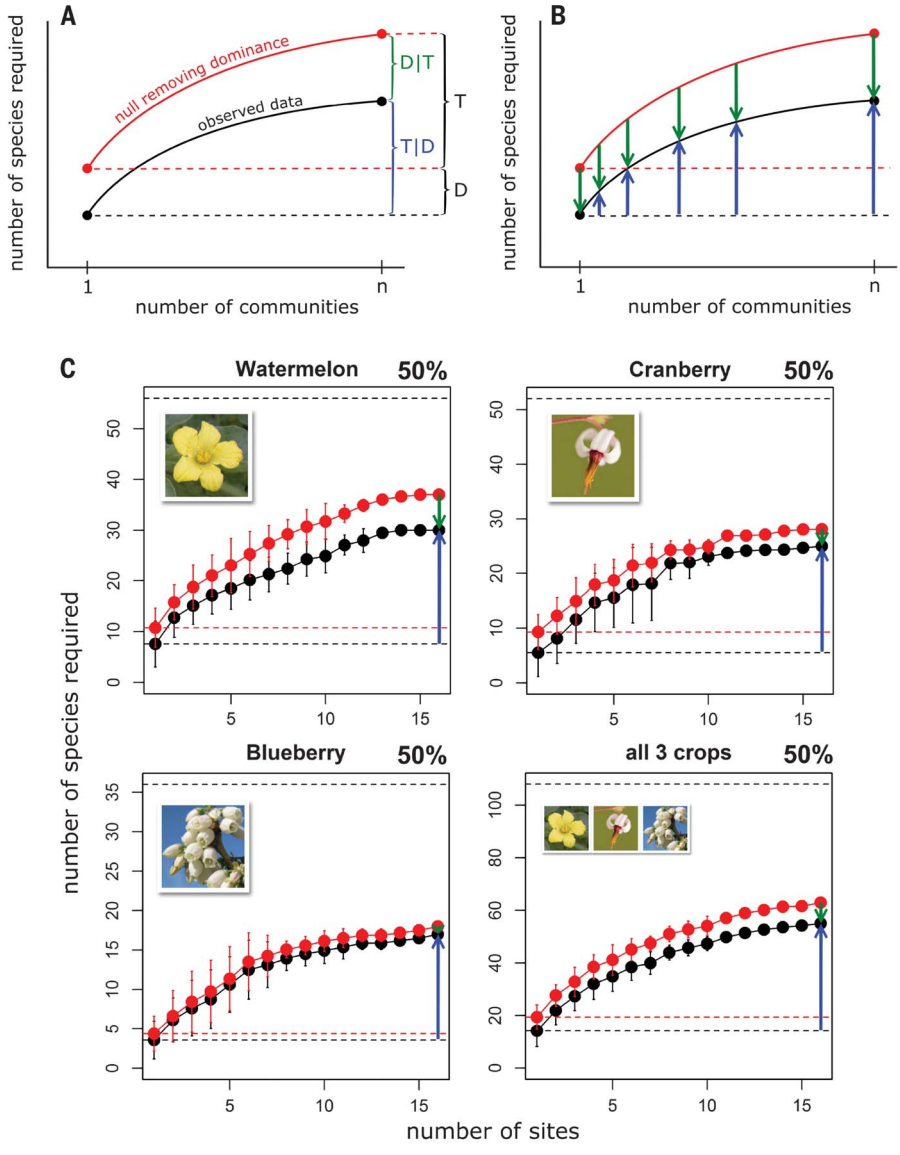

Fig. 2. How species turnover and dominance determine the number of species required for ecosystem services. (**A**) Conceptual diagram showing how observations (black; as in Fig. 1D) could be compared with a null model (red) that assumes each species in a community contributes the same amount of ecosystem services. D represents the effect of dominance in the absence of turnover (i.e., at only one site). T denotes the effect of turnover in the absence of dominance. T|D represents the effect of turnover in the presence of dominance, thus matching data as observed in the field. D|T is the effect of dominance in the presence of turnover (i.e., the number of additional species that would be needed in the absence of dominance). (**B**) Same as (A), but showing how the relative contribution of T|D increases with increasing spatial scale (blue arrows), whereas that of D|T may not (green arrows). (**C**) Observed data from this study (black) plotted against the null model (red), as in (A). Green and blue arrows are as in (B); horizontal dashed lines are conceptually the same as those in (A) and (B) (i.e., the lines show baseline values at number of sites = 1). Data were plotted for the 50% threshold.

In this study, we took a different approach based on an absolute rather than proportional measure, and we found many species to be important. We believe that the difference arises from contrasting approaches to scaling up biodiversity–ecosystem function research from experiments to nature, for which there is currently no accepted method (*2*). Our approach requires that a fixed threshold level of pollination be provided at all sites as the number of sites increases. Unlike the proportional approaches described above, a threshold approach is sensitive to species turnover not only of the dominant species but also of less abundant species that may be important contributors to pollination at a single site or year (*25*). It is also sensitive to variation across sites in the total amount of pollination received, such that sites with low levels of pollination will require most or all of their species, including the rare ones, to reach the threshold (fig. S5). Lastly, our method aligns with the human perspective on ecosystem services, because each farmer requires his or her crops to be adequately pollinated. We believe this is the conceptual approach that best corresponds to the goal of scaling up biodiversity–ecosystem functioning research from experiments to nature, and it shows that as area increases, most species are found to be important.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/359/6377/791/suppl/DC1
Materials and Methods
Figs. S1 to S5
Tables S1 and S2
References (*26*–*39*)

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STRUCTURAL IMMUNOLOGY

Structures of C1-IgG1 provide insights into how danger pattern recognition activates complement

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Danger patterns on microbes or damaged host cells bind and activate C1, inducing innate immune responses and clearance through the complement cascade. How these patterns trigger complement initiation remains elusive. Here, we present cryo–electron microscopy analyses of C1 bound to monoclonal antibodies in which we observed heterogeneous structures of single and clustered C1–immunoglobulin G1 (IgG1) hexamer complexes. Distinct C1q binding sites are observed on the two Fc-CH2 domains of each IgG molecule. These are consistent with known interactions and also reveal additional interactions, which are supported by functional IgG1-mutant analysis. Upon antibody binding, the C1q arms condense, inducing rearrangements of the $C1r_2s_2$ proteases and tilting C1q's cone-shaped stalk. The data suggest that C1r may activate C1s within single, strained C1 complexes or between neighboring C1 complexes on surfaces.

The complement system is part of our innate immune system. The classical complement pathway is triggered by activation of the C1 initiation complex upon binding to cell surfaces. C1, or $C1qr_2s_2$, consists of four proteases, C1r and C1s, that associate with C1q, which contains antibody-binding sites. The homologous serine proteases C1r and C1s each consist of six domains (fig. S1A). C1q comprises 18 polypeptide chains; three chains of C1q-A, -B, and -C trimerize to form six collagen-like triple helices connected to six globular (trimeric) ligand-recognition (gC1q) modules (fig. S1B) (*1*). Binding of C1 through its gC1q modules to mediators of inflammation, such as immunoglobulin G (IgG) or IgM antibodies (fig. S1, C and D), on cell surfaces activates the associated proteases and initiates the proteolytic cascade of complement (*2*–*4*). Previously, we demonstrated that IgG molecules, bound to their cognate antigens on liposomes or cell membranes, oligomerize through interactions between their Fc regions and form a hexameric, high-avidity, C1-binding structure reminiscent of multimeric IgM antibodies (fig. S1D) (*5*). Mutagenesis studies (*6*–*8*) showed that amino acid residues in IgG1 that are important for direct C1 binding are situated in the CH2 domains near the Fab-Fc hinge at the periphery of these Fc-platforms (fig. S1C). In C1q, globular head residues of predominantly C1q-B mediate IgG binding (*4*, *9*, *10*). However, the molecular sequence of events leading to C1 activation by IgG hexamers remains poorly understood (*11*). We used IgG monoclonal antibodies (mAbs) oligomerized through antigen-binding on liposomes or preformed antibody complexes in solution and applied tomography and single-particle cryo–electron microscopy (cryo-EM) to resolve the mechanisms of C1 binding and activation.

Liposomes carrying di-nitrophenyl (DNP) haptens were incubated with an anti-DNP chimeric IgG1 mAb and C1 to allow extensive formation of surface-bound C1-IgG1 complexes (Fig. 1A). Tomograms showed marked structural variations in C1 binding to antibodies on these liposomes (Fig. 1A and fig S2, A and B). Alignment and classification of single-membrane–bound C1-IgG1 complexes (Fig. 1B) yielded a reconstruction at ~25-Å resolution (fig. S2, C and D). Focused alignment and classification on the Fc-C1 complex [excluding the membrane and Fab domains (fig. S2, B and E)] revealed six densities corresponding to gC1q domains binding an Fc-platform formed by six IgG1 molecules, a rhomboidal platform accounting for bound $C1r_2s_2$ proteases, and a protruding C1q-collagen stalk on top (Fig. 1C), which is consistent with a previous reconstruction obtained with a goat polyclonal antibody to DNP at ~65-Å resolution (*5*). Analysis of subvolumes of C1-IgG1 complexes revealed persistent density for neighboring C1 complexes (Fig. 1D and fig. S2E), as previously observed by using normal human serum (*12*). Distances between nearest neighbors varied from ~11 to 40 nm center-to-center, with a peak at 23 nm (fig. S2F), reflecting a variation of arrangements of neighboring complexes. The C1 complexes

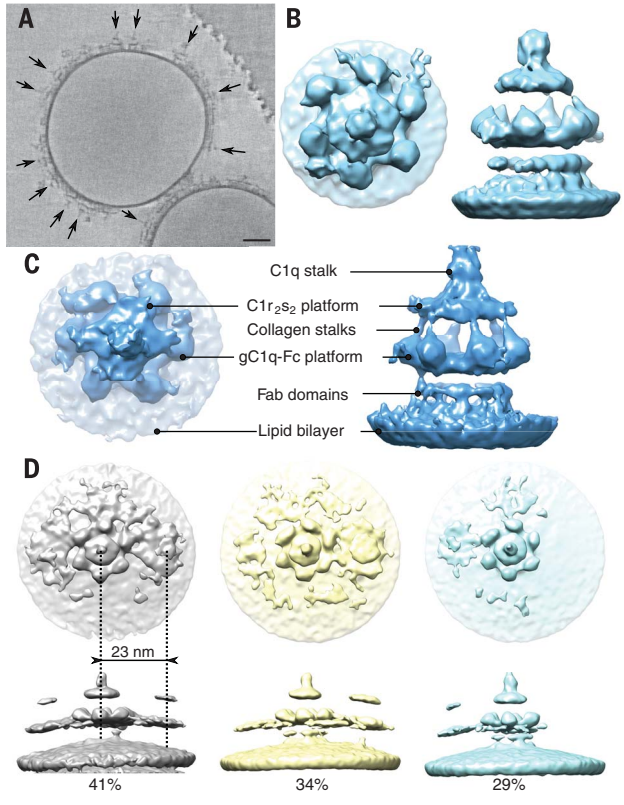

Fig. 1. C1-mAb complexes observed on liposomes with tomography. (**A**) A 10-nm-thick slice through a dual-axis tomogram showing C1 complexes (arrows) bound to surface-associated antibody complexes. Scale bar, 20 nm. (**B**) Reconstruction of a single C1-IgG1 complex shown from the top (left) and side (right) at 25 Å resolution. (**C**) Focused alignment and classification of the complexes, excluding the membrane and Fab regions (masks used in focused reconstructions are provided in fig. S2E), revealed density from the $C1r_2s_2$ platform extending out either side of the C1q stalk. (**D**) Neighboring C1-mAb complexes from larger subvolumes showing a common spacing of 23 nm between complexes, as measured from centers of IgG1 platforms. All volumes were filtered to 25-nm resolution and masked, and disconnected densities with volumes less than 5 nm^3 were removed for clarity.

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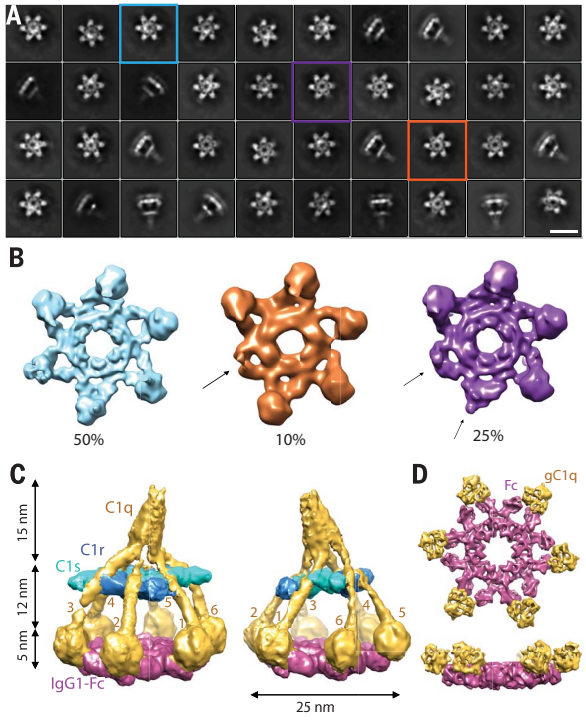

Fig. 2. Soluble C1-IgG1$_6$ complexes display heterogeneous structures. (**A**) Representative two-dimensional (2D) class averages. Colored boxes indicate three classes corresponding to main 3D classes, as shown below. Scale bar, 25 nm. (**B**) Main 3D classes after focused 3D classification and 3D refinement, showing the "bottom platform" segment of the reconstructions indicating heterogeneities (highlighted by arrows). Percentage of particles in each class are indicated. Particle colors correspond to the color of the boxes in (A). (**C**) 3D reconstructions after post-processing of the major class, showing two side views (left and middle). Densities have been colored to indicate density for C1q (yellow; with collagen arms and gC1q units numbered 1 through 6), C1r and C1s (blue and magenta, respectively) and IgG1-Fc regions (pink). (**D**) Top and side views of the bottom platform after sixfold averaging (right, top and bottom, respectively).

are not evenly distributed across the surfaces of the liposomes, suggesting that there is preference for the complexes to associate rather than occupy all available liposome surface (Fig. 1A and fig. S2A).

Soluble C1-IgG1$_6$ complexes of 1.7 MDa were obtained (fig. S3, A and B) by incubating C1, with catalytically inactive proteases C1r (Ser^{654}Ala) and C1s (Ser^{632}Ala), with a human IgG1 mAb containing three mutations that drive the formation of IgG hexamers in solution (IgG1-Glu^{345}Arg, Glu^{430}Gly, and Ser^{440}Tyr) (*5*, *13*, *14*). Classification and averaging of single-particle densities yielded separate classes with four, five, or six gC1q domains in contact with the Fc platforms (Fig. 2, A and B, and fig. S4C). One class containing ~79,000 particles with six gC1q domains bound to the Fc platform yielded a map at 10-Å resolution (fig. S4D), resulting in an overall structure 32 nm high and 25 nm wide that is consistent with densities observed in tomography (fig. S5). The reconstruction reveals densities for all C1q collagen-like triple helices and gC1q modules, C1r and C1s proteases, and IgG1-Fc regions (Fig. 2, C and D).

Imposing sixfold symmetry on the IgG1 platform bound to gC1q yielded a density map at 7.3-Å resolution (Fig. 3A and fig. S4D). Crystal structures of Fc CH2 and CH3 domains (pdb-code 1HZH) (*15*) and gC1q (1PK6) (*16*) were modeled in this density map (Fig. 3A). In the resulting model, each gC1q domain contacts peripheral areas on both CH2 and CH2′ domains of an IgG-Fc dimeric segment, burying ~540 Å^2 of surface area (fig. S6A). The Fc segments adopt an open conformation, characterized by a long distance of 31 Å between Pro^{329} and Pro$^{329'}$ of the CH2 domains (fig. S6B). This contrasts with observations of closed conformations in many crystal structures of Fc domains with Pro^{329}-Pro$^{329'}$ distances of ~12 to 19 Å but resembles that of full-length IgG1-b12 (1HZH) (*15*) and deglycosylated Fc fragments of human IgG4 (4D2N) (*17*), both of which exhibit a sixfold (crystal) packing of their Fc portions, which have Pro^{329}-Pro$^{329'}$ distances of 24 and 29 Å, respectively. Densities are present for N-linked glycans at Asn^{297} and Asn$^{297'}$ (Fig. 3A). However, no direct contact is observed between the glycans and gC1q, supporting the idea that glycosylation affects C1 binding through IgG hexamerization (*13*). Fitting of heterotrimeric gC1q to the density yielded similar correlation coefficients for three possible A-B-C domain orientations, with a marginally higher score for chains B and C facing the antibodies, which is consistent with mutation data that has identified chains B and C harboring the antibody-binding sites (*9*).

The Fc-gC1q structure identified distinct C1q-binding sites on the two Fc-CH2 domains of an IgG1. The observed binding sites are corroborated with extensive mutagenesis, which shows that both previously established amino acid contacts and contacts newly identified in our structure modulate complement activation (Fig. 3, B and C, and fig. S6C) (*6*–*8*, *18*). Mutations were introduced in the CD20 mAb IgG1-7D8, and the impact on complement-dependent cytotoxicity (CDC) of CD20-expressing Raji cells was assessed (Fig. 3C and table S1). The first binding site is formed by loop FG (residues 325 to 331) of Fc CH2, which is known to be involved in binding both C1q and Fcγ receptors (*18*–*20*). Critical residues Pro^{329}-Ala^{330}-Pro^{331} (*3*, *6*, *18*) form the tip of the FG loop, with Pro^{329} making contact with hydrophobic C1q-B residue Phe^{178} (Fig. 3B). IgG1 CH2 residue Lys^{322} (*21*) provides additional charged interactions with C1q-C residue Asp^{195} (Fig. 3B). Mutation of Ala^{327} into a positively charged lysine decreased CDC, whereas the mutation Ala^{327}Gly enhanced CDC (Fig. 3C). Consistent with previous observations, variant Lys^{326}Ala/Glu^{333}Ala stimulated CDC (*6*). The secondary binding site consists of loop BC (residues 266 to 272) and loop DE (residues 294 to 300) of CH2′, which form a negatively charged patch that interacts with C1q-B residues Arg^{114} and Arg^{129} (Fig. 3B) (*4*, *22*). Introducing a positive charge at residues Glu^{269}, Glu^{294}, or Tyr^{300} abolished CDC (Fig. 3C). By contrast, the mutation Tyr^{300}Asp enhanced CDC (Fig. 3C). Mutations Asn^{297}Gln and Ser^{298}Lys decreased CDC, likely because of the absence of glycosylation. Furhermore, Fab-Fc hinge region residues Glu^{233}, Leu^{234}, Leu^{235}, Gly^{236}, and Gly^{237}, contributed to C1q binding and CDC (fig. S6C). Alanine substitutions of these residues decreased CDC, whereas Gly^{236}Asp enhanced CDC, suggesting a possible charge interaction with C1q-B Arg^{150}. The Fab regions themselves are positioned flexibly below the Fc platform, as is apparent in the tomography reconstructions (Fig. 1, B and C, and fig. S5), and appear not to contribute directly to C1 binding and activation.

We fitted structural models of C1q, C1r, and C1s into the density reconstruction of C1-IgG1$_6$ (Fig. 4 and fig. S7). On top of the C1 structure, the six C1q-A, -B, and -C collagen-like triple helices form a stalk that adopts a continuous, hollow cone-shaped structure, which is tilted by 15° from the vertical axis. Six triple helices emerge from the stalk, extend downward (with an irregular small right-handed supercoil), and connect to the gC1q modules that bind the IgG1-Fc hexamer platform. In particular, the collagen-like helices 3 and 6 display a marked bending (Fig. 4A). Density positioned in between the collagen-like helices is consistent with previously proposed binding of N-terminal domains of C1r$_2$C1s$_2$ between the C1q arms, with arms 2, 3, 5, and 6 contacting C1r and arms 1 and 4 contacting C1s molecules (Fig. 4B) (*23*–*25*). Using crystal structures of C1r and C1s (*25*–*28*) and their homologs MASP1 and MASP2 (*29*, *30*), domains CUB1-EGF-CUB2-CCP1 of both C1r and C1s (fig. S1A) were modeled into the densities (fig. S7). No density is observed for the CCP2-SP domains of either C1r or C1s in the 10-Å resolution single-particle reconstruction, indicating flexible arrangements for these parts. However, density obtained for CCP1 domains allows completion of the model with the superposition of CCP1-CCP2-SP crystal structures onto CCP1 of C1r and C1s (Fig. 4C and fig. S1A). This results in a model in which C1r CCP1 orients CCP2-SP to curve around the C1q collagen-like helix

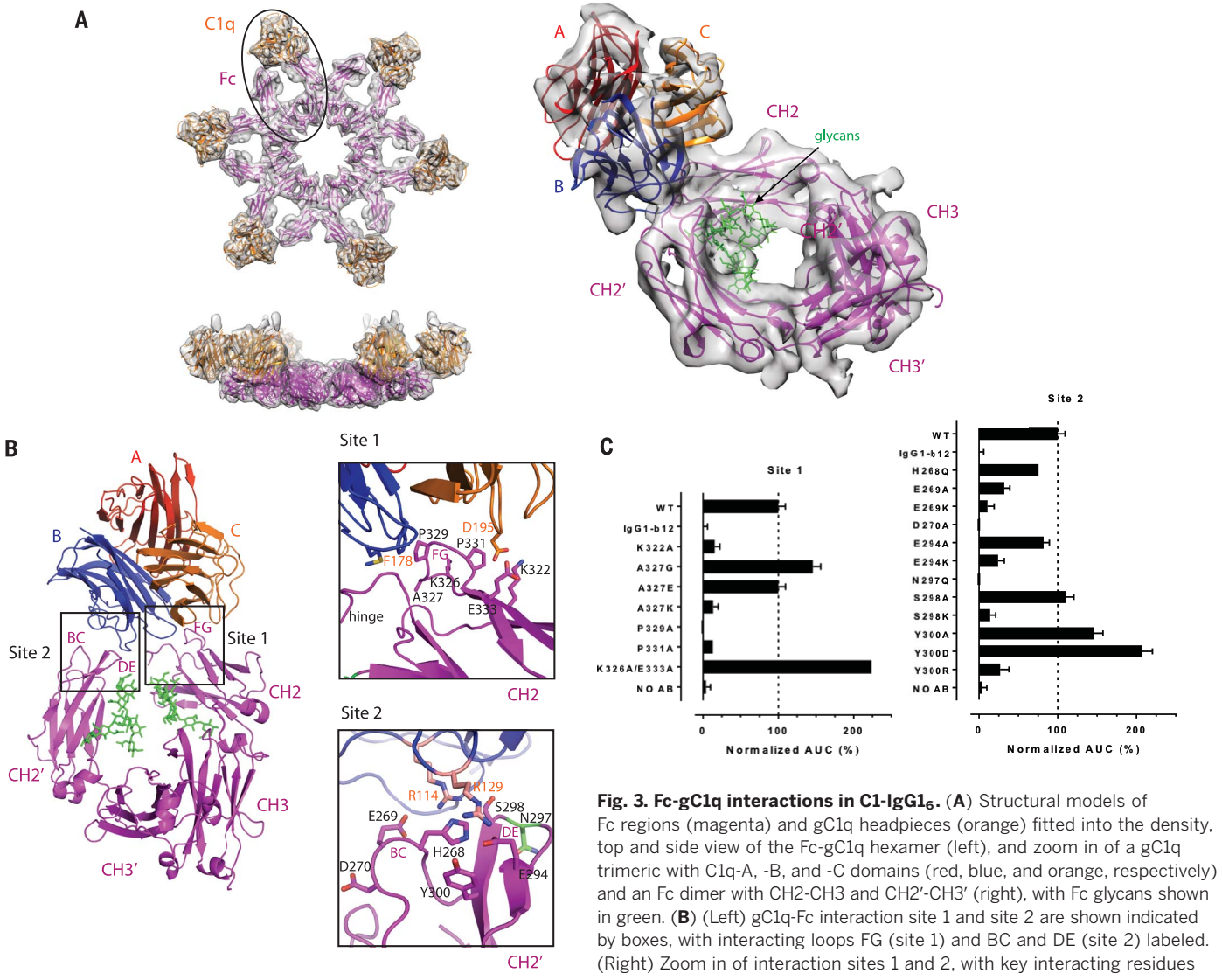

Fig. 3. Fc-gC1q interactions in C1-IgG1$_6$. (**A**) Structural models of Fc regions (magenta) and gC1q headpieces (orange) fitted into the density, top and side view of the Fc-gC1q hexamer (left), and zoom in of a gC1q trimeric with C1q-A, -B, and -C domains (red, blue, and orange, respectively) and an Fc dimer with CH2-CH3 and CH2′-CH3′ (right), with Fc glycans shown in green. (**B**) (Left) gC1q-Fc interaction site 1 and site 2 are shown indicated by boxes, with interacting loops FG (site 1) and BC and DE (site 2) labeled. (Right) Zoom in of interaction sites 1 and 2, with key interacting residues shown in stick representation and labeled. (**C**) Complement-dependent cytotoxicity assays of Raji cells opsonized with wild-type (WT) and mutated CD20 mAb IgG1-7D8 (n = 3 independent experiments) exposed to C1q-deficient serum to which a titration of 1 ng/mL to 60 μg/mL C1q was added. Cell lysis was assessed with flow cytometry by using propidium iodide staining. Bars show the average area under the curve (AUC) for this dose response normalized against the AUC obtained with the unmutated WT IgG1-7D8 set to 100% NO AB:control reactions without IgG1 added.

toward C1s and in which C1s CCP1-CCP2-SP sticks outward, which is consistent with their proteolytic functions in the complement cascade (Fig. 4C and fig. S7D).

The observed arrangement of the C1r and C1s heterotetramer differs from predictions based on a tetrameric C1s arrangement (*25*, *31*). The CUB2 domains of C1r and C1s are rotated, and the C1r-C1s dimers are shifted along each other, shortening the contact sites of C1q-collagen helices 2 and 5 from 14 (*31*) to 11 nm in C1-IgG1$_6$ (fig. S7, A to C). The arrangement of the C1q arms, induced upon binding the Fc hexamer, is also indicative of a compaction. The gC1q domains in unbound C1 are spread apart up to 30 to 35 nm (*31*). Bending of the collagen-like helices of arms 3 and 6, which embrace C1r$_2$s$_2$ in the longest dimension, and incomplete binding of the gC1q heads (on arms 5 and 6) to Fc platforms support the notion of a surface-induced conformational change.

The affinity of gC1q modules for single-IgG-antibody molecules is very low. For IgG antibody molecules to form a recognition pattern therefore requires their clustering or aggregation, allowing the formation of a multivalent complex with C1. IgM molecules are already multivalent but require their occluded C1 binding sites to be revealed upon interacting with surface antigen. Here, we show that the multivalent binding of C1 to IgG hexamers results in compaction of C1q arms, which rearranges the N-terminal (CUB1-EGF-CUB2) platform of the C1r$_2$s$_2$ proteases and may allow the catalytic SP domain of the C1r CCP1-CCP2-SP arm to reach the scissile loop in C1s CCP1-CCP2-SP. Alternatively, the extended conformations of the CCP1-CCP2-SP domains may allow intercomplex proteolysis induced by neighboring complexes. This is consistent with the C1-antibody complexes that form on crowded surfaces, as observed in tomograms of IgG mAb hexamers bound to liposomes. Intercomplex activation has been proposed for MBL-MASP2$_2$ complexes of the lectin-binding complement pathway, in which MASP1 proteases present in separate MBL-MASP1$_2$ complexes mediate activation (*31*, *32*). Direct binding of C1 to ubiquitous and fluid ligands in a membrane, such as phosphatidylserines on apoptotic

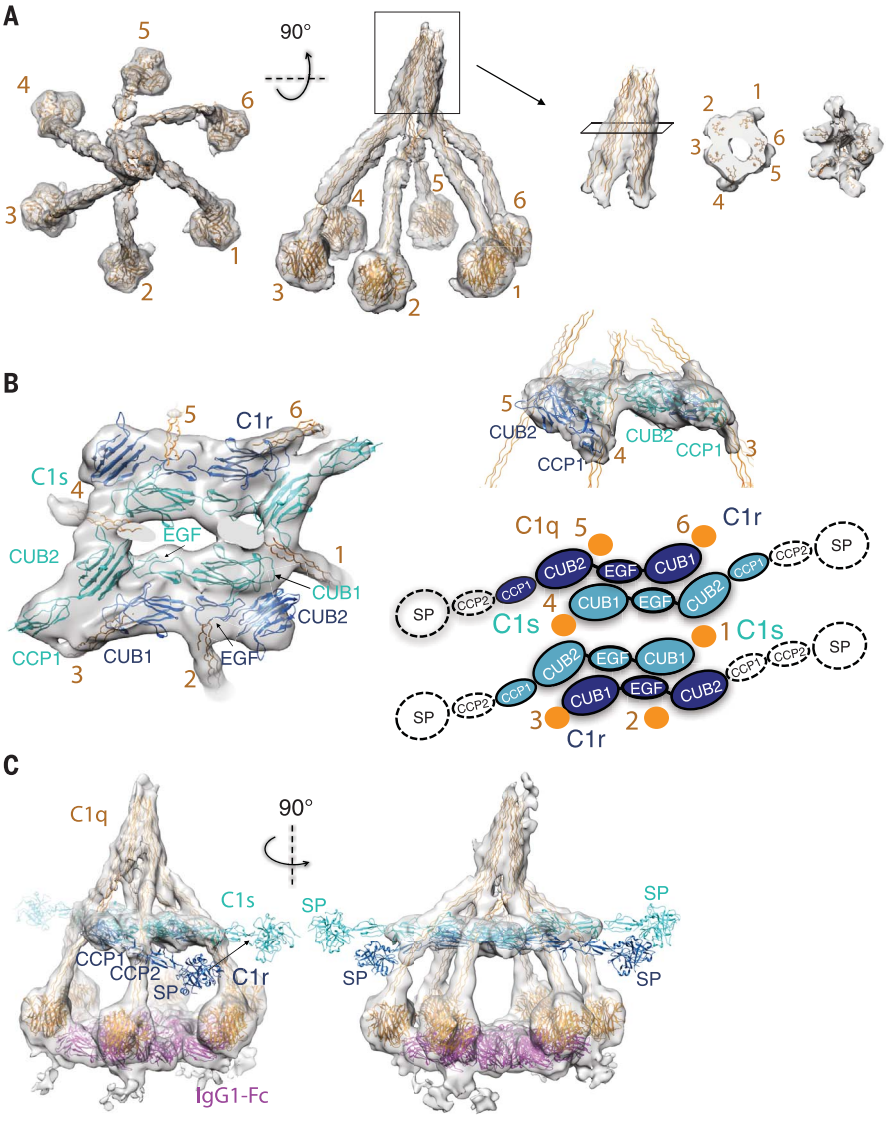

Fig. 4. Structural model of C1 fitted into C1-IgG1$_6$ density. (**A**) Model for C1q-A, -B, and -C hexamer indicating collagen-like segments forming a N-terminal stalk region, six collagen-like triple helices, and C-terminal trimeric gC1q modules. Shown are top and side views (left and middle) of C1q and side, sliced through top and bottom view (third column, left to right) of the C1q stalk region. Numbering of each C1q arm is as in Fig. 2. (**B**) Model for C1r and C1s heterotetramer showing C1r CUB1-EGF-CUB2 (blue) and C1s CUB1-EGF-CUB2-CCP1 domains (cyan). Shown are (left) top view and (top right) side view at lower contour level, with the latter revealing density for the CCP1 domain of C1r. An illustration of the domain arrangement is shown for clarity (bottom right). (**C**) Overall C1-IgG1$_6$ models in density. CCP2-SP domains lacking density have been added by using orientations derived from crystal structures.

cells, would likely not induce compaction of the C1q arms, and activation may depend on intercomplex proteolysis of surface-bound C1 complexes. Our data suggest that danger pattern recognition by C1 may lead to proteolysis and activation within an isolated complex through a conformational change, as suggested by an observed bending of C1q arms and the arrangement of proteases. Close interactions observed between separate C1-IgG complexes, however, suggest that proteolysis may also result from intercomplex activation.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/359/6377/794/suppl/DC1
Materials and Methods
Figs. S1 to S7
Tables S1
References (*33*–*47*)

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BIOCHEMISTRY

Lipopolysaccharide is transported to the cell surface by a membrane-to-membrane protein bridge

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Gram-negative bacteria have an outer membrane that serves as a barrier to noxious agents in the environment. This protective function is dependent on lipopolysaccharide, a large glycolipid located in the outer leaflet of the outer membrane. Lipopolysaccharide is synthesized at the cytoplasmic membrane and must be transported to the cell surface. To understand this transport process, we reconstituted membrane-to-membrane movement of lipopolysaccharide by incorporating purified inner and outer membrane transport complexes into separate proteoliposomes. Transport involved stable association between the inner and outer membrane proteoliposomes. Our results support a model in which lipopolysaccharide molecules are pushed one after the other in a PEZ dispenser–like manner across a protein bridge that connects the inner and outer membranes.

The cell envelope of Gram-negative bacteria consists of an outer membrane (OM) and an inner membrane (IM). The outer membrane has an asymmetric structure, with the outer leaflet composed of lipopolysaccharide (LPS) and the inner leaflet composed of phospholipid. LPS is a large glycolipid with six fatty acyl chains and numerous sugars (Fig. 1A) (*1*). LPS must be transported from its site of synthesis at the inner (cytoplasmic) membrane across the aqueous space between the two membranes (the periplasm) to the cell surface (*2*–*4*). Lipid transport is fundamental to cellular physiology; however, it is not known how this membrane-to-membrane LPS transport is accomplished or how transport against a concentration gradient is achieved given that there is no adenosine 5′-triphosphate (ATP) in the periplasm (*5*–*9*).

LPS transport requires seven lipopolysaccharide transport (Lpt) proteins (*10*, *11*). At the inner membrane, the heteromeric ATP-binding cassette transporter (LptBFG) associates with a membrane-bound protein (LptC) to form an inner membrane complex. This complex uses ATP hydrolysis to extract LPS from the outer leaflet of the inner membrane and transfer it to LptC and then to a periplasmic protein, LptA (*11*–*16*). LPS is then transported across the periplasm to an outer membrane translocon, LptDE, a large β-barrel protein with a separate luminal protein plug. LptDE inserts LPS into the outer leaflet of the outer membrane (*17*–*21*).

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Indirect evidence suggests that LptA associates with LptC and LptD to form a protein bridge that spans the periplasm, but the existence of such a bridge has not been established (Fig. 1A) (*22*–*25*).

To investigate whether LPS is transported via a protein bridge, we sought to reconstitute LPS transport using purified components. First, to monitor LPS transfer to LptC, we purified LptBFGC with the photocrosslinkable amino acid *p*-benzoylphenylalanine (*p*BPA) incorporated in LptC at an LPS binding site (fig. S1) (*24*, *26*). We incorporated the complex into liposomes containing LPS and confirmed adenosine triphosphatase (ATPase) activity (fig. S2). We incubated the proteoliposomes with ATP for various lengths of time before exposing them to ultraviolet (UV) light. We observed increasing cross-linking of LPS to LptC over time and in a manner that was dependent on ATP (Fig. 1B).

Next, we wanted to observe LPS transfer to LptA in our purified system and test whether this transfer depends on LptC. We incubated proteoliposomes containing either LptBFG or LptBFGC with LptA containing *p*BPA (*24*). We also prepared liposomes containing the inactive mutant LptB-E163Q in the LptBFGC complex (*15*). We observed that LPS cross-linked to LptA, and the extent of cross-linking was strongly stimulated by LptC (Fig. 1C). This is consistent with earlier in vivo experiments that suggest that LPS is transferred from LptC to LptA (*24*).

With the goal of achieving transport to a second membrane, we generated proteoliposomes containing the outer membrane LptDE translocon with *p*BPA incorporated in LptD (fig. S3) (*27*). Previous work suggests that LptA preferentially associates with the outer membrane (*22*). Therefore, we preincubated the outer membrane proteoliposomes with excess LptA, isolated the LptA-associated outer membrane proteoliposomes, and incubated them with LptBFGC proteoliposomes containing LPS. LPS cross-linked strongly to LptD in the presence of ATP (Fig. 2A and fig. S4). We did not observe cross-linking without LptBFGC or LptA. Thus, all seven Lpt proteins and ATP are necessary and sufficient for membrane-to-membrane transport to occur.

We tested if the rate of LPS transport was affected by ATP concentration using two concentrations flanking the Michaelis constant (K_m) for ATP hydrolysis (fig. S2). Cross-linking intensity was greater at the low ATP concentration and persisted for a longer period (Fig. 2B). At high ATP concentrations, the LPS likely moves more quickly through the site where *p*BPA is incorporated in LptD. This would decrease the probability of cross-link formation because cross-linking efficiency of a ligand to a protein increases with ligand residence time (*28*). These observations are consistent with a process that is powered by ATP hydrolysis.

We wanted to monitor flux of LPS through the pathway at two sites simultaneously, so we incorporated *p*BPA into both LptC and LptD and monitored cross-linking over time. Cross-links between LPS and LptC were observed at the same time as cross-links between LPS and LptD (Fig. 2C). This suggests that release from the inner membrane is coincident with arrival at LptD. Although this is not direct evidence, this result is consistent with rapid transit across a bridge.

If the bridge model is correct, it should be possible to observe an LptA-dependent association between inner and outer membrane Lpt complexes. To allow analysis by flow cytometry, we labeled inner membrane and outer membrane proteoliposomes with different fluorophores and confirmed that transport activity was maintained (Fig. 3A and figs. S5 to S7) (*29*, *30*). Inner membrane or outer membrane proteoliposomes analyzed alone showed fluorescence only in a single channel, as expected (fig. S8). Next, we mixed inner and outer membrane proteoliposomes in the presence or absence of LptA. Without LptA, flow cytometry revealed two populations of fluorescent particles corresponding to either inner or outer membrane proteoliposomes (Fig. 3B, top left panel). Addition of LptA, in contrast, resulted in a large increase in particles with signal in both fluorescence channels. Most of these two-color particles localized to a distinct population (population B) located approximately along the diagonal between the individual IM and OM populations, but there was also a region of more disperse particles located between the IM population and population B, termed population A (Fig. 3B, top right panel).

We wanted to know whether the two-color particles were the result of either liposome fusion or nonspecific association. A fluorescence dequenching assay showed that fusion did not occur in our system (fig. S9) (*31*). Furthermore, we repeated the flow cytometry experiments with a blocked LptA variant containing a protein tag that impedes interaction with LptC or, in a separate experiment, with a truncated LptD variant that is incapable of interaction with LptA. LptA-dependent proteoliposome association was not observed in either case (Fig. 3B, lower panels, and fig. S8). In toto, these data demonstrate that LptA drives a

specific, protein-mediated association between inner and outer membrane proteoliposomes.

We used our flow cytometry system to measure the extent to which LptA stimulates interactions between inner and outer membrane proteoliposomes. We quantified the number of particles in each population (IM, OM, A, and B in Fig. 3, B and C, and table S1). In the absence of LptA, the majority of particles were in either the inner membrane (IM) population (49.5%) or the outer membrane (OM) population (42.5%), whereas the A and B populations were small (4.2 and 3.8% respectively). Addition of LptA led to a 15-fold increase in the particles in the B population (60%) and a fivefold increase in the A population (23.1%). Thus, LptA causes a high proportion of the proteoliposomes to associate with one another.

Our final objective was to visualize the LptA-dependent association of inner and outer membrane proteoliposomes using confocal microscopy. We used fluorescence-activated cell sorting (FACS)

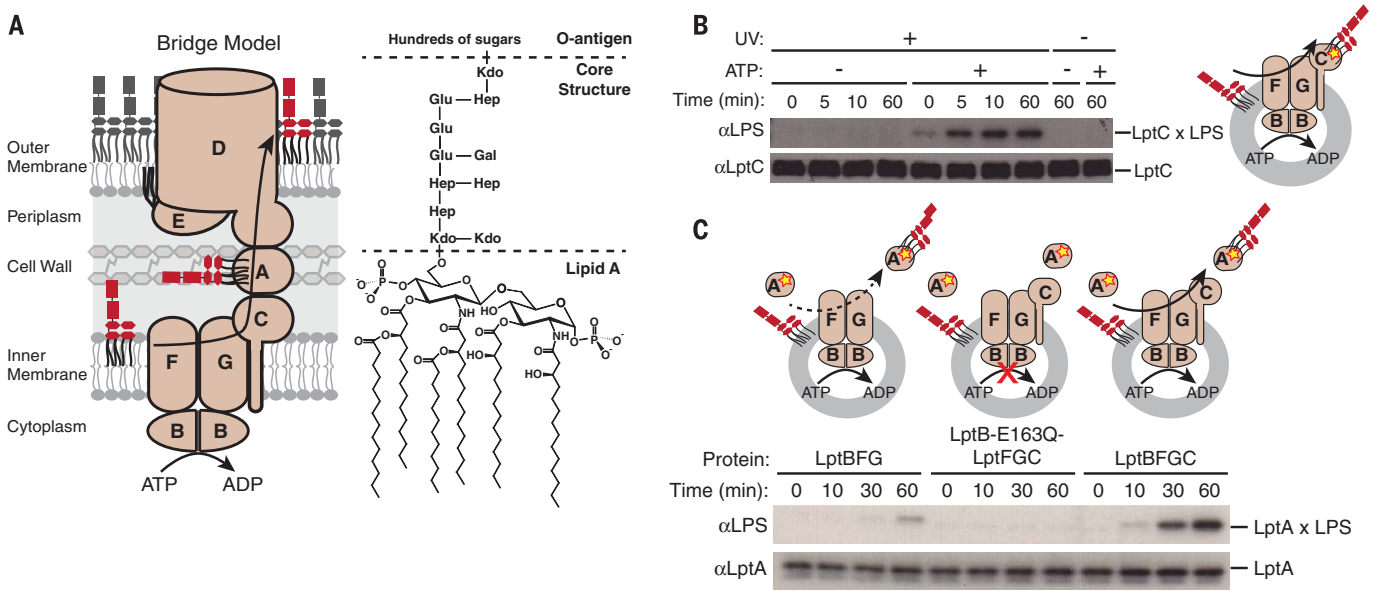

Fig. 1. Energy-dependent LPS transport to LptA is stimulated by LptC. (**A**) Bridge model of LPS biogenesis and chemical structure of *Escherichia coli* LPS. The *E. coli* lipopolysaccharide transport proteins and *E. coli* LPS were used for all experiments presented here. LptBFG extracts LPS from the inner membrane and transports it to LptC using energy from ATP hydrolysis. Additional energy from ATP hydrolysis is harnessed to push LPS from LptC to LptA. Kdo, 3-deoxy-D-manno-octo-2-ulosonic acid; Hep, L-glycero-D-manno-heptose; Glu, D-glucose; Gal, D-galactose. (**B**) LPS photocrosslinks to LptC in an ATP- and time-dependent manner. Assays were initiated by adding 5 mM ATP or buffer ("- ATP") to proteoliposomes containing LPS and LptBFGC-T47*p*BPA. (**C**) Time dependence of LPS release to LptA. Assays were initiated by adding 5 mM ATP to proteoliposomes containing LPS and LptBFG, LptB-E163Q-LptFGC, or LptBFGC mixed with soluble LptA-I36*p*BPA. In (B) and (C), aliquots were taken at the indicated time points and UV-irradiated. Cross-linking was detected by immunoblotting. Cartoons show experimental designs of the reconstituted systems. Proteins and LPS can be inserted into liposomes in either orientation, but only the productive orientation is shown for simplicity. The yellow star denotes the photocrosslinking amino acid.

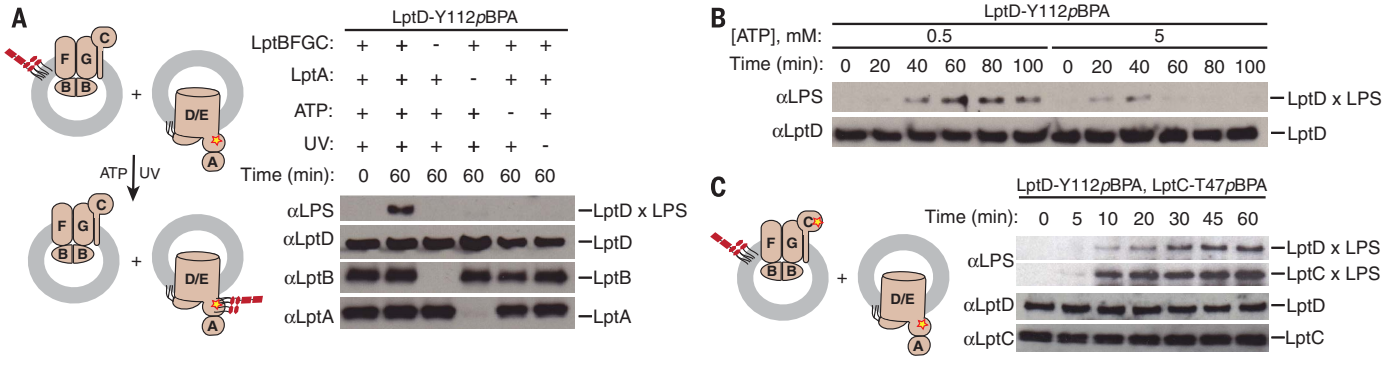

Fig. 2. Reconstitution of membrane-to-membrane LPS transport. (**A**) Seven Lpt proteins and ATP are necessary and sufficient to observe LPS cross-linking to LptD. Proteoliposomes containing LptD-Y112*p*BPA/LptE and associated LptA were incubated with LPS-containing liposomes with or without LptBFGC. Assays were initiated with 5 mM ATP (or buffer). (**B**) LPS transport to LptD depends on time and ATP concentration. Assays were conducted as in (A), initiating with either 0.5 mM or 5 mM ATP. (**C**) LPS simultaneously cross-links to LptC and LptD. Proteoliposomes containing purified LptD-Y112*p*BPA/LptE with LptA were incubated with proteoliposomes containing LPS and LptBFGC-T47*p*BPA. In (A) to (C), aliquots were taken at the indicated time points and UV-irradiated. Cross-linking was detected by immunoblotting. Cartoons show experimental designs of the reconstituted systems. Proteins and LPS can be inserted into liposomes in either orientation, but only the productive orientation is shown for simplicity. The yellow star denotes the photocrosslinking amino acid.

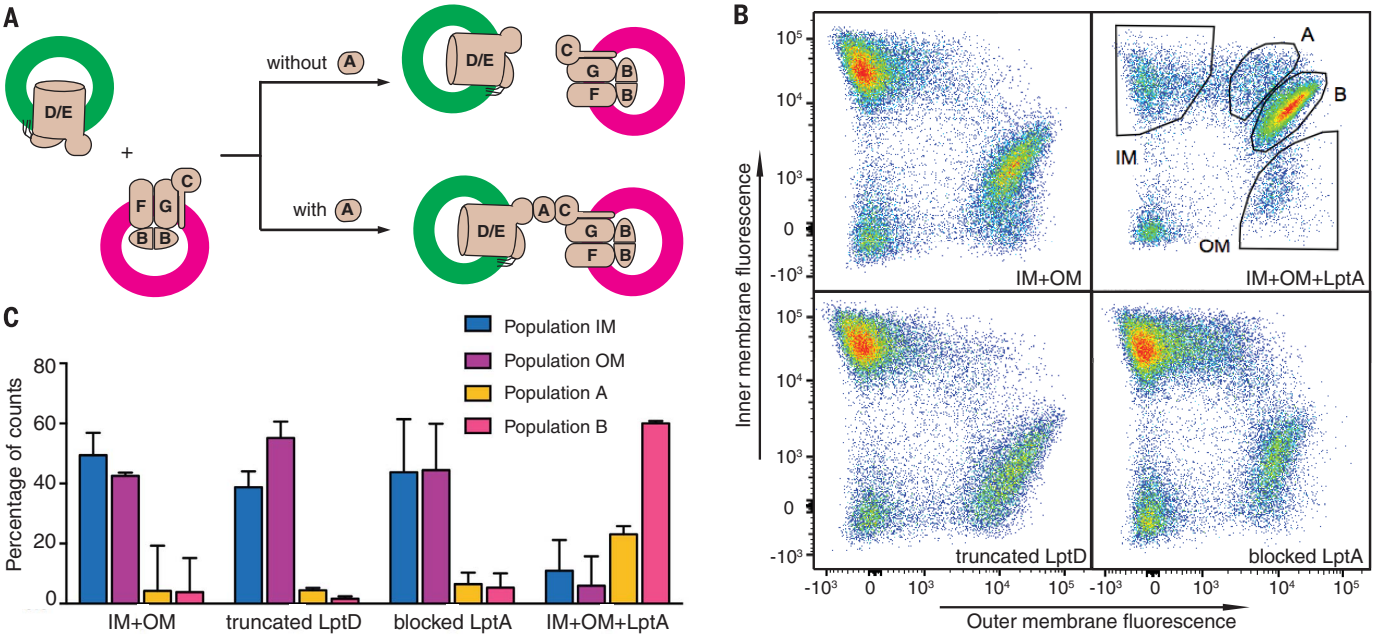

Fig. 3. LptA induces the physical association of inner membrane (IM) and outer membrane (OM) proteoliposomes. (**A**) Schematic of predicted proteoliposome states in the presence or absence of LptA. Proteoliposomes containing LptD-Y112*p*BPA/LptE were labeled with Atto-488 fluorophore, and proteoliposomes containing LptBFGC and LPS (not shown for simplicity) were labeled with Atto-565 fluorophore. (**B**) Flow cytometric analysis of reaction mixtures containing fluorescent proteoliposomes. Atto-488–labeled proteoliposomes containing LptD-Y112*p*BPA/LptE with or without preincubation with LptA were incubated with Atto-565–labeled proteoliposomes containing LptBFGC and LPS. An N-terminal truncated variant of LptD and an N-terminal blocked LptA were used in separate experiments as controls to substitute the corresponding Lpt components in the reaction mixtures. Samples were incubated as described for cross-linking experiments, initiating with buffer instead of ATP. After incubation, samples were diluted 10-fold and analyzed on a BD FACSAria flow cytometer. Equivalent particle distributions were observed in the presence of ATP. (**C**) Distribution of particle counts in gated populations shown in (B). Data were normalized such that percentages of counts represent the portion of the total number of counts in all gated subpopulations. Data represent the mean and SD of triplicate experiments.

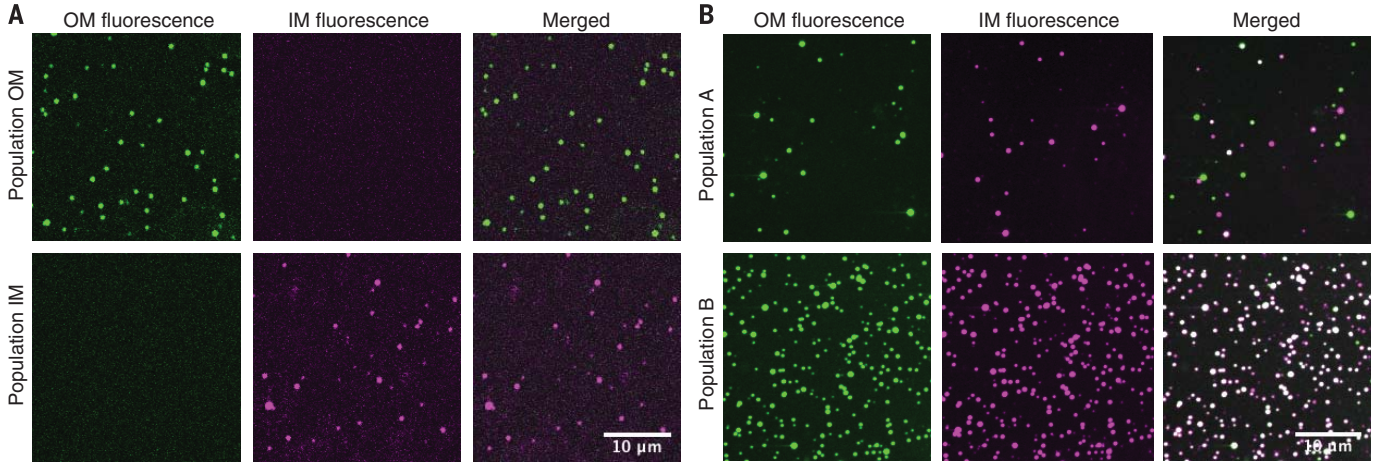

Fig. 4. Observation of a long-lived, protein-mediated bridge by confocal microscopy. (**A**) Representative confocal microscope images of population IM and population OM sorted particles. Atto-488–labeled proteoliposomes containing LptDE with associated LptA were incubated with Atto-565–labeled proteoliposomes containing LptBFGC and LPS and were sorted by gating based on fluorescence thresholds with a BD FACSAria flow cytometer and imaged at 100× magnification. Scale bar: 10 μm. (**B**) Representative confocal microscope images of population A and population B. Atto-488–labeled proteoliposomes containing LptDE with associated LptA were incubated with Atto-565–labeled proteoliposomes containing LptBFGC and LPS and sorted by gating based on fluorescence thresholds using a BD FACSAria flow cytometer and imaged at 100× magnification. Scale bar: 10 μm.

to isolate particles from the four populations observed by flow cytometry (Fig. 3B and fig. S10). Images of the single-color populations (IM or OM) confirmed that they contained only inner or outer membrane proteoliposomes (Fig. 4A). In contrast, the B population contained both inner and outer membrane proteoliposomes with the majority co-localized (fig. S11). This high level of colocalization persisted for at least an hour (Fig. 4B and fig. S12). The A population also contained inner and outer membrane proteoliposomes but had a low level of colocalization (Fig. 4B). The nature of the A population is unclear, but one possibility is that this population contains proteoliposomes that formed unstable complexes that dissociated

following flow cytometry. The bridge and chaperone models of transport can be differentiated by lifetime of the complexes. The LptA-induced association of inner and outer membrane proteoliposomes observed in the B population is not transient, which provides clear evidence for the protein bridge. Notably, these long-lived complexes remain functional. Cross-links between LptD and LPS were observed when ATP was added to the sorted B population (fig. S13).

Our biochemical and flow cytometry experiments show that transport of LPS is mediated by a protein bridge. Based on the dimensions of the periplasm, one or two LptAs would be sufficient, together with LptC and the periplasmic domain of LptD, to span the necessary distance. It is unclear whether there is a fixed stoichiometry of LptA in cells, but LptA is synthesized in cells at the same rate as the membrane components of the Lpt pathway (*32*).

A long-standing question in the field is how energy generated in the cytoplasm can be harnessed to drive LPS molecules to the cell surface against a concentration gradient. The existence of a bridge provides a possible explanation. In our model, LptBFGC extracts LPS molecules from the inner membrane and loads them into the bridge. Each new LPS molecule then pushes molecules already in the bridge toward the outer membrane. This is similar to the action of a PEZ dispenser, in which candies at the top of a stack are pushed out of the top of the dispenser by a spring acting at the base. The PEZ model allows for efficient transport of LPS because movement along a single dimension is faster than movement involving a diffusible chaperone. Millions of LPS molecules must be transported during each round of cell division, and movement along a bridge makes this possible (*1*).

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S13
Tables S1 to S4
References (*33*–*38*)

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Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma

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Immune checkpoint inhibitors targeting the programmed cell death-1 receptor (PD-1) improve survival in a subset of patients with clear cell renal cell carcinoma (ccRCC). To identify genomic alterations in ccRCC that correlate with response to anti-PD-1 monotherapy, we performed whole exome sequencing of metastatic ccRCC from 35 patients. We found that clinical benefit was associated with loss-of-function mutations in the *PBRM1* gene (p=0.012), which encodes a subunit of a SWI/SNF chromatin remodeling complex (the PBAF subtype). We confirmed this finding in an independent validation cohort of 63 ccRCC patients treated with PD-(L)1 blockade therapy alone or in combination with anti-CTLA-4 therapies (p=0.0071). Gene expression analysis of PBAF-deficient ccRCC cell lines and *PBRM1*-deficient tumors revealed altered transcriptional output in JAK/STAT, hypoxia, and immune signaling pathways. *PBRM1* loss in ccRCC may alter global tumor cell expression profiles to influence responsiveness to immune checkpoint therapy.

Immune checkpoint inhibitors such as nivolumab extend the survival of a subset of patients with metastatic ccRCC (*1*). Whether specific genomic features of ccRCC are associated with clinical benefit is unclear. In contrast to other human tumor types that respond to immunotherapy, such as non-small cell lung cancer (NSCLC), melanoma, and microsatellite-unstable colorectal adenocarcinoma, ccRCC harbors a low burden of somatic mutations (*2–5*). Melanoma and NSCLC typically harbor 10 to 400 mutations per megabase (Mb) and these genetic variants can generate tumor-specific antigens (neoantigens) that stimulate a strong anti-tumor immune response (*1–4*). In contrast, ccRCC harbors an average of only 1.1 mutations/Mb (*6*, *7*) yet it ranks highly among tumor types in terms of immune cytolytic activity (*8*), immune infiltration score, and T cell infiltration score in the tumor microenvironment (*9*). These observations led us to hypothesize that distinct molecular mechanisms underlie the immunologically active tumor microenvironment and responsiveness to immune checkpoint therapy in patients with ccRCC.

As part of a prospective clinical trial (*10*), we first analyzed pre-treatment tumors from 35 patients with metastatic ccRCC on a clinical trial of anti-programmed cell death-1 receptor (anti-PD-1) therapy (nivolumab). Whole exome sequencing (WES) from paired tumor/normal tissue was performed to identify genetic correlates of clinical benefit. To validate the findings, we analyzed an independent cohort of 63 patients with metastatic ccRCC treated with therapies blocking PD-1 (e.g., nivolumab) or its ligand PD-L1 (e.g., atezolizumab) (Fig. 1A and table S1A) (*11*).

Baseline clinical and demographic features in the discovery cohort have been previously described (10). The subset of patients with complete pre-treatment molecular profiling did not differ substantially in clinical or demographic features from patients whose data did not meet technical quality control standards (fig. S1, A and B, and Supplemental Methods) or from the larger published cohort (*10*). Given previous evidence suggesting that refined clinical stratifications are necessary to assess clinical benefit from immune checkpoint

blockade (*12*), we defined a composite response endpoint incorporating RECIST (Response Evaluation Criteria In Solid Tumors) (*13*), radiographic tumor shrinkage, and progression-free survival (PFS) (Fig. 1B and table S1B). Clinical benefit (CB) included patients with complete response (CR) or partial response (PR) by RECIST 1.1 (i.e., tumor shrinkage >30% from baseline) (*13*) or stable disease (SD) if they had any objective reduction in tumor burden lasting at least 6 months. This modification to include some patients with SD is intended to differentiate those patients with naturally indolent disease (i.e., slow tumor growth not surpassing 20% of baseline tumor size) from those with tumor response to immune checkpoint inhibitors (*14*). No clinical benefit (NCB) patients experienced progressive disease (PD) by RECIST 1.1 and were discontinued from immunotherapy within three months. All other patients were termed "intermediate benefit" (IB). One patient in the discovery cohort was classified as CB despite PFS < 6 months because there was continued tumor shrinkage (-67% of baseline tumor size) after an initial period of minor tumor progression, and the patient had overall survival exceeding 32 months (fig. S2, A and B). Consistent with prior observations (*1*), the dose of nivolumab, patient gender, and baseline PD-L1 immunohistochemical staining from metastatic biopsies did not predict patient overall survival (OS) following initiation of anti-PD-1 therapy (p>0.05 for all; log-rank test) (fig. S3).

Mean exome-wide target coverage in the discovery cohort was 128-fold for tumor sequencing and 91-fold for matched germline sequencing (tables S1A and S2A). Overall nonsynonymous mutation burden was moderate in the discovery cohort (median 82 per exome, range 45-157). The tumors of patients with CB and those with NCB showed similar mutation burdens and intratumoral heterogeneity (Fig. 1, C and D, and table S1, C and D). Mutations and copy number alterations affecting antigen presentation machinery and HLA class I alleles were uncommon and were present in tumors of both CB and NCB patients (fig. S4, A and B).

We next focused our analysis on the mutations most likely to be functionally important. We applied MutSig2CV (*15*) to identify genes recurrently mutated in the discovery cohort. Of these genes, we limited our search to highly deleterious variants, meaning known hotspot or putative truncating (frameshift insertion or deletion, nonsense mutation, or splice-site) mutations. Of the seven recurrently mutated genes (Fig. 2A and table S1E) (*6*), *PBRM1* was the only gene in which truncating, or loss-of-function (LOF) (*11*), mutations were enriched in tumors from patients in the CB vs. NCB group (9/11 vs. 3/13; Fisher's exact p=0.012, q=0.086, odds ratio for CB=12.93, 95% C.I. 1.54-190.8) (Fig. 2B and table S1F). In this cohort, all truncating *PBRM1* alterations co-occurred with deletion of the non-mutated allele on chromosome 3p (Fig. 2A), resulting in complete LOF of *PBRM1*, and most of the mutations were predicted to be clonal (present in all tumor cells) (table S1F). Prior large-scale sequencing studies have shown that *PBRM1* LOF alterations occur in up to 41% of ccRCC tumors (*16*) and are commonly clonal events present in all or nearly all tumor cells (*17*). Patients whose tumors showed biallelic *PBRM1* loss had significantly prolonged OS and PFS compared to patients without *PBRM1* LOF (log-rank p=0.0074 and p=0.029, respectively) (Fig. 2C and fig. S5), and they experienced sustained reductions in tumor burden (Fig. 2D).

To evaluate the reproducibility of this finding, we then examined matched pre-treatment tumor and germline genomic data from an additional 63 patients treated with anti-PD-(L)1 therapy, either alone or in combination with anti-CTLA-4 therapy. Of these 63 patients, *PBRM1* mutation status was derived from WES in 49 and panel sequencing in 14 patients (Fig. 3, A and B, and table S2, A and B) (*11*). Tumors from CB patients were more likely to harbor truncating alterations in *PBRM1* (17/27 vs. 4/19, Fisher's exact p=0.0071, odds ratio for CB=6.10, 95% C.I. 1.42-32.64) (Fig. 3, C and D, and table S2C). Although we could not assess copy number alterations in all samples in the validation cohort, the *PBRM1* LOF mutations likely represented biallelic loss, as chromosome 3p deletions are nearly ubiquitous in ccRCC (*6*). Notably, one of the four NCB patients whose tumor showed a *PBRM1* LOF mutation also had an alteration in *B2M*, which codes for a protein important in antigen presentation. This provides a potential explanation for the patient's lack of clinical benefit from immune checkpoint blockade therapy despite having a truncating *PBRM1* mutation.

While primary analyses excluded patients with intermediate benefit (IB) due to the unclear effect of immune checkpoint blockade therapy on patient outcomes in this group, the observed trend between *PBRM1* mutation status and clinical benefit persisted with the inclusion of these patients as an intermediate phenotype. In both the discovery and validation cohorts, patients in the IB group had intermediate rates of *PBRM1* LOF (82%, 64%, 23% for CB, IB, NCB in the discovery cohort and 63%, 41%, 21% for CB, IB, NCB in the validation cohort; Fisher-Freeman-Halton Exact p = 0.017 and 0.017). Additionally, while no difference in clinical benefit was observed between treatment-naive and previously-treated patients in the discovery cohort (fig. S2), the progression-free survival benefit conferred by *PBRM1* LOF was more prominent in tumors from previously-treated patients compared to those from patients receiving anti-PD-1 therapy as their first cancer therapy (p=0.009) (fig. S6 and tables S1 and S2).

The *PBRM1* gene codes for BAF180, a subunit of the PBAF subtype of the SWI/SNF chromatin remodeling complex. The PBAF complex suppresses the hypoxia transcriptional signature in *VHL*$^{-/-}$ ccRCC (*18*, *19*) but its effects on tumor-immune interactions have not been thoroughly studied. To explore the

potential impact of this complex on the immunophenotype of ccRCC, we analyzed previously reported whole transcriptome sequencing (RNA-seq) data from A704 ccRCC cell lines with perturbations in the PBAF complex (*19*). Loss of BAF180 or the related PBAF subunit BRG1, encoded by the gene *SMARCA4*, prevent formation of the intact PBAF complex (*19*). We performed gene expression analyses of BAF180-null ($A704^{BAF180-/-}$) cell lines vs. PBAF-wildtype ($A704^{BAF180wt}$) cell lines, as well as BRG1-null ($A704^{BAF180wt, BRG1-/-}$) cell lines vs. PBAF-wildtype ($A704^{BAF180wt}$) cell lines (Fig. 4A). Differential gene expression analysis showed substantial overlaps (~50%) between the top 100 genes differentially expressed in $A704^{BAF180-/-}$ vs. $A704^{BAF180wt}$ and $A704^{BAF180wt, BRG1-/-}$ vs. $A704^{BAF180wt}$ (table S4). This reflects the fact that BAF180 is essential to the PBAF but not the BAF complex, while BRG1 is a required subunit of both. Thus, the BAF180-null and BRG1-null cell lines have some shared characteristics but are also biologically and phenotypically distinct.

Gene set enrichment analysis (GSEA) on 50 "hallmark" gene sets representing major biological processes (*20*) revealed five gene sets whose expression was significantly enriched in cell lines that were PBAF-deficient. These included genes linked to IL6/JAK-STAT3 signaling, TNF-α signaling via NF-κB, and IL2/STAT5 signaling (Fig. 4A and table S5, A and B). As expected, the hallmark hypoxia gene set was upregulated in $A704^{BAF180-/-}$ vs. $A704^{BAF180wt}$ cell lines (family-wise error rate - FWER q=0.071) (table S5A) (*19*). Across the more refined "founder" gene sets describing these five significantly enriched hallmark gene sets, the most strongly enriched gene set in PBAF-deficient cell lines was the KEGG cytokine-cytokine receptor interaction gene set (FWER q=0.0020 for $A704^{BAF180-/-}$ vs. $A704^{BAF180wt}$ and q=0.023 for $A704^{BAF180wt, BRG1-/-}$ vs. $A704^{BAF180wt}$) (Fig. 4A and table S5, C to L). This gene set includes both immune-stimulatory (e.g., *IL12, CCL21*) and immune-inhibitory (e.g., *IL10*) genes, but Gene Ontology term analysis (*11*) showed that the genes most strongly enriched in PBAF-deficient cell lines were immune-stimulatory (table S6). Previously reported GSEA analysis of untreated ccRCC from The Cancer Genome Atlas (TCGA) and a murine model of *PBRM1* loss also show amplified transcriptional outputs of HIF1 and STAT3, involved in hypoxia response and JAK-STAT signaling respectively, in *PBRM1*-mutant vs. *PBRM1*-wildtype states (*18*). GSEA analysis of RNA-seq from pre-treatment tumors in the discovery and validation cohorts of this study (n = 18 *PBRM1*-LOF vs. n = 14 *PBRM1*-intact) confirmed increased expression of the hypoxia and IL6/JAK-STAT3 gene sets in the *PBRM1*-LOF tumors (Fig. 4B and tables S7, A and B, and S8). Given JAK-STAT3 pathway gene involvement in the interferon gamma (IFN-γ-) signaling pathway and IFN-γ-dependent cancer immunostimulation (*21*), differential expression of these genes may impact *PBRM1*-LOF patients' response to anti-PD-(L)1 therapy.

In addition to assessing tumor-intrinsic gene expression with GSEA, we further characterized the quality of the tumor-immune microenvironment in *PBRM1*-LOF vs. *PBRM1*-intact ccRCC in three independent cohorts: TCGA (*6*), an independent cohort of untreated ccRCC tumors (Sato) (*22*), and patient tumors from this study (table S8). In all three cohorts, tumors harboring LOF mutations in *PBRM1* showed lower expression of immune inhibitory ligands (e.g., CD276 and BTLA) (*23*) than those without *PBRM1* mutations. This finding was somewhat unexpected, as high PD-L1 staining is associated with increased responsiveness to anti-PD-1 and anti-PD-L1 agents in other cancer types (*24*, *25*). However, the magnitudes of these differences were small and potentially confounded by differing degrees of tumor-stromal admixture (fig. S7, A to C) (*9*). We also examined LOF mutations in *VHL*, the most commonly-mutated gene in the TCGA ccRCC cohort. *VHL* mutation status did not correlate with immune-related gene expression (fig. S8), suggesting that observed differences in immune gene expression in the context of *PBRM1* LOF may be specific to the *PBRM1* gene.

In summary, we have shown that patients with metastatic ccRCC harboring truncating mutations in *PBRM1* experienced increased clinical benefit from immune checkpoint therapy. This may be due to distinct immune-related gene expression profiles in *PBRM1*-mutant or PBAF-deficient tumor cells compared to their PBAF-intact counterparts, as shown by RNA-seq analyses in this study, though further in vivo studies will be needed to further explore these findings. Given the high prevalence of *PBRM1* LOF in ccRCC and of SWI/SNF alterations across all cancer types (more than 20%) (*26*), this finding has important implications as a molecular tool for considering immunotherapy-responsiveness in ccRCC and across cancer types.

In vivo studies of mice harboring tumor clones with inactivation of *PBRM1* – or the related essential PBAF complex components *ARID2* or *BRD7* – show that cells with PBAF loss are more sensitive to T-cell-mediated cytotoxicity compared to their PBAF-intact counterparts (*27*). This finding lends a mechanistic basis to the results observed here, and helps explain the conflicting results regarding *PBRM1* mutation status as a prognostic variable in ccRCC (in the absence of immunotherapy) in prior studies (*28–36*). *PBRM1* also previously has been linked to longer PFS with VEGF-targeted therapies (*37*). The observed interaction between *PBRM1* status, prior treatment (largely with VEGF inhibitors), and response to immune checkpoint therapy in this study argues for further investigation of patient outcomes from sequential and combination treatment regimens that include anti-PD-(L)1. The relationship between *PBRM1* LOF and clinical benefit from anti-PD-(L)1 therapies in ccRCC, as well as the immunological significance of PBAF loss in other cancer types, merit further preclinical and prospective clinical validation.

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SUPPLEMENTARY MATERIALS

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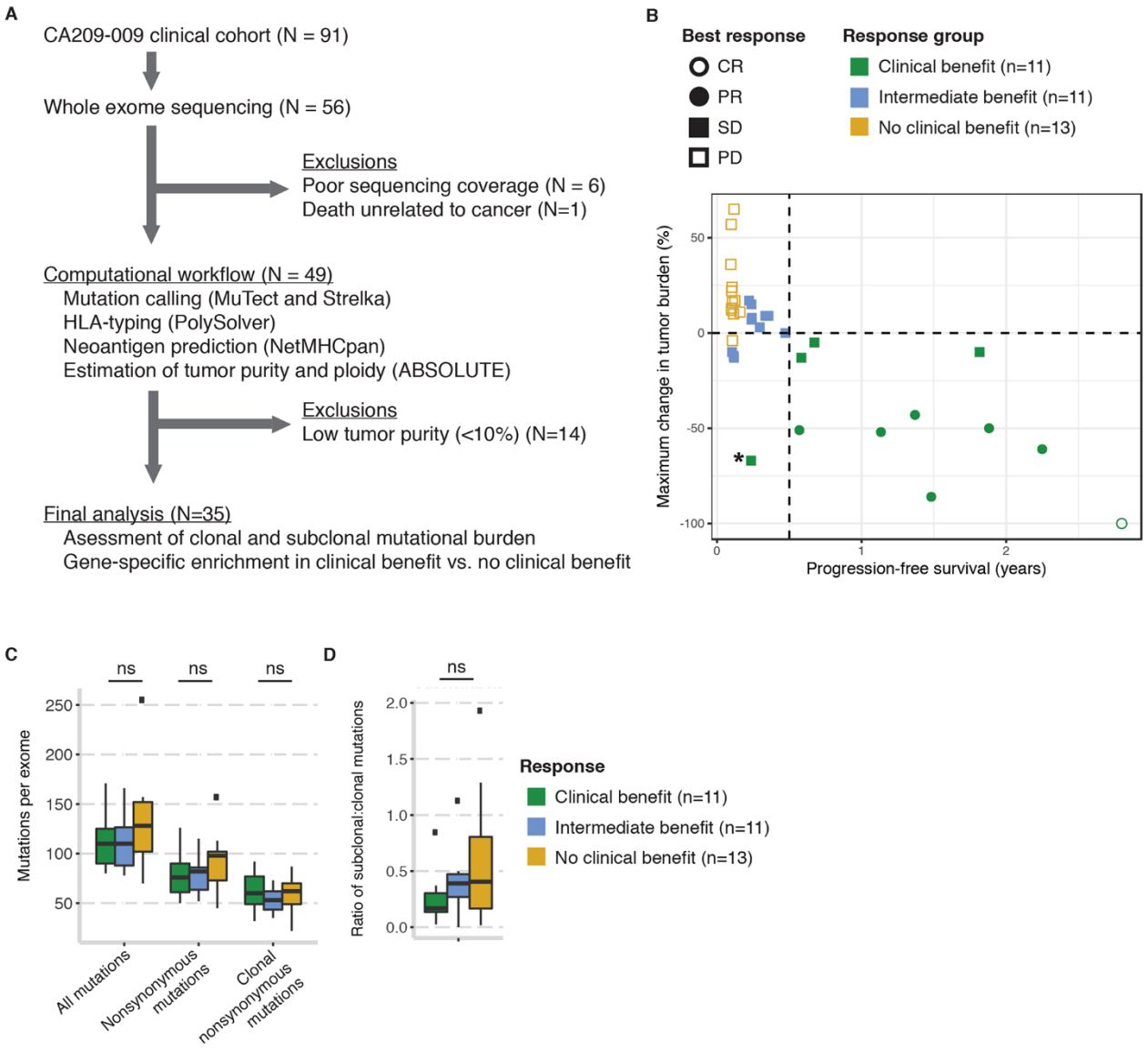

Fig. 1. Cohort consolidation and clinical characteristics of the discovery cohort. (**A**) Sample inclusion/exclusion criteria and computational workflow. (**B**) Clinical stratification by degree of objective change in tumor burden (y-axis) and duration of progression-free survival (x-axis). One patient (RCC_99) not shown due to lack of tumor response data. *Patient RCC_50 was classified as clinical benefit despite PFS<6 months because there was continued tumor shrinkage after an initial period of minor tumor progression (see fig. S2). (**C**) Mutation burden in the discovery cohort by response group. (**D**) Ratio of subclonal to clonal mutations, as estimated by ABSOLUTE, by response group. ns = not significant. Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

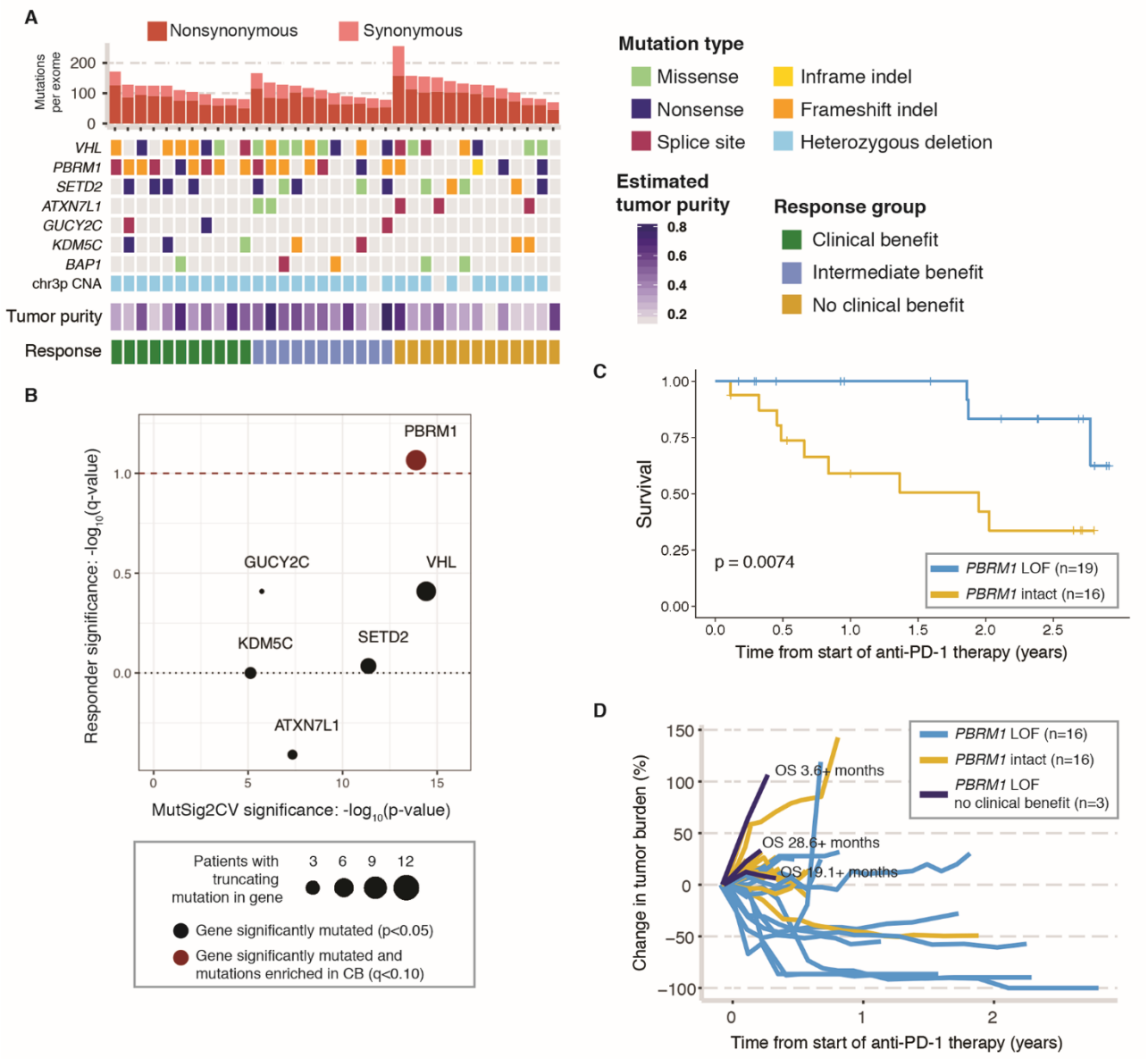

Fig. 2. Analysis of tumor genome features in discovery cohort reveals a correlation between *PBRM1* LOF mutations and clinical benefit from anti-PD-1 therapy. (**A**) Mutations in the discovery cohort. Patients are ordered by response category, with tumor mutation burden in decreasing order within each response category. Shown are the genes that were recurrently mutated at a significant frequency, as assessed by MutSig2CV analysis (table S1E). CNA = copy number alteration. (**B**) Enrichment of truncating mutations in tumors from patients in the CB vs. NCB groups. Red dashed line denotes q<0.1 (Fisher's exact test). Mutations in genes above the black dotted line are enriched in tumors of patients with CB from anti-PD-1 therapy and mutations in genes below the line are enriched in tumors of patients with NCB. (**C**) Kaplan-Meier curve comparing overall survival of patients treated with anti-PD-1 therapy whose tumors did or did not harbor LOF mutations in *PBRM1.* See also fig. S5 for Kaplan-Meier curve comparing progression-free survival of these patients. (**D**) Spider plot showing objective decrease in tumor burden in *PBRM1*-LOF (blue) vs. *PBRM1*-intact (yellow) tumors. Three patients with early progression on anti-PD-1 therapy and truncating mutations in *PBRM1* (dark blue) had long and/or censored OS.

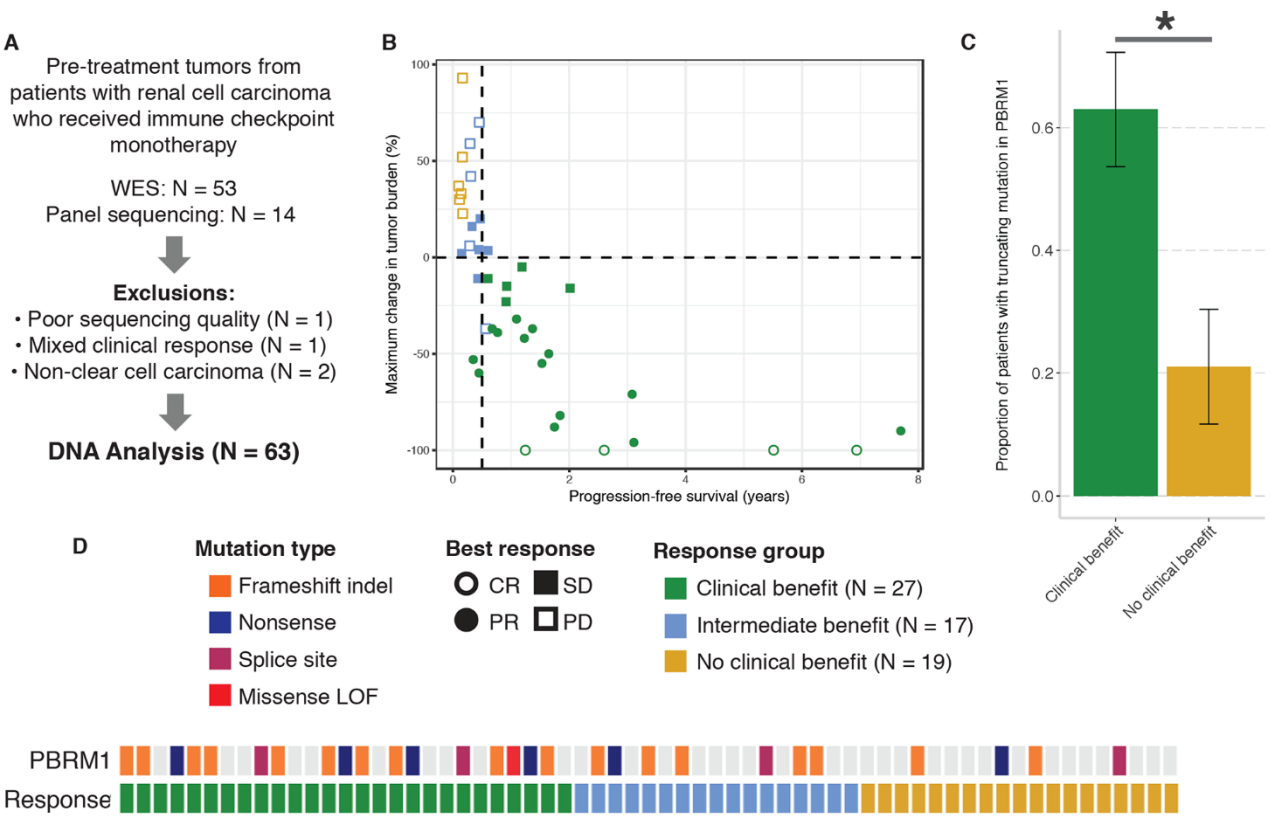

Fig. 3. *PBRM1* LOF mutations correlate with clinical benefit in a validation cohort of ccRCC patients treated with immune checkpoint inhibitors. (**A**) Selection of the validation cohort. (**B**) Clinical outcomes in the validation cohort. Ten patients without post-treatment re-staging scans (eight with clinical PD, two with SD, and one with PR) as well as 14 patients with targeted panel sequencing are not shown. (**C**) Proportion of tumors harboring *PBRM1* LOF mutations in patients in the CB vs. NCB groups. Error bars are S.E. *Fisher's exact $p<0.05$. (**D**) Truncating alterations in *PBRM1* and response to anti-PD-(L)1 therapies by sample. Colored boxes indicate samples with truncating mutations in *PBRM1* while gray denotes samples without *PBRM1* truncating mutations. Missense LOF denotes a missense mutation detected by targeted sequencing that was confirmed to be LOF by PBRM1 immunohistochemistry (see Supplemental Methods).

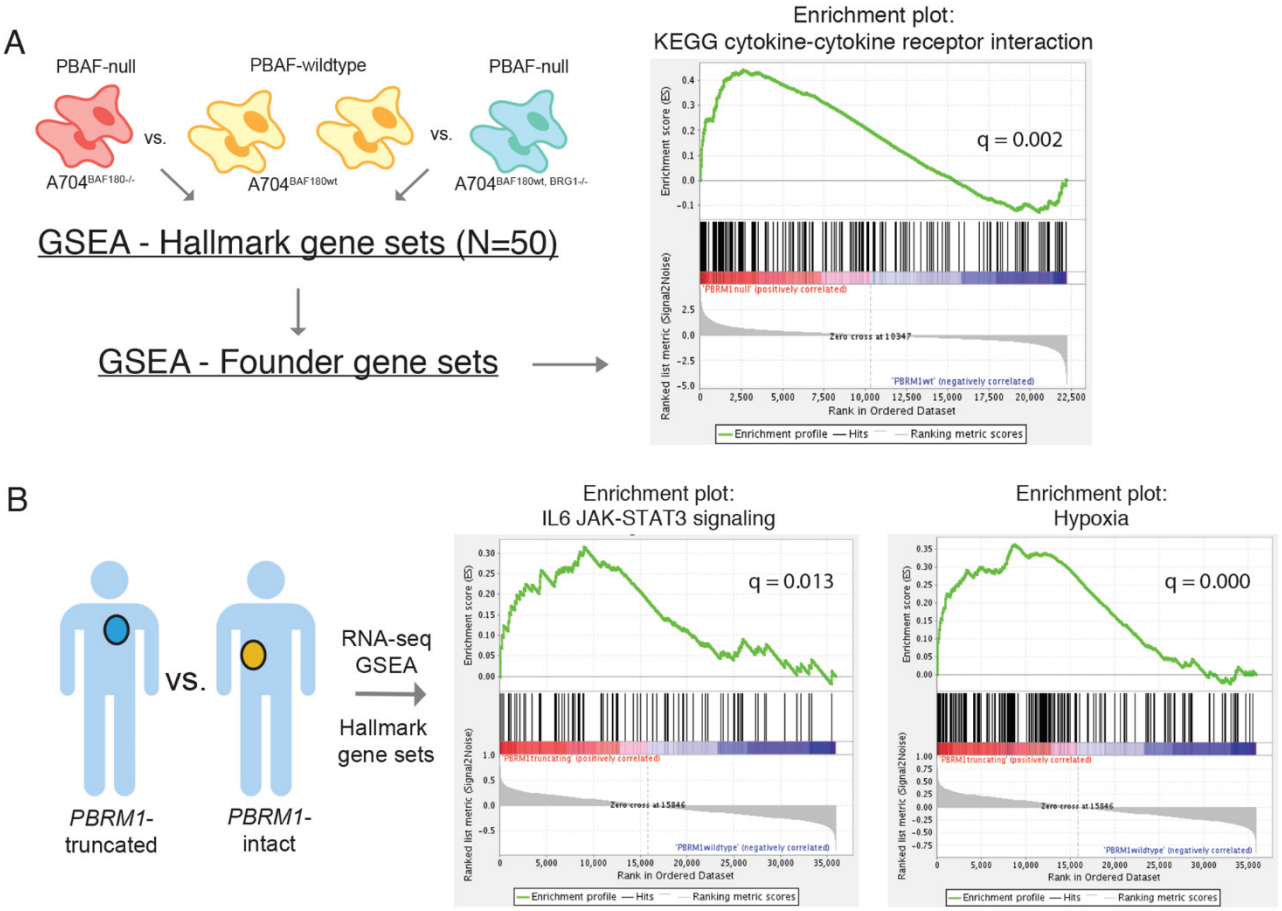

Fig. 4. *PBRM1* mutational status in ccRCC influences immune gene expression. (**A**) GSEA was performed on PBAF-deficient (A704$^{BAF180-/-}$ and A704$^{BAF180wt, BRG1-/-}$) vs. PBAF-proficient (A704^{BAF180wt}) kidney cancer cell lines using both Hallmark and corresponding Founder gene sets. GSEA enrichment plot shown for the KEGG cytokine-cytokine receptor interaction gene set in A704$^{BAF180-/-}$ vs. A704^{BAF180wt} (*PBRM1* null vs. wildtype). Enrichment plot is similar for A704$^{BAF180wt, BRG1-/-}$ vs. A704^{BAF180wt} (*BRG1* null vs. wildtype); see table S4. (**B**) GSEA was also performed on RNA-seq from pre-treatment tumors in the discovery and validation cohorts of this study (n = 18 *PBRM1*-LOF vs. n = 14 *PBRM1*-intact) using the Hallmark gene sets. Enrichment plots show increased expression of the hypoxia and IL6/JAK-STAT3 gene sets in the *PBRM1*-LOF tumors.

TECHNICAL COMMENT

METHANE CHEMISTRY

Comment on "Selective anaerobic oxidation of methane enables direct synthesis of methanol"

Jay A. Labinger

The comment and response concerning the report of oxidation of methane to methanol by water (Reports, 5 May 2017, p. 523) do not fully capture the implications of thermodynamic limitations. A nonisothermal process in which each cycle requires a large temperature swing and permits only substoichiometric methane conversion surely could not be carried out on any practical scale.

The report by Sushkevich *et al.* (*1*) of the oxidation of methane to methanol plus H_2 by water, catalyzed by a copper-exchanged zeolite, stimulated a comment by Periana (*2*) concerning the thermodynamic unfavorability of the net reaction, followed by a response from the original authors (*3*) that includes a detailed thermodynamic analysis. Although the latter may well be strictly correct, it leaves out a key aspect of the thermodynamic limitation on the potential feasibility of a process based on this chemistry.

The oxidation of methane here is carried out in a cyclic process, in which an "activated" catalyst reacts with methane to give bound methoxide, followed by extraction of the methoxide as methanol by water and regeneration of the active site by oxidation. There have been many prior reports of such cyclic processes involving methane activation by zeolite-supported transition metal centers, most frequently Fe or Cu, with regeneration commonly effected by oxidants such as O_2, H_2O_2, or N_2O (*4*). The temporal separation of methane activation from reoxidation is one important reason why this approach can afford methanol in high selectivity, sometimes exceeding 90%. Another key factor for selectivity is the fact that the initial product is sequestered at a surface site, thus retarding overoxidation, which would otherwise compete effectively.

The distinguishing feature of the present work is the oxidation by water: The second half of the cycle entails treatment with H_2O, which both liberates methanol and reoxidizes the metal (here Cu) centers, accompanied by the formation of H_2. The various steps of a cyclic process are represented schematically in the following equations, where the active site is an M^n oxide species (M^n = Cu^{II} or Fe^{III}; the actual species will, of course, have much more complex structures) that activates methane to form a methoxide in Eq. 1, accompanied by reduction to M^{n-1}. Methanol is extracted by water in Eq. 2. In earlier work, the metal is reoxidized to M^n by an oxidant, shown as O_2 in Eq. 3a; the sum of these three steps is overall reaction Eq. 4a. In the present work, water effects both methanol extraction as in Eq. 2 and reoxidation as in Eq. 3b, followed by purging under He to remove bound water (Eq. 3c); the overall reaction is thus Eq. 4b. As Periana notes, whereas Eq. 4a is strongly favored thermodynamically, Eq. 4b is highly unfavorable. At 200°C, the temperature at which methane activation takes place, the calculated equilibrium constant is around 10^{-13} (*2*).

$$2M^nO + CH_4 \rightarrow M^{n-1}(OCH_3) + M^{n-1}(OH) \quad (1)$$

$$M^{n-1}(OCH_3) + H_2O \rightarrow M^{n-1}(OH) + CH_3OH \quad (2)$$

$$2M^{n-1}(OH) + {}^1/_2O_2 \rightarrow 2M^nO + H_2O \quad (3a)$$

$$2M^{n-1}(OH) + H_2O \rightarrow (2M^nO)\cdot H_2O + H_2 \quad (3b)$$

$$(2M^nO)\cdot H_2O \rightarrow 2M^nO + H_2O \quad (3c)$$

$$CH_4 + {}^1/_2O_2 \rightarrow CH_3OH \quad (4a)$$

$$CH_4 + H_2O \rightarrow CH_3OH + H_2 \quad (4b)$$

The response takes issue with several aspects of Periana's comment: that it assumes standard states for all reactants; that it ignores adsorption energies and intermediates that can provide stabilization along the way; and that it fails to recognize that the methanol desorption, reactivation, and dehydration steps are carried out at elevated temperatures, ramping up to 400°C (*3*). Only the last of these is really important: That methane is supplied at elevated pressure and H_2 released at much lower pressure could have only a minor impact on an unfavorable K_{eq} of such a magnitude, and the nature of intermediate species would have no effect at all on the thermodynamics of the overall transformation if it were isothermal. However, because Eqs. 3b and 3c (along with Eq. 2) take place at a higher temperature than Eq. 1, additivity no longer applies, and the net process of Eq. 4b may indeed be thermodynamically allowed. One way of explaining this effect is that a step with highly positive ΔS (Eq. 3c) takes place at a higher temperature than one with highly negative ΔS (Eq. 1), thus maximizing favorable entropic contributions to the overall ΔG of the process.

Note that the use of a so-called "soft" oxidant, water, does not in itself afford any inherent improvement in selectivity for this process, as the reoxidation is temporally separated from the methane reaction. Sushkevich *et al.* do in fact find somewhat poorer selectivity when they carry out the reoxidation with O_2, which they ascribe to formation of some harsher oxidizing sites (*1*), but that need not be the case for all such catalysts; indeed, as noted above, some studies on cyclic processes using "harder" oxidants have reported excellent selectivity.

More important, what their analysis neglects is the crucial role of thermal cycling. As Periana's comment shows, that is a requisite part of the process: Thermodynamics precludes isothermal operation at any reasonable temperature, in contrast to the earlier work with O_2 or other traditional oxidants. It is true that in many of those studies, reoxidation is carried out at a higher temperature as well, but that is not a thermodynamically imposed requirement; isothermal operation—sometimes even in continuous, noncyclic mode—has been achieved in a few instances (*4*). Here, that could not be possible.

Where does the heat needed to achieve this required temperature increase come from? Obviously, from burning something! When viewed globally, this is not really an anaerobic process at all; rather, the introduction of O_2 is separated from the methane activation both temporally and spatially, taking place outside the main reactor. Ideally one could imagine that burning the H_2 liberated in Eq. 3b would produce the needed heat, giving us the additional Eq. 5:

$$H_2 + {}^1/_2O_2 \rightarrow H_2O \quad (5)$$

When that is added in, the overall transformation reported here—counting everything—becomes Eq. 4a, not 4b, which provides an alternative explanation of why it is thermodynamically allowed. (In a real process, the amount of heat thus generated would surely be insufficient, requiring the combustion of additional feedstock and thus substantially reducing the efficiency of the overall process.)

Sushkevich *et al.* conclude that "…it is too early to estimate the financial costs of this process and to doubt the possibility of its commercialization"

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(*3*). Could a large-scale process (as will certainly be needed for methane conversion) that is restricted on thermodynamic grounds to a cyclic mode, in which a maximum of half an equivalent of methane per metal center can be converted per cycle, and that requires a substantial temperature swing on each cycle, really prove to be commercially feasible? Given such constraints, I do not believe it is at all too early to doubt.

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10.1126/science.aar4968

TECHNICAL RESPONSE

METHANE CHEMISTRY

Response to Comment on "Selective anaerobic oxidation of methane enables direct synthesis of methanol"

Vitaly L. Sushkevich,[1]* Dennis Palagin,[1] Marco Ranocchiari,[1] Jeroen A. van Bokhoven[1,2]*

Labinger argues that stepwise reaction of methane with water to produce methanol and hydrogen will never be commercially feasible because of its substoichiometric basis with respect to the active site and the requirement of a large temperature swing. This comment is not touching any new ground, beyond describing the thermodynamic feasibility, thermal cycling, and the role of water as discussed previously. Most important, it does not have a solid numerical basis.

Labinger (*1*) questions the applicability of anaerobic oxidation of methane into methanol (*2*), citing the thermodynamic limitation and the substoichiometric nature of the reaction with respect to the number of copper atoms in the active site. He accepts our discussion of thermodynamics, following the conditions in each step as well as the modeling of the actual reactive species, without which false conclusions like those of Periana are drawn (*3*, *4*).

Labinger takes issue with the energy required to complete the cycle, and with the presence of the temperature increase at the reactivation step. Besides once again referring the author to the response to the original comment (*4*)—where the same questions of thermodynamic feasibility, thermal cycling, and the role of water were discussed in great detail—we emphasize that the net reaction corresponding to the anaerobic transformation of methane into methanol is, from the enthalpic point of view, equivalent to the two-step synthesis of methanol from methane via syngas, which is widely used in industry without any restriction. This means that in an ideal case, one needs the same amount of energy per ton of methanol for both methods. The harsh conditions of methane steam reforming and methanol synthesis are not impediments to its efficiency and widespread commercial application.

Furthermore, there are numerous large-capacity industrial processes, such as fluidized catalytic cracking and methanol conversion into olefins, that use the temperature swing at different steps (i.e., the main reaction and the regeneration step), without limitations. This fact directly indicates that a rapid temperature switch is a solvable "problem" of chemical engineering rather than a fundamental limitation.

Labinger correctly suggests that the energy required for the temperature increase can be, for instance, obtained from burning hydrogen formed in the reaction. In a favorable scenario where this process is integrated within the reaction, the latter becomes thermodynamically favorable. Whether this is possible remains to be determined. Also, the optimized materials have not yet been developed, and the ideal process conditions (and the size of the temperature swing, if any) have not yet been identified. Our initial report (*2*) presents a scientific discovery, not an optimized process that is ready to be implemented. Future development of novel materials and optimization of the conditions are clearly a necessity.

Labinger further contests whether a process in which "a maximum of half an equivalent of methane per metal center can be converted per cycle [could] really prove to be commercially feasible?" From an industrial feasibility point of view, the methanol productivity per reactor volume per unit of time parameter is important, rather than the number of copper atoms in the active site. The amount of methanol per reactor volume per unit of time can be improved by maximizing the density of active sites and increasing the rates of reaction and product desorption, thus shortening the time required for the full reaction cycle. To compare, typical productivities of industrial processes based on heterogeneous catalysts account for 50 to 500 kg(product) m^{-3}(reactor) $hour^{-1}$ (*5*), which is about two to three orders of magnitude higher than the methanol productivity in the reported process (*2*). Therefore, achievement of fast cycling in a stepwise process with maximal methanol yield per cycle is feasible by material, process, and reactor development—the parameters that will determine whether industrial application is feasible. At this stage, it is too early to make this determination (*4*).

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18 December 2017; accepted 21 December 2017
10.1126/science.aar6868

Discussion leaders are noted in bold italics.

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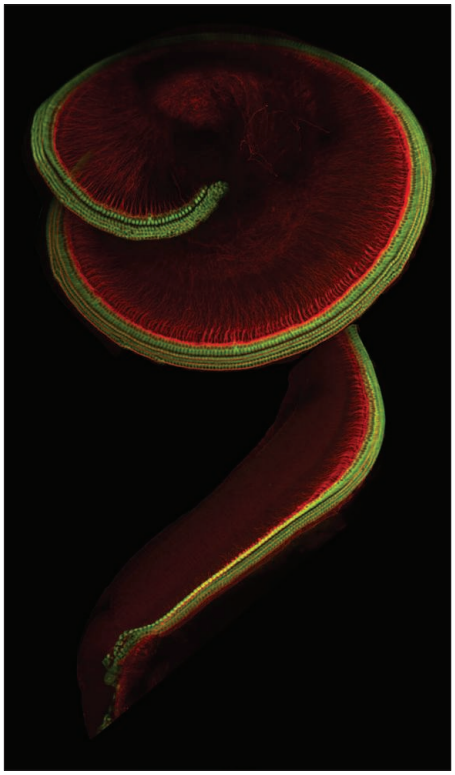

The developing mouse cochlea, the peripheral sensory organ in the auditory system. The spiral-shaped cochlea includes ~4,000 sensory hair cells stained in green and ~20,000 neurons stained in red. CREATED BY CARL NIST-LUND AND BIFENG PAN. SUBMITTED BY THE 2018 AUDITORY SYSTEM GRC CHAIRS.

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VICE CHAIRS: Gerrit Poelarends & Birgit Kosjek

- **Keynote Session: New Vistas in Enzyme Catalysis and Biocatalytic Systems** *Bernhard Hauer,* Jay Keasling, Emily Balskus
- **Pathway Construction and Design** *Wei Niu,* Kristala Jones-Prather, Magali Remaud-Simeon, Gregg Whited, Emma Master
- **Emerging Techniques, Structural Biology (Cryo-EM; XFEL Crystallography)** *David Rockcliffe,* Wah Chiu, So Iwata,
- **New Enzymes, Activities** *Sabine Flitsch,* Yi Tang, Alison Narayan, Uwe Bornscheuer, Dunming Zhu
- **Bioinformatics, In Silico Tools; Biodynamics** *Janine Copp,* Rene De Jong, Dick Janssen, Dorothee Kern
- **New Transformations, Sequences** *Todd Hyster,* Melanie Hall, Helen Hailes, Elaine O'Reilly, Rajesh Kumar
- **Biocatalysis Moving Forward: Developments at the Interface with Systems Biology, Synthetic Chemistry and Systems Engineering** *Andreas Schmid,* Nicholas Turner, Theresa Good, Richard Dickinson, Robert Stack
- **New Strategies in Biocatalysis** *Stefan Lutz,* Michelle Chang, James Lalonde, David Weiner, Jason Micklefield
- **Selected Poster Presentations** *Gerrit Poelarends, Birgit Kosjek*
- **Power Hour** *Birgit Kosjek, Joelle Pelletier*

Biocatalysis
From the Basics of Biocatalysis to Industrial Applications
JULY 7-8, 2018
CHAIRS: Charlotte LM. Kürten & Lisa Marx

Biogenic Hydrocarbons and the Atmosphere

Connecting Volatiles and the Climate System from Leaf to Planet

JUNE 10-15, 2018 • LES DIABLERETS CONFERENCE CENTER, LES DIABLERETS, SWITZERLAND

CHAIRS: Nadine Unger & Riikka Rinnan
VICE CHAIRS: Mark J. Potosnak & Jaana K. Back

- **Keynote Session: Biogenic Hydrocarbons in the Earth System: Cracking the Enigma** *Markku Kulmala,* Almut Arneth, Thanos Nenes

- **Vegetation: From Plant Ecophysiology to Microbial Interactions** *Ulo Niinemets,* Kolby Jardine, Jaana Back, Consuelo De Moraes
- **Role of Microbes in Exchange of Biogenic Volatiles (Soil and Water)** *Francesco Loreto,* Dolores Asensio, Michael Steinke
- **Ecosystem Fluxes and Connections to Biogeochemical Cycles** *Allison Steiner,* Dan Yakir, Zhaozhong Feng, Sonia Seneviratne
- **Nitrogen and Methane in the Earth System** *Nick Hewitt,* Sönke Zaehle, Mari Pihlatie
- **Young Investigator Presentations** *Mark Potosnak*
- **Past and Future Worlds: From Ice Cores to Plant Engineering** *Alex Guenther,* Osamu Seki, Joerg-Peter Schnitzler
- **Understanding Atmospheric Impacts: Air Quality, Clouds and Climate** *Delphine Farmer,* Neil Donahue, Hong Liao, Ilona Riipinen
- **New Discoveries in Biogenic Hydrocarbons and the Earth System Climate Sensitivity** *Allen Goldstein,* Lain Prentice, Dominick Spracklen

Biogenic Hydrocarbons and the Atmosphere
Building Bridges in Hydrocarbon Research: Understanding Emissions to Impacts
JUNE 9-10, 2018
CHAIRS: Juho Aalto & Kandice L. Harper

Bioinspired Materials

Bioinspired Multifunctional Dynamic Materials

JUNE 24-29, 2018 • LES DIABLERETS CONFERENCE CENTER, LES DIABLERETS, SWITZERLAND

CHAIR: Zhibin N. Guan
VICE CHAIR: Daniel A. Hammer

- **Keynote Session: Inspiration from Nature** *Timothy Deming,* Herb Waite, David Baker
- **Active and Adaptive Materials** *Phillip Messersmith,* Joanna Aizenberg, Eric Dufresne, Jan van Esch
- **Systems and Living Materials** *Ximin He,* Neel Joshi, Rebecca Schulman
- **Bioinspired Materials for Medicine** *Ellen Sletten,* Kristi Anseth, Evan Scott, Molly Stevens
- **Bioinspired Devices** *Esther Amstad,* Roisin Owens, David Weitz
- **Bioinspired Assemblies** *Nico Bruns,* Takuzo Aida, Akif Tezcan, Xi Zhang
- **Peptide and Protein Materials** *Allon Hochbaum,* Rein Ulijn, Dek Woolfson
- **Bioinspired Synthetic Polymers** *Hongbin Li,* Alon Gorodetsky, Rainer Haag
- **Hybrid/Photonic Materials** *Lauren Zarzar,* Mathias Kolle, Andre Studart

Bioinspired Materials
Leveraging Bio-Molecular Complexity in Multi-Functional Synthetic Materials
JUNE 23-24, 2018
CHAIRS: Nathan A. Carter & Joel A. Finbloom

Biointerface Science

Surfaces and Compartments in Biology and Medicine

JUNE 17-22, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIR: Hagan Bayley

VICE CHAIR: Jay Groves

- **Keynote Session: Surfaces and Compartments in Biology and Medicine** *Ashutosh Chilkoti,* Dennis Discher, Cees Dekker
- **Characterization of Biointerfaces: Advances in Technology** *Lorenzo Abertazzi,* Sriram Subramaniam, Philipp Kukura, Ke Xu
- **Chemistry at Biointerfaces** *Patricia Dankers,* Adam Perriman, Zev Gartner
- **Compartmentalization** *Atul Parikh,* Wilhelm Huck, Rumiana Dimova, Joanna Aizenberg
- **Synthetic Cells** *Katarzyna Adamala,* Bert Poolman, John Sutherland
- **Molecular Assemblies on Membranes** *Marileen Dogterom,* Christine Keating, Enfu Hui, Michael Dustin
- **Cell Colonies and Communities** *Knut Drescher,* Reza Ghadiri, Jean-Marc Ghigo
- **Biointerfaces in Medicine** *Katharina Maniura,* Haifeng Ye, Yan Yan Huang, William Wagner
- **Late-Breaking Topics** *Oscar Ces, Daniel Mueller*

Biointerface Science
Bridging the Gaps Between Biology, Chemistry and Functional Materials
JUNE 16-17, 2018
CHAIRS: Alexander F. Mason & Tagbo H. Niepa

Biology of Host-Parasite Interactions

Eukaryotic Parasites: From Discovery Research to Clinical Interventions

JUNE 10-15, 2018 • SALVE REGINA UNIVERSITY, NEWPORT, RI

CHAIRS: Margaret A. Phillips & Luisa M. Figueiredo

VICE CHAIRS: Kirk W. Deitsch & Michael Barrett

- **Global Impact of Parasitic Pathogens on Human Health** *David Fidock,* Jeremy Burrows, Annette MacLeod, Rick Tarleton
- **Genome and Genes, Expression and Regulation** *Nicolai Siegel,* Artur Scherf, David Horn, Upinder Singh, David Roos
- **Pathogenesis and Host Cell Remodeling** *Manoj Duraisingh,* Patricia Johnson, Barbara Burleigh, Alan Cowman
- **Antigenic Variation** *Nina Papavasiliou,* Kirk Deitsch, Joe Smith, Monica Mugnier, David Sibley
- **Immunity and Vaccines** *Kim Williamson,* Miguel Prudencio, Steve Beverley, Klaus Brehm
- **Metabolic Vulnerabilities and Impact on Life Cycle** *Sean Prigge,* Michael Barrett, Maria Lafuente, Geoffrey McFadden, Sebastian Lourido
- **Parasite and Host Cell Communication** *Isabel Roditi,* Kent Hill, Elissa Hallem, Katie Ralston
- **Drug Development** *Elizabeth Winzeler,* Kelly Chibale, Leah Frye, Paul Wyatt, Thierry Diagana
- **Challenges to Effective Therapy** *Nicole Andenmatten,* Jayne Raper, Pradipsinh Rathod, Dyann Wirth
- **Power Hour** *Nina Papavasiliou, Jayne Raper*

Biology of Host-Parasite Interactions
Parasitic Diseases: From Basic to Translational Research
JUNE 9-10, 2018
CHAIRS: Gustavo A. Afanador & Sandra Trindade

Biomineralization

Fundamental Biotic and Abiotic Mechanisms of Biomineralization

JULY 29 – AUGUST 3, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIR: Derk Joester

VICE CHAIR: Janet Moradian-Oldak

- **The Mineral-Water Interface** *Hendrik Heinz,* Rosa M. Espinosa-Marzal, Takeshi Fukuma
- **The Role of Vesicular Transport and Processing** *Mike Hubbard,* Lia Addadi, Jonathan Erez, Catherine Shanahan
- **Of Mechanisms and Proxies** *Jennifer Fehrenbacher,* Kristen Fichthorn
- **Mechanisms of Biological Crystal Growth Control** *Felicitas Bidlack,* Fabio Nudelman, Yael Politi, Andre Scheffel
- **Fundamentals of Phase Transformations** *Mike Sleutel,* Lara Estroff, Jeffrey Rimer
- **From Genes to Biomineralized Tissues** *Smadar Ben Tabou de Leon,* Ophir Klein, Cynthia Bradham, Yue Him Wong
- **Bio-Inspired Processes and Materials** *Ana Bedran-Russo,* Christine Keating, Sarah Staniland
- **Mineralization in Collagenous Matrices** *Eli Sone,* Nico Sommerdijk, Franklin Tay, Kathryn Grandfield
- **Keynote Session: On Growth and Form** *Derk Joester,* Jukka Jernvall, Shunai Che
- **Power Hour** *Noah Metoki, Utthara Rameshbabu*

Biomineralization
Biomineralization Across Disciplines: Integrating In Vivo, In Vitro and In Silico into an Overall View
JULY 28-29, 2018
CHAIRS: Keren Kahil & Giulia Mirabello

Bioorganic Chemistry

The Development of Chemical Probes to Decipher Biology

JUNE 10-15, 2018 • PROCTOR ACADEMY, ANDOVER, NH

CHAIRS: Paul R. Thompson & Erik C. Hett

VICE CHAIRS: Jason E. Gestwicki & Paola Castaldi

- **Covalent Inhibitors as Drugs** *Daniel Nomura,* Benjamin Cravatt, Nathanael Gray, Sherry Niessen, Bryan Dickinson
- **Chromatin Modifying Enzymes** *Champak Chatterjee,* James Bradner, Philip Cole, Danica Fujimori, Jordan Meier, William Pomerantz, Kabirul Islam
- **Liganding Undruggable Targets** *Raymond Moellering,* Michelle Arkin, Lawrence Hamann, Craig Crews
- **Chemical Microbiology** *Stavroula Hatzios,* Suzanne Walker, Wilfred van der Donk, Sarah O'Connor, Elizabeth Sattely, Sarah Slavoff
- **Chemical Biology in Drug Discovery** *Catherine Leimkuhler Grimes,* Steve Zimmerman, Gitte Neubauer, Kay Ahn, John Howe
- **Imaging and Optochemical Control** *Ellen Sletten,* Jin Zhang, Dirk Trauner, Alexander Deiters, Jennifer Heemstra
- **Modulating Protein Function** *Rongsheng (Ross) Wang,* Benjamin Davis, Herbert Waldmann, Shana Kelley
- **Targeting RNA with Small Molecules** *Ming Hammond,* Matthew Disney, Hashim Al-Hashimi, Russell Petter, Atwood Cheung, Amanda Hargrove, Jay Schneekloth
- **New Chemical Tools to Unlock Biology** *Darci Trader,* Yimon Aye, Kevin Weeks, Dorothea Fiedler

Bioorganic Chemistry
Unraveling Complex Biological Problems in Disease with Creative Bioorganic Chemical Solutions
JUNE 9-10, 2018
CHAIRS: Tyler Bechtel & Kristen E. DeMeester

Cardiac Regulatory Mechanisms

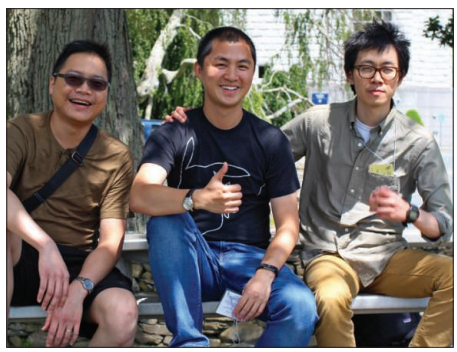
From Cardiac Mechanisms to Novel Therapeutic Approaches

JUNE 3-8, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIRS: Brian O'Rourke & Thomas Eschenhagen

VICE CHAIRS: Jill Tardiff & Christoph Maack

- **New Aspects of Cardiac Regeneration, Repair and Development** *Maria Kontaridis, William Pu,* Nipavan Chiamvimonvat, Chulan Kwon, Miguel Torres, Jop VanBerlo
- **Pathophysiological Signal Transduction in Myocardial Remodeling** *Burns Blaxall,* Kimberly Dodge-Kafka, Emilio Hirsch, Walter Koch, Jeffrey Saucerman
- **Regulation of the Heart by Non-Coding RNAs and Chromatin** *Tom Vondriska,* Reinier Boon, Saptarsi Haldar, Susmita Sahoo, Thomas Thum
- **Metabolic and Mitochondrial Dysfunction in Cardiovascular Disease** *Asa Gustafsson,* Dale Abel, Mark Anderson, Jun Sadoshima, Rong Tian, Rosario Rizzuto



- **Role of Non-Myocytes in Cardiac Regulation** *Jennifer Davis,* Raj Kishore, David Paterson, Christian Soeller, Serena Zacchingna
- **Aberrant Ca Signaling and Arrhythmia Mechanisms** *Karin Sipido,* Donald Bers, Mario Delmar, John Elrod, Bjorn Knollmann, Geoffrey Pitt
- **Regulation of and by Myofilaments** *Leslie Leinwand,* Anthony Cammarato, Stuart Campbell, Michael Gotthardt
- **Novel Technologies and Therapies** *Jolanda Van Der Velden,* Lucie Carrier, Amedee des Georges, Jennifer Van Eyk, Tom Vondriska
- **Keynote Session: Translating Mechanisms to Therapies** *Jill Tardiff, Christoph Maack,* David Kass, Jeffery Molkentin

Cardiac Regulatory Mechanisms
Pioneering Developments in Basic and Translational Cardiovascular Research
JUNE 2-3, 2018
CHAIRS: Pearl J. Quijada & Catherine A. Makarewich

Carotenoids

Carotenoids, Apocarotenoids and Retinoids: From Nature to Bedside

JUNE 17-22, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Giovanni Giuliano

VICE CHAIR: Loredana Quadro

- **Keynote Session: Landmarks in Carotenoid Research** *George Britton, Paul Bernstein,* Peter Beyer, John Landrum, Koichi Yoneyama
- **Enzymology and Metabolism** *Li Li,* Johannes Von Lintig, Joseph Hirschberg, Eugenia Poliakov
- **Regulation and Systems Biology** *Dean Dellapenna,* Barry Pogson, Michel Havaux
- **Biofortification and Bioavailability** *Eleanore Wurtzel,* Amanda Palmer, Yaakov Tadmor, Torbert Rocheford
- **Carotenoids and Vision** *Joseph Corbo,* Belinda Chang, Julie Mares
- **Apocarotenoids and Retinoids** *Earl Harrison,* William Blaner, Salim Al-Babili, Natalia Kedishvili
- **Carotenoids in Photosynthesis** *Roberto Bassi,* Graham Fleming, Mei Li, Roberta Croce
- **Carotenoids and Chronic Disease** *Elizabeth Johnson,* Xiang-Dong Wang, Howard Sesso, Dingbo Lin
- **Microorganisms and Biotechnology** *Paul Fraser,* Krishna Niyogi, Javier Avalos
- **Power Hour** *Jessica Cooperstone*

Carotenoids
Carotenoids, Apocarotenoids and Retinoids: From Nature to Bedside
JUNE 16-17, 2018
CHAIRS: Alexandra J. Dickinson & Jessica L. Cooperstone

Catalysis

Accelerating Catalytic Solutions to Global Grand Challenges

JUNE 24-29, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIR: Fabio H. Ribeiro

VICE CHAIR: Susannah Scott

- **Hydrocarbon Catalysis** *Unni Olsbye,* James Rekoske, Aditya Bhan
- **New Materials for Catalysis** *Matteo Cargnello,* Jeffrey Rimer, Rajamani Gounder, Mizuki Tada
- **Electrocatalysis** *Bingjun Xu,* Thomas Jaramillo, Marc Koper
- **New Chemistries** *Placidus Amama,* Beatriz Cuenya, Xiulian Pan, Beata Kilos-Reaume
- **Connecting Homogeneous and Heterogeneous Catalysis** *Nicholas Brunelli,* T. Brent Gunnoe, Christophe Copere
- **New Concepts in Theory for Catalysis** *Jean-Sabin McEwen,* Linda Broadbelt, Andrew Peterson, Thomas Bligaard
- **Young Investigator Presentations** *David Flaherty,* Aleksandra Vojvodic, David Hibbitts, Eranda Nikolla
- **New Characterization Techniques** *Andrew (Bean) Getsoian,* Silvia Bordiga, Robert Rioux, Lynn Gladden
- **Keynote Session: Surface Chemistry of Catalytic Systems** *Susannah Scott,* Enrique Iglesia
- **Power Hour** *Beata Kilos-Reaume, Eranda Nikolla*

Catalysis
Accelerating Catalytic Solutions to Global Grand Challenges
JUNE 23-24, 2018
CHAIRS: Viktor J. Cybulskis & James Harris

Cell Biology of the Neuron

Emerging Themes in Neuronal Trafficking, Homeostasis, Synapse Function and Disease Mechanisms

JUNE 24-29, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIRS: Erika L.F. Holzbaur & Matthijs Verhage
VICE CHAIRS: Kang Shen & Valeria Cavalli

- **Keynote Session: The Cell Biology Revolution in Neuroscience** *Matthijs Verhage,* Reinhard Jahn, Thomas Sudhof
- **Organelle, Protein and RNA Trafficking** *Casper Hoogenraad,* Juan Bonifacino, Franck Polleux, Thomas Schwarz
- **Transcriptional, Translational and Posttranslational Regulation** *Valeria Cavalli,* Claudia Bagni, Jens Hjerling Leffler, Antonina Roll-Mecak
- **Synapse Dynamics and Function** *Daniel Colon-Ramos,* Volker Haucke, Erik Jorgensen, Timothy Ryan
- **Neurons in Context** *Kelsey Martin,* Monica Driscoll, Thomas Kuner, Avital Rodal
- **Synaptic Alignment and Connectivity** *Kang Shen,* Thomas Blanpied, Joris de Wit, Pascal Kaeser
- **Homeostasis, Aggregation and Autophagy** *Patrik Verstreken,* Zu-Hang Sheng, Ai Yamamoto
- **Cell Biology of Neuronal Degeneration and Regeneration** *Shelley Halpain,* Yishi Jin, Charlotte Sumner
- **Keynote Session: From Static Images to Imaging Dynamics in Living Neurons** *Erika Holzbaur,* Lily Jan, Jennifer Lippincott-Schwartz
- **Power Hour** *Valeria Cavalli, Erika Holzbaur*

GRS Cell Biology of the Neuron
The Dynamic Neuron: Trafficking, Development and Synaptic Plasticity
JUNE 23-24, 2018
CHAIRS: Rebecca Cox & Robyn L. McAdam

Cell Death

Cell Death Mediators in Normal and Disease Physiology

AUGUST 5-10, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Marion MacFarlane
VICE CHAIR: Francis K. Chan

- **Keynote Session: Perspectives on Cell Death and Disease** *Marion MacFarlane,* Henning Walczak, Andreas Strasser
- **Peering into the Molecular Machines that Regulate Cell Death and Inflammation** *Francis Chan,* Douglas Green, Hao Wu, Mads Gyrd-Hansen, Guy Salvesen
- **Living a Double Life: Death Receptors and Their Functions Beyond Cell Death** *Henning Walczak,* Seamus Martin, Marcus Peter, Pascal Meier
- **View from Another World: Non-Primate Models of Cell Death** *J. Marie Hardwick,* Barbara Conradt, John Abrams, Eric Baehrecke
- **The Command Center: How the Mitochondrion Controls Life and Death Decisions** *Douglas Green,* Ruth Kluck, Ana Garcia-Saez, Stephen Tait, Lisa Drew
- **The Many Faces of RIP Kinases in Pathological and Normal Physiology** *Andreas Strasser,* Junying Yuan, Kim Newton, Peter Vandenabeele, Domagoj Vucic
- **The Yin and Yang of Cell Death Signal Adaptors in Cancer** *John Abrams,* Christine Watson, Kevin Ryan, Andreas Villunger
- **Atypical Forms of Cell Death** *Eric Baehrecke,* Brent Stockwell, Christian Mayer, J. Marie Hardwick
- **Cell Death and Inflammation in Health and Disease** *Guy Salvesen,* John Silke, John Bertin, James Vince, Shigekazu Nagata

GRS Cell Death
Challenges in Cell Death Modalities and Their Impact on Homeostasis
AUGUST 4-5, 2018
CHAIRS: Isabel Jaco & Danielle Sliter

Cell Polarity Signaling

The Role of Cell Polarity Networks in Development, Growth Control and Regeneration

JUNE 3-8, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIR: Ulrich Tepass
VICE CHAIR: Jeremy F. Nance

- **Keynote Session: Polarity: From Yeast to Vertebrates** *Ulrich Tepass,* Rong Li, Lilianna Solnica-Krezel
- **Polarity and Embryos** *Bob Goldstein,* Fumio Motegi, Nicolas Plachta, Kathryn Anderson
- **Polarity in Tissue Organization** *Orion Weiner,* Francois Schweisguth, Enrique Rodriguez-Boulan, Jeremy Nance

> **"GRCs provide a platform for intense exchange of the latest scientific achievements, unpublished results, novel ideas, and prospective collaborations."**
>
> DR. BERND LORENZ
> Multiferroic and Magnetoelectric Materials GRC

- **Polarity and Tissue Dynamics** *Jennifer Zallen,* Carl-Philipp Heisenberg, Yohanns Bellaiche, Celeste Nelson
- **Polarity, Stem Cells and Cell Division** *Benjamin (Buzz) Baum,* Marcos Gonzalez-Gaitan, Cecilia Moens, Yukiko Yamashita
- **Polarity and Growth Regulation** *Senthil Muthuswamy,* David Bilder, Tatsushi Igaki, Katja Röper
- **Polarity and Cancer** *Richard Fehon,* Nic Tapon, Ian Macara
- **Polarity, Extrusion and Would Healing** *Susan Parkhurst,* Yasuyuki Fujita, Rodrigo Fernandez-Gonzalez
- **Polarity, Stem Cells and Regeneration** *Carien Niessen,* Laura Johnston, Lucy O'Brien, Fiona Watt

GRS Cell Polarity Signaling
From Molecules to Organs: How to Build a Polarized Organism
JUNE 2-3, 2018
CHAIRS: Florent Peglion & Erin R. Williams

Cellular and Molecular Fungal Biology

Harnessing Diversity to Understand Molecular Mechanisms, Pathogenicity and Fungal Factories

JUNE 17-22, 2018 • HOLDERNESS SCHOOL, HOLDERNESS, NH

CHAIRS: Antonis Rokas & Alistair J.P. Brown
VICE CHAIRS: Jason E. Stajich & Alexandra C. Brand

- **Dimensions of Fungal Diversity** *David Hibbett,* Louise Glass, Chris Hittinger, An Martel, A. Elizabeth Arnold
- **Morphology, Movement and Motors** *Michelle Momany,* Samara Reck-Peterson, Meritxell Riquelme, Nicolas Minc, Larisa Gheber, Yen-Ping Hsueh, Michael McMurray
- **Sex and Development** *Paul Dyer,* Joseph Heitman, Sara Branco, Frances Trail, Richard Bennett
- **Sensing and Signalling in Dynamic Environments** *Leah Cowen,* Nicholas Talbot, Natalia Requena, Gustavo Goldman, Luis Larrondo, Hana El Samad, Anastasia Baryshnikova
- **Designing and Exploiting Fungal Systems** *Dawn-Anne Thompson,* Michelle O'Malley, Annie Tsong, Clay Wang, Kevin Verstrepen
- **Fungal Evolution— Mode, Tempo and Impact** *Toni Gabaldon,* Judith Berman, Eva Stukenbrock, Guilhem Janbon, Cathie Aime, Kenneth Wolfe, Benjamin Wolfe
- **Late-Breaking Topics** *Alexandra Brand, Jason Stajich*
- **Mechanistic Diversity Underlying Human Pathogenesis** *Kirsten Nielsen,* Neil Gow, J. Claire Hoving, Robert Cramer, Xiaorong Lin, Julia Koehler, Raymond St. Leger
- **Mechanistic Diversity Underlying Plant Pathogenesis** *Regine Kahmann,* Li-Jun Ma, Armin Djamei, Bart Thomma, Loannis Stergiopoulos
- **Power Hour** *Natalia Requena, Meritxell Riquelme*

GRS Cellular and Molecular Fungal Biology
The Power of Fungi: From Cell Biology to Ecology
JUNE 16-17, 2018
CHAIRS: Dana Opulente & Brad Bartholomai

Centromere Biology

The Structure, Function and Evolution of Centromeres

JULY 29 – AUGUST 3, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIR: Aaron F. Straight
VICE CHAIR: Sylvia Erhardt

- **Keynote Session: Centromeres: Genetic and Epigenetic Control of Chromosome Segregation** *Aaron Straight,* Don Cleveland, Robin Allshire
- **Centromere Biophysics and Structure** *Karolin Luger,* Stephen Harrison, Hitoshi Kurumizaka, Andrea Musacchio, Stefan Westermann
- **Mitotic and Meiotic Centromere Functions** *Judith Berman,* Ben Black, Julie Cooper, Kelly Dawe, Elaine Dunleavy
- **Centromere Function in Disease** *Sylvia Erhardt,* Yamini Dalal, Claire Francastel, Gary Karpen
- **Centromere Genomics and Evolution** *Harmit Malik,* Bungo Akiyoshi, James Birchler, Steven Henikoff, Karen Miga
- **Centromere and Kinetochore Dynamics** *Kevin Sullivan,* Kerry Bloom, Ian Cheeseman, Arshad Desai, Sue Biggins
- **Centromere Epigenetics** *Hironori Funabiki,* William Earnshaw, Daniel Foltz, Tatsuo Fukagawa, Lars Jansen
- **Non-Coding Elements Involved in Centromere Function** *Michael Blower,* Genevieve Almouzni, Rachel O'Neill, Beth Sullivan, Patrick Heun
- **Control of Centromeric Chromatin** *Paul Maddox,* Daniele Fachinetti, Guohong Li, Hiroshi Masumoto, Barbara Mellone

GRS Centromere Biology
Centromere Dynamics: A View from Evolutionary and Molecular Biology
JULY 28-29, 2018
CHAIRS: Leah Bury & Owen Kabnick Smith

Chemistry and Biology of Tetrapyrroles

The Movement and Trafficking of Tetrapyrroles (Hemes, B12/Corrins, Bilins and Chlorophyll)

JULY 15-20, 2018 • SALVE REGINA UNIVERSITY, NEWPORT, RI

CHAIR: Iqbal Hamza
VICE CHAIR: Emma Raven

- **Tetrapyrroles: Chemistry and Catalysis** *Judith Burstyn,* Yoshitsugu Shiro, Kara Bren, Koichiro Ishimori
- **Heme Synthesis and Pathophysiology** *Jean-Charles Deybach,* Barry Paw, Herve Puy, Miguel Soares, Amy Simon
- **Regulatory Pathways in Chlorophyll and Energy Production** *Mats Hansson,* Bernhard Grimm, Ayumi Tanaka, Carl Bauer
- **Heme Trafficking and Imaging** *Michael Marletta,* Robert Kranz, Amit Reddi, Jacquin Niles, Ji-Xin Cheng
- **Linear Tetrapyrroles and Photoreceptors** *Nicole Frankenberg-Dinkel,* Donald Bryant, Rei Narikawa, Wendy Schluchter
- **Biosynthesis, Trafficking and Homeostasis of B12 and Corrinoids** *Alison Smith,* Nigel Robinson, Michiko Taga, Ruma Banerjee, Aaron Wright
- **Tetrapyrroles: Degradation and Signaling** *Angela Wilks,* Elizabeth Boon, Vladislav Verkhusha, Michael Bauer
- **Tetrapyrroles at the Host-Pathogen Interface** *Celia Goulding,* Pedro Oliveira, Jose Maria Perez-Victoria, Delphine Lechardeur, Paul Sigala
- **Keynote Session: Tetrapyrrole Homeostasis: From Microbes to Man** *Mark O'Brian,* Martin Warren, David Rosenblatt

Chemotactic Cytokines

The Chemokine System at the Crossroads of Physiology and Disease

JUNE 3-8, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Reinhold J. Förster
VICE CHAIR: Marcus Thelen

- **Keynote Session: Mechanisms of Immune Cell Migration** *Reinhold Förster,* Michael Sixt
- **Chemokines in Immune Cell Targeting to Non-Lymphoid Organs** *Bernhard Moser,* Ulf Panzer, Richard Ransohoff, Alexander Flügel, Andy Luster
- **Atypical Chemokine Receptors** *Ronen Alon,* Gerry Graham, Antal Rot, Marcus Thelen
- **Chemokines and Lipid Mediators in Lymphoid Organ Organization and Function** *Gudrun Debes,* Jason Cyster, Susan Schwab, Wolfgang Kastenmüller, Matteo Iannacone
- **Chemokines in Effector T Cell Function and Positioning** *Sergio Lira,* Ulrich Von Andrian, Jens Stein, Axel Kallies
- **Chemokines in Myeloid Cell Migration** *Philip Murphy,* Paul Kubes, Klaus Ley, Anna Huttenlocher, Milka Sarris
- **Lymphatic and Stromal Cells in Chemokine Biology** *Antal Rot,* Karl Balabanian, Gwendalyn Randolph, Burkhard Ludewig
- **Crystal Structure and Therapeutic Targeting of the Chemokine System** *Brian Volkman,* Tracy Handel, Michel Bouvier, Thomas Schall, Mette Rosenkilde
- **Sensing of Chemokines** *Michael Sixt,* Ronen Alon, Philippe Bousso

GRS Chemotactic Cytokines
Chemokine Control of Immunity: From Homeostasis to Disease
JUNE 2-3, 2018
CHAIRS: Caroline Sokol & Tamara N. Girbl

"I volunteered to Chair a GRS because I wanted to communicate to people just how pivotal this conference can be in your career in terms of new ways of thinking, new research paths and collaborations."

DR. RICHARD WILLIAMS
Collagen GRS

Chromatin Structure and Function

Chromatin Encounters: Shaping Genome Architecture and Function

JULY 22-27, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Karolin Luger
VICE CHAIR: Asifa Akhtar

- **Chromatin Structure: The Nucleosome and Beyond** *Song Tan,* Yi Zhang, Hiroshi Kimura, Geeta Narlikar, Zhucheng Chen
- **Chromatin in Focus: Visualizing Chromatin Interactions** *Carl Wu,* Xiaowei Zhuang, Wendy Bickmore, Bing Ren, Ana Pombo, Carolyn Larabell
- **Chromatin Assembly in Replication and Repair** *Peter Verrijzer,* Gaelle Legube, Danesh Moazed, Lars Jansen, Yang Shi
- **Chromatin Encounter with Molecular Motors** *Geeta Narlikar,* Frank Pugh, Bradley Cairns, Carlos Bustamante, Iestyn Whitehouse, Cigall Kadoch
- **Linking Epigenetics with Metabolism** *David Tremethick,* Paolo Sassone-Corsi, Jerry Workman, Jane Mellor, Peter Verrijzer
- **Reprogramming Chromatin** *Ana Pombo,* Amanda Fisher, Kenneth Zaret, Anne Ferguson-Smith, Mitch Guttman, Joost Gribnau
- **Non-Coding RNA in Chromatin Biology** *John Rinn,* L. Stirling Churchman, Robert Kingston, Peter Becker, Bradley Bernstein
- **Histone Modifications and Disease** *Paolo Sassone-Corsi,* Thomas Jenuwein, Danny Reinberg, Ali Shilatifard, David Allis, Konrad Hochedlinger
- **Engineering Chromatin** *L. Stirling Churchman,* Jeff Boeke, Steven Henikoff, Tom Muir, David Tremethick
- **Power Hour** *Cigall Kadoch, Anne Ferguson-Smith*

Chromatin Structure and Function
Chromatin: Plasticity and Genome Regulation in Physiology and Disease
JULY 21-22, 2018
CHAIRS: Jorge V. Beira & Narsis Attar

Colloidal Semiconductor Nanocrystals

Semiconductor Nanocrystals: From Atomistic Insights to Applications

JULY 15-20, 2018 • BRYANT UNIVERSITY, SMITHFIELD, RI

CHAIRS: Daniel R. Gamelin & Zeger Hens
VICE CHAIRS: Maksym V. Kovalenko & Matt Law

- **Synthetic Challenges and Innovations** *Doh Lee,* Janet Macdonald, Xiaogang Peng
- **Structure, Bonding and Surfaces** *Vanessa Wood,* Christophe Coperet, Jill Millstone, Ivan Infante
- **Dopants, Defects and Emergent Properties** *Gerd Bacher,* Andries Meijerink, Angshuman Nag, Giulia Galli
- **Surface Functionalization for Applications** *Jill Millstone,* Hedi Mattoussi, Doh Lee
- **Photochemistry** *Arjan Houtepen,* Raffaella Buonsanti, Lilac Amirav
- **Spins in Nanocrystals** *Angshuman Nag,* Gerd Bacher, Louis Biadala
- **Interfacing and Integration** *Janet Macdonald,* Arjan Houtepen, Dmitri Talapin
- **Carriers and Excitons** *Ivan Infante,* William Tisdale, Alexander Efros
- **Optoelectronic Devices** *Dmitri Talapin,* Vanessa Wood, Moonsub Shim

Colloidal Semiconductor Nanocrystals
Synthetic Strategies and Photochemical Properties of Semiconductor Nanocrystals
JULY 14-15, 2018
CHAIRS: Chen He & Michelle Blemker

Computational Chemistry

Towards Next-Generation Challenges in Computational Chemistry: From Quantum Chemistry and Molecular Simulation to Data Discovery and Quantum Computing

JULY 22-27, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIR: Angela Wilson
VICE CHAIRS: Adrian E. Roitberg & Zoe Cournia

- **Accurate Predictions of Energetics for Biomolecules** *Rommie Amaro,* Bernard Brooks
- **Enhanced Sampling Towards Free Energy Calculations** *Adrian Roitberg,* Teresa Head-Gordon, Chris Chipot
- **From Data-Driven and Machine-Learning Based Discovery to Quantum Computing Challenges and Opportunities** *Garnet Chan,* Alan Aspuru-Guzik, John Parkhill
- **Catalyst and Reaction Design** *Cong Liu,* Natalie Fey, Thomas Cundari, Mu-Hyun Baik, Adrian Mulholland
- **Strong Electron Correlation** *Paul Ayers,* Frank Neese, Eugene DePrince
- **Chemistry at the Interface** *Julia Rice,* Ilja Siepmann, Thomas Miller, Victor Batista
- **Quantum Chemistry** *Martin Head-Gordon,* Markus Reiher, Kieron Burke, Stefan Grimme
- **Reactivity and Interactions: Prediction and Control of Molecular Behavior** *Thomas Cundari,* Monte Pettitt, Carlos Simmerling, Lillian Chong
- **Advances Towards Drug Design** *Zoe Cournia,* Woody Sherman

Computational Chemistry
Emerging Directions in Computational Chemistry: From Quantum Chemistry and Molecular Simulation to Data Discovery
JULY 21-22, 2018
CHAIRS: Michael R. Jones & Anna Tomberg

Conductivity and Magnetism in Molecular Materials

Emergent Materials and Phenomena as Foundation for Future Molecule-Based Devices

AUGUST 12-17, 2018 • BRYANT UNIVERSITY, SMITHFIELD, RI

CHAIRS: Kazushi Kanoda & Michael Shatruk
VICE CHAIRS: Martin Dressel & David Harris

- **Conductivity and Magnetism on Interfaces: Toward Molecular Spintronics** *Stephen Hill,* Z. Valy Vardeny, H.S.J. Van Der Zant
- **Strongly Correlated Systems and Emergent Phenomena** *Michael Lang,* Natalia Drichko, Chisa Hotta, Yasumasa Takano, Bin Zhang
- **New Aspects in Magnetism and Switching** *Jeffrey Long,* José Galán-Mascarós, Michael Nippe
- **Molecular Qubits and Quantum Technologies** *Danna Freedman,* Sophia Economou, Wolfgang Wernsdorfer, Kim Dunbar, Stephen Hill
- **Superconductivity Under Extreme Conditions** *Joachim Wosnitza,* Yoshihiro Iwasa, Kosmas Prassides, Masayuki Suda
- **Topological States, Chiral Materials** *Roser Valenti,* Martin Dressel, Michihiro Hirata, Reizo Kato, Narcis Avarvari
- **Light-Induced Processes** *Mark Meisel,* Osamu Sato, Renske van der Veen, Hiroshi Okamoto
- **Molecular Spintronics and Molecule-Based Devices** *Wolfgang Wernsdorfer,* Mirko Cinchetti, Natalia Shustova, Jeffrey Rinehart
- **Novel Materials, Functionalities and Ideas** *David Harris,* Hatsumi Mori, Roland Wiesendanger

Conductivity and Magnetism in Molecular Materials
Charge and Spin on Molecules: Tunable Interactions and Potential Applications
AUGUST 11-12, 2018
CHAIRS: Andrej Pustogow & Lakshmi Bhaskaran

Correlated Electron Systems

Entanglement and Coherence in Quantum Materials

JUNE 24-29, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA

CHAIRS: Piers Coleman & Nigel Hussey
VICE CHAIRS: Nandini Trivedi & James G. Analytis

- **Edge States, Interfaces and Monolayers: New Developments** *Harold Hwang,* Lena Kourkoutis, Justin Ye, Andrea Young
- **Strange Metals and Hydrodynamics in Correlated Electron Systems** *Andrew Mackenzie,* Daniel Dessau, Joel Moore, Subir Sachdev, Philip Moll
- **Entanglement and Quantum Computational Approaches** *Sean Hartnoll,* Glen Evenbly, Antoine Georges, Jan Von Delft
- **Topological Materials with Strong Correlations** *Andrei Bernevig,* Po-Yao Chang, Vidya Madhavan, Suchitra Sebastian, Stefan Wiedmann
- **New Aspects of Quantum Criticality** *Qimiao Si,* Satoru Nakatsuji, Senthil Todadri, James Analytis
- **Frustration, Quantum Entanglement and Electron Correlations** *Arthur Ramirez,* Meigan Aronson, Yoshi Tokiwa, Xiaodong Xu
- **Non-Equilibrium Phenomena: Many Body Localization, Quenches, Time-Resolved Spectroscopy and Time Crystals** *Alessandra Lanzara,* Nuh Gedik, Curt von Keyserlingk, Jiehang Zhang
- **Exotic and Hidden Order in Strongly Correlated Electron Materials** *Premala Chandra,* Kamran Behnia, J.C. Seamus Davis, Yuji Matsuda, Marie-Aude Measson
- **New Techniques and New Paradigms in Strongly Correlated Electron Systems** *Hidenori Takagi,* Peter Abbamonte, Silke Biermann, Filip Ronning, Leslie Schoop

Correlated Electron Systems
New Developments in the Understanding, Visualization and Manipulation of Quantum Materials
JUNE 23-24, 2018
CHAIRS: Fahad Mahmood & Samuel S. Lederer

Crystal Engineering

Progress in Crystal Engineering: Design, Properties and Function

JUNE 24-29, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Len R. MacGillivray
VICE CHAIR: Jennifer A. Swift

- **Crystal Engineering: Functional Design** *Piero Sozzani,* Gautam Desiraju, Andy Cooper
- **Crystal Nucleation, Growth and Self-Assembly** *Jason Benedict,* Cristobal Viedma, Lian Yu, Kenneth Harris, Jonathan Steed
- **Structure Prediction and Polymorphism** *Sarah Price,* Aurora Cruz-Cabeza, Leslie Vogt, Reiko Kuroda
- **Single-Crystal Processes to Device Applications** *Alexei Tivanski,* Leonard Barbour, Christopher Bardeen, Lucia Maini, John Anthony
- **Crystals to Covalent Networks** *Qianli Rick Chu,* James Wuest, Angiolina Comotti
- **Pharmaceutics, Co-Crystals and Amorphous Solids** *Jane Li,* Mike Zaworotko, Fengjuan Cao, Sreenivas Lingireddy, Geoff Zhang
- **Metal-Organic Materials** *Ashlee Howarth,* Praveen K. Thallapally, Mohamed Eddaoudi
- **Porosity to Gas Capture** *Pierangelo Metrangolo,* Michaele Hardie, Travis Holman, Radu Custelcean, Jerry Atwood
- **Mechanical Effects and Mechanochemistry** *Malla Chilla,* Pance Naumov, Cristina Mottillo, Mark Hollingsworth
- **Power Hour** *Jennifer Swift*

Crystal Engineering
Applications and Interfaces of Crystal Engineering
JUNE 23-24, 2018
CHAIRS: Igor Huskic & Filip Topic

Cyclic Nucleotide Phosphodiesterases

Targeting PDEs: Realizing the Therapeutic Potential

JUNE 10-15, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIRS: George S. Baillie & Christopher Schmidt
VICE CHAIRS: Jin Zhang & Jos Prickaerts

- **Keynote Session: Enhancing PDE Activity as a Therapeutic Strategy** *Manuela Zaccolo,* Rodolphe Fischmeister, Miles Houslay
- **PDE as Targets in Cancer Therapy** *George Baillie,* Ralf Hoffmann, Toshiyuki Tsunoda, Gary Piazza
- **Novel PDE Inhibitor Actions** *Rodolphe Fischmeister,* Charles Hoffmann, Matthew Movsesian, Viacheslav Nikolaev
- **Targeting PDE Microdomains in Disease** *Viacheslav Nikolaev,* Carmen Dessauer, John Scott, Manuela Zaccolo, Donald Maurice, David Kass
- **Targets in Non-Canonical cAMP Signaling Systems** *Donald Maurice,* Thomas Brand, Harry de Koning, Roland Seifert, Mark Johnson

- **PDE Inhibitors in Psychiatric Disorders** *Jos Prickaerts,* Eugenii (Ilan) Rabiner, Charles Vorhees, Zoe Hughes
- **PDE Inhibitors in CNS Disorders Related to Neurodegeneration** *Christopher Schmidt,* Laurent Gomez, Ellanor Whiteley, Anthony West
- **Targeting PDEs in the Treatment of Inflammatory Disease** *Zoe Hughes,* Stefan Brocke, Lawrence Wennogle, Michy Kelly
- **Targeting PDEs in Vascular and Metabolic Disease** *Frank Menniti,* Christina Kruuse, Rúbia Maria de Oliveira, Coleen Atkins

GRS Cyclic Nucleotide Phosphodiesterases

Novel Approaches, Technology and Therapeutic Targets in Cyclic Nucleotide Phosphodiesterase Signaling

JUNE 9-10, 2018

CHAIRS: Lise Roman Moltzau & Ellanor L. Whiteley

Cytoskeletal Motors

Cytoskeletal Motors from Structure to Mechanism to Disease

JULY 8-13, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIR: Samara L. Reck-Peterson
VICE CHAIR: Steven S. Rosenfeld

- **Keynote Session: Motors, Tracks and How Their Interactions Drive Their Functions** *Steven Rosenfeld,* Eva Nogales, Don Cleveland
- **Motor Structure and Mechanism** *Marija Zanic,* Andrew Carter, Kathleen Trybus, Gregory Alushin, Carolyn Moores
- **Motors in Cardiovascular and Muscle Disease** *Gregory Alushin,* James Spudich, Christine Seidman, Benjamin Prosser, David Thomas
- **Tracks: Structure, Dynamics and Interactions with Motors** *Radhika Subramanian,* Antonina Roll-Mecak, Emil Reisler, Peter Bieling, Thomas Surrey
- **Recent Breakthroughs in Cytoskeletal Motors** *Jason Stumpff,* Radhika Subramanian, Michael Greenberg
- **Motor Engineering and Nanotechnology** *Weihong Qiu,* Zev Bryant, Kristen Verhey, Sivaraj Sivaramakrishnan, Manuel Thery
- **Motors in Cancer** *Silvia Jansen,* David Pellman, Jody Rosenblatt, Douglas Robinson, Matthieu Piel
- **Motors in Neurological Function and Disease** *Jessica Henty-Ridilla,* Lawrence Goldstein, Elizabeth Engle, John Hammer, Erika Holzbaur, Lukas Kapitein
- **Late-Breaking Topics** *Peter Bieling,* Gaia Pigino

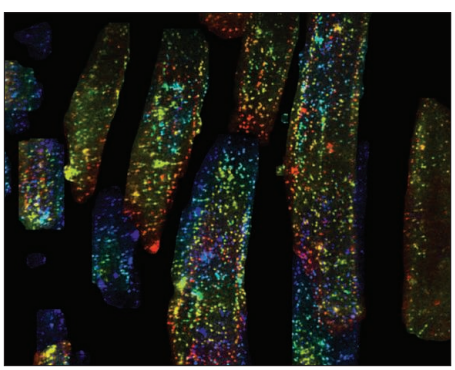
NEW! Deep Carbon Science

Deep Carbon Science in the Context of Geologic Time

JUNE 17-22, 2018 • BRYANT UNIVERSITY, SMITHFIELD, RI

CHAIRS: Craig Manning & Isabelle Daniel
VICE CHAIRS: Edward D. Young & Kai-Uwe Hinrichs

- **Carbon and Planet Assembly** *George Cody,* Monika Kress, Laurent Remusat
- **Earliest Earth Evolution** *Linda Elkins Tanton,* Sarah Stewart, Rajdeep Dasgupta



Clathrin-mediated endocytosis in zebrafish. The image shows individual clathrin-coated pits in a section of a 3D volume from muscle tissue in the dorsal tail region of a developing zebrafish embryo 80 hpf. The live zebrafish was imaged using a lattice light sheet microscope with adaptive optics. Several muscle fibers were computationally separated as a way to facilitate the visualization of the complex image. The color coding associated with each coated pit maps to the distance away from the observer (blue is close; red is far). CREATED BY TOM KIRCHHAUSEN AND SRIGOKUL UPADHYAYULA. SUBMITTED BY THE 2018 LYSOSOMES AND ENDOCYTOSIS GRC CHAIRS.

- **Volatiles in the Hadean** *Marc Hirschmann,* Laura Schaefer
- **Populating the Deep Biosphere** *Fumio Inagaki,* Douglas Bartlett, Karyn Rogers, Catherine Royer
- **Early Deep Life** *Steve D'Hondt,* Jan Amend
- **Biosphere Feedbacks Through Time** *Karen Lloyd,* Beth Orcutt, Doug LaRowe
- **Deep Carbon Reservoirs Through Time** *Louise Kellogg,* Erik Hauri, Barbara Sherwood-Lollar
- **The Geologic History of Carbon Subduction and Outgassing** *Terry Plank,* Tamsin Mather, Dietmar Müller, Joshua West
- **Evolution of the Deep Carbon Cycle** *James Badro,* Cin-Ty Lee

Defects in Semiconductors

Insight, Characterization and Control of Defects in Advanced Materials

AUGUST 19-24, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIR: Mary Ellen Zvanut
VICE CHAIR: Jeffrey C. McCallum

- **Dealing with Dopants** *Stephan Lany,* Klaus Irmscher, Alfredo Pasquarello
- **Detecting Defects** *Gregory Fuchs, Cory Cress,* Christoph Boehme, Junhao Lin, Michio Tajima
- **Dealing with Complexity** *Oliver Bierwagen,* Larry Halliburton, Lasse Vines
- **Extracting and Emitting Light** *Mete Atature,* Lee Basset, Igor Aharonovich, Audrius Alkauskas
- **Theory of Complexity** *Chris Van De Walle,* Joel Varley, Beall Fowler
- **In-Grown Defects, Thin Films** *Matt McCluskey,* Ryan Comes, Rachel Goldman, Carol Trager-Cowan
- **Making Spins Work for You** *Carlos Meriles,* Kai-Mei Fu, Nick Vamivakas
- **The Role of Defects in Energy Efficiency** *John Murphy,* Leigh Weston, David Scanlon, Sam Stranks
- **The Energy of Defects** *Mary Ellen Zvanut,* Joerg Weber
- **Power Hour** *Courtney Au-Yeung*

GRS Defects in Semiconductors

Utilizing and Mitigating Defects in Emerging Functional Materials

AUGUST 18-19, 2018

CHAIRS: Cyrus E. Dreyer & Courtney Au-Yeung

Diffraction Methods in Structural Biology

Revisiting Old Models and Assumptions in Diffraction Methods for Structural Biology: Addressing the Challenges Arising from New Sources, Detectors and Data Collection Methods

JULY 29 – AUGUST 3, 2018 • BATES COLLEGE, LEWISTON, ME

CHAIR: Arwen R. Pearson
VICE CHAIR: James M. Holton

- **Quo Vadis Crystallography: The Current State-of-the-Art and What Challenges Lie Ahead** *Piotr Sliz,* Martin Fuchs, Thomas Ursby, Adrian Mancuso
- **Understanding Our Detectors Better: Including Noise Structure, Non-Uniformity and Missed Photons** *Joseph Ferrara,* Clemens Schulze-Briese, Sol Gruner, Manuela Kuhn
- **Error Modelling and Propagation** *Gerard Bricogne,* Garib Murshudov
- **Is the "American Method" Coming Back: Revisiting Experiment Design and Data Processing** *Aina Cohen,* Max Nanao, Graeme Winter
- **Measuring Dynamics and Modelling Ensembles** *Carrie Wilmot,* Daniel Keedy, Nicholas Pearce, Helen Ginn
- **Non-Classical Diffraction Experiments and Sparse Data** *Anton Barty,* Kay Diederichs, Leonie Flueckiger, Briony Yorke
- **Searching Fast and Digging Deep: Big Computing and Big Data in Structural Biology** *Monarin Uervirojnangkoorn,* Filipe Maia, Edward Snell
- **Selected Poster Presentations** *Ho-Leung Ng*
- **The Future of Diffraction Experiments in the Era of Imaging** *Janet Smith,* Eike Schulz, Ashwin Chari, Gwyndaf Evans

GRS Diffraction Methods in Structural Biology

Crystallography 2.0: Restructuring the Field Around a New Wave of Experiments

JULY 28-29, 2018

CHAIRS: Nicholas M. Pearce & Jessica E. Besaw

DNA Topoisomerases in Biology and Medicine

Topoisomerases in Chromatin, Transcription and Replication Regulation and Their Importance in the Origin and Treatment of Human Diseases

JULY 29 – AUGUST 3, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA

CHAIR: Yves G. Pommier
VICE CHAIRS: Elizabeth L. Zechiedrich & Keir C. Neuman

- **Keynote Session: The Topoisomerase World from Phylogeny to Molecular Structures** *Mary-Ann Bjornsti,* Patrick Forterre, Nancy Kleckner
- **Antibacterial Drugs Targeting Topoisomerases and Antibiotic Resistance** *Mark Fisher,* Anthony Maxwell, Valakunja Nagaraja, Yuk-Ching Tse-Dinh
- **Anticancer Drugs Targeting Topoisomerases: The Challenge to Make Them Better** *Giovanni Capranico,* Scott Kaufmann, Anish Thomas
- **Topoisomerases and Chromatin Structure** *Andrzej Stasiak,* Andre Nussenzweig, Camilla Sjogren, Anna Bizard
- **Topoisomerases, Transcription and RNA Topoisomerases** *James Berger,* Weidong Wang, David Levens
- **Topoisomerase-Induced Damage** *Brigitta Knudsen,* Sue Jinks-Robertson, Shunichi Takeda, John Nitiss
- **Repair of Topoisomerase-Induced Damage** *Felipe Cortés-Ledesma,* Scott Williams, Shar-Yin Huang
- **Topoisomerases and Human Diseases (Neurodegenerative Diseases and Cancers)** *Caroline Austin,* Peter McKinnon, Sherif El-Khamisy, Ram Madabhushi
- **Tyrosyl DNA Phosphodiesterases, Recombinations, Mitochondrial and Viral Replication** *Heidrun Interthal,* Keith Caldecott, Michael Weinfeld

GRS DNA Topoisomerases in Biology and Medicine

Mechanisms, Interactions and Roles of Topoisomerases in Origin and Treatment of Human Disease

JULY 28-29, 2018

CHAIRS: Roketa S. Sloan & Lorena Infante

Drug Carriers in Medicine and Biology

Multidisciplinary and Multimodal Approaches to Drug Delivery: Translation from Principles to Patients

AUGUST 12-17, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIRS: Muthiah Manoharan & Jeffrey A. Hubbell
VICE CHAIRS: Suzie Pun & Samir S. Mitragotri

- **Keynote Session: Nucleic Acid Therapeutics** *Paul Burke,* John Maraganore, Charles Gersbach
- **Drug Delivery for Global Health** *Susan Hershenson,* Darrell Irvine, Ana Jaklenec
- **Regeneration** *Rogerio Gaspar,* Kevin Healy, Tatiana Segura
- **Immunomodulation and Cancer Immunotherapy** *Piotr Grodzinski,* Melody Swartz
- **Cancer Chemotherapy** *Paula Hammond,* Mark Grinstaff, Jindrich Kopecek, Francis Szoka
- **Therapeutic Antibody-Drug Conjugates, Peptides and Proteins** *Maria Vicent,* Ravi Chari, Heather Maynard, David Rabuka, Peter Senter
- **Selected Poster Presentations** *Suzie Pun, Samir Mitragotri*
- **Local Delivery** *Anna Schwendeman,* Tejal Desai, Patrick Stayton
- **Novel Carriers and Systems** *Millicent O'Sullivan,* Jacob Brenner

GRS Drug Carriers in Medicine and Biology

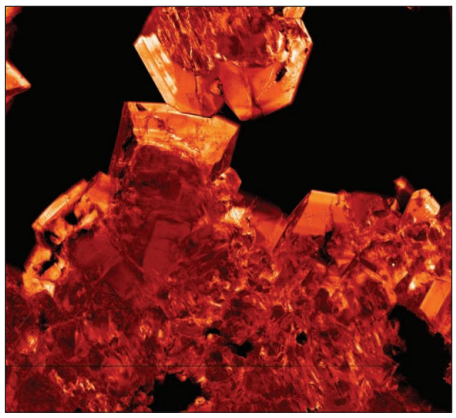
Advances at the Interface of Drug Carriers and the Immune System

AUGUST 11-12, 2018

CHAIRS: Coralie M. Backlund & Ioana L. Aanei

"I remember my first GRC experience because I met the leaders in my field that have now become colleagues and collaborators."

DR. MELISSA BROWN
Multi-Drug Efflux Systems GRC



X-ray fluorescence element map of strontium in well-formed epidote crystals from the Yerington mining district, Nevada. Strontium shows strong sector-zoning whereby the concentration of Sr is higher along certain crystal faces in the epidote structure. CREATED BY AYESHA AHMED, LOUISE FISHER, MARK PEARCE, AND ANGELA ESCOLME. SUBMITTED BY THE 2018 GEOCHEMISTRY OF MINERAL DEPOSITS GRC CHAIRS.

Drug Metabolism

Uncovering Complexity in Drug Metabolism in the Cell and the Clinic

JULY 8-13, 2018 • HOLDERNESS SCHOOL, HOLDERNESS, NH

CHAIR: Swati Nagar

VICE CHAIR: Griff Humphreys

- **Keynote Session: The Leading Edge in Uncovering Complex Drug Disposition and Toxicity** *Swati Nagar,* Deanna Kroetz
- **New Knowledge on Structure and Function of Drug Metabolizing Enzymes** *Nina Isoherranen,* Zeruesenay Desta, Fernando Estrada, Margaret James, Jeffrey Jones
- **The Cell Membrane in Relation to Enzymes and Transporters** *Kenneth Korzekwa,* Ute Hellmich, Michal Otyepka, Ronald Oude Elferink
- **Drug-Drug Interactions and Toxicity** *Upendra Argikar,* Kim Brouwer, R. Scott Obach, Konstantine Skordos, Yuichi Sugiyama
- **Models for Complex Metabolism and Transport** *Sukyung Woo,* Valeriu Damian-Iordache, Daniel Scotcher, Greg Thurber
- **Special Populations: Pediatric Drug Metabolism and Pharmacokinetics** *Sara Van Driest,* Saskia de Wildt, Tracy McGregor, Gilbert Burckart, Jennifer Goldman
- **Young Investigator Presentations** *Henry Strobel*
- **Special Populations: Intricacies in Drug Disposition** *Nathan Cherrington,* Ken Thummel, John Clarke, Lauren Aleksunes, Steven Leeder
- **The Complexity of Regulation: FDA Guidelines and Case Studies** *Lisa Shipley,* Thomas Baillie, Shiew-Mei Huang, Karsten Menzel

Drug Resistance

Looking for Common Themes and Solutions in Drug Resistance for Cancer, Infectious Disease and Agriculture

JULY 22-27, 2018 • BRYANT UNIVERSITY, SMITHFIELD, RI

CHAIRS: Jared A. Silverman & Juswinder Singh

VICE CHAIR: Michael H. Cynamon

- **Keynote Session: Reviewing Progress and Setbacks on the Front Lines of Drug Resistance** *Jared Silverman,* Vance Fowler, Stephen Fawell
- **Modeling of Resistance** *Dominik Wodarz,* Natalia Komarova, Bruce Levin, Paul Neve
- **New and Emerging Drug Resistance Mechanisms** *Priscilla Yang,* Shawn Lockhart, Tanguy Seiwert
- **Tackling Resistance in Discovery and Development for Cancer** *Aaron Goldman,* Erica Evans, Daruka Mahadevan, Sara Buhrlage
- **Tackling Resistance in Discovery and Development for Anti-Infectives** *Michael Cynamon,* Tim van Opijnen, Paul Ambrose, Ann Kwong
- **New Approaches to Drug Resistance** *Manuel A. Navia,* John Overington, Jean-Marie Pages, Cassandra Quave
- **A Century Beyond the Spanish Flu: Addressing Pandemic Threats** *Carolyn Shore,* Jo-Anne Dillon
- **Heterogeneity** *Alexis Kaushansky,* John Aitchison, Andriy Marusyk, Paul Mischel
- **Diagnostics** *Andrew Tomaras,* Ellen Foxman, Shana Kelley

Drug Safety

Contemporary Advances and Challenges in Drug Safety Assessment

JUNE 10-15, 2018 • STONEHILL COLLEGE, EASTON, MA

CHAIR: James L. Stevens

VICE CHAIR: Myrtle Davis

- **Keynote Session: Modeling Complex Biological Systems** *James Stevens,* Gunter Wagner, Patrick Cahan
- **Quantitative and Systems Toxicology** *Donald Mager,* Doug Lauffenburger, Nicolas Le Novere, Jason Papin
- **Application of Systems Models in Drug Safety Assessment** *Yvonne Dragan,* Cindy Afshari, Blanca Rodriguez
- **Microphysiological Systems: Engineering Human Biology** *Brian Berridge,* Mary Estes, Christopher Hughes, Lansing Taylor
- **Stem Cells in Health and Disease** *Donna Mendrick,* Jorge Nieva, Joseph Wu
- **Challenges and Opportunities for Immunomodulator Development** *Helen Haggerty,* Laura Johnson, Jeffrey Ravetech, Agne Taraseviciute
- **Patient Safety and Immunomodulators in Clinical Development** *Anja Stauber,* Amy Rosenberg
- **Pharmacovigilance and Adverse Event Monitoring** *Lori Minasian,* Robert Ball, Nicholas Tatonetti, Charles Cleeland
- **Keynote Session: Therapeutic Opportunities and Safety Issues in Immune Modulation** *Myrtle Davis,* Jedd Wolchok

Drug Safety
Drug Safety in the Modern Development Landscape: Innovations from Industry, Academia and Government
JUNE 9-10, 2018
CHAIRS: Natalie S. Holman & Julia Tobacyk

Electron Donor-Acceptor Interactions

Electron Flow: From the Molecular to the Global Scale

AUGUST 5-10, 2018 • SALVE REGINA UNIVERSITY, NEWPORT, RI

CHAIRS: David N. Beratan & Elena Galoppini

VICE CHAIRS: Felix N. Castellano & Claudia Turro

- **Electron, Protons and Life** *Robert Cave, David Waldeck,* Moh El-Naggar, Sharon Hammes-Schiffer
- **Infra-Red Control of the Electron Transfer Reaction Coordinate** *Joseph Subotnik,* Spiros Skourtis, Igor Rubtsov, Julia Weinstein, Eric Bittner
- **Extracellular Electron Transfer** *Leonard Tender,* Jochen Blumberger, Julea Butt
- **Multi-Electron Redox Processes in Biology** *Judith Klinman,* Carolyn Lubner, Brian Hoffman, Stefan Weber, Gary Brudvig
- **Electron Transfer Based Materials and Complex Systems** *Michael Therien,* GuanHua Chen, Piotr Piotrowiak
- **Solar Photochemistry** *Maria Abrahamsson,* Jillian Dempsey, Petter Persson, Jonathan Rochford, Niels Damrauer
- **Electronic Coherence and Charge Transfer** *Greg Scholes,* Nongjian Tao, Bern Kohler, Lars Gundlach
- **From Change Transport to Functional Nanostructures** *Michele Maggini,* Emily Weiss, H.S.J. Van Der Zant, Joakim Andreasson, Kevin Belfield
- **Late-Breaking Topics** *Ana Moore, Thomas Moore,* Luisa De Cola, William DeGrado

Electron Donor-Acceptor Interactions
Connecting Charge and Energy Transfer in Synthetic and Biological Systems
AUGUST 4-5, 2018
CHAIRS: Kevin Felter & Ryan Harmer

Electronic Processes in Organic Materials

From Spin Physics to Bioelectronics and Novel Approaches to Doping in Organic Materials

JULY 22-27, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIRS: Antoine Kahn & Anna Köhler

VICE CHAIRS: Carlos Silva & Ana Claudia Arias

- **Spin and Excitons in Organic Semiconductors and Devices** *Andrew Musser,* Stephen Forrest, Andy Monkman
- **Carrier Transport in Organic Materials and Devices** *Oana Jurchescu,* Clemence Corminboeuf, Karl Leo, Garry Rumbles
- **Organic Bioelectronics** *Eleni Stavrinidou,* Guglielmo Lanzani, Gabriela Schlau-Cohen
- **Metal Halide Perovskites: Carrier Transport and Photophysics** *Philip Schulz,* David Egger, Laura Herz, Maria Loi
- **Interfaces of Organic Semiconductors: Theory and Experiments** *Steffen Duhm,* Norbert Koch, Leeor Kronik
- **Charge Separation in Organic Photovoltaic Devices** *Carsten Deibel,* Derya Baran, Dieter Neher, Barry Rand
- **New Organic Electronic Materials** *Feng Gao,* Lain McCulloch, John Reynolds
- **Self-Assembly and Structure** *Ellen Moons,* Luisa De Cola, Claudia Draxl, Christian Muller
- **Novel Aspects of Chemical Doping in Organic Semiconductors and Devices** *Ingo Salzmann,* Peter Ho, Bjorn Lussem

Electronic Processes in Organic Materials
Development of New Materials, Fundamental Processes, Device Physics and Emerging Applications of Organic Electronics
JULY 21-22, 2018
CHAIRS: Rebecca J. Wilson & David Kiefer

Endothelial Cell Phenotypes in Health and Disease

Endothelial Cell Specialization, Functional Heterogeneity and Niche Function

JULY 15-20, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIR: Ralf H. Adams

VICE CHAIR: Karen Hirschi

- **Endothelial Cell Heterogeneity and Specification** *Susan Quaggin,* Sarah De Val, Elisabetta Dejana, Anna Randi, Mervin Yoder
- **Molecular Control of Endothelial Cell Behavior** *Dietmar Vestweber,* Anne Eichmann, Timothy Hla, Michael Potente, Martin Schwartz
- **Endothelial Cell Transdifferentiation** *Joyce Bischoff,* Mary Dickinson, Luisa Iruela-Arispe, Michael Simons, Nancy Speck
- **Specialization of Lymphatic Endothelial Cells** *Victoria Bautch,* Taija Makinen, Tatiana Petrova, Susan Quaggin, Stefan Schulte-Merker
- **Sources of Endothelial Cells in Organ Morphogenesis** *Kenneth Walsh,* Kristy Red-Horse, Karina Yaniv, Bin Zhou
- **Functional Specialization of Endothelial Cells** *Eckhard Lammert,* Holger Gerhardt, Gou Young Koh, Naoki Mochizuki, Nobuyuki Takakura
- **Endothelial Cells in the Nervous System** *Anne Eichmann,* Christer Betsholtz, Chenghua Gu, Yoshiaki Kubota, Yoh-suke Mukouyama, Christiana Ruhrberg
- **Niche Function of Endothelial Cells** *Christopher Hughes,* Hellmut Augustin, Paul Frenette, Eli Keshet, Sean Morrison, Shahin Rafii
- **Endothelial Cell Dysfunction in Disease** *Asrar Malik,* Kari Alitalo, Mark Kahn, Miikka Vikkula, Nicholas Gale
- **Power Hour** *Victoria Bautch*

Endothelial Cell Phenotypes in Health and Disease
The Molecular Basis of Vascular Biology and Endothelial Cell Heterogeneity
JULY 14-15, 2018
CHAIRS: Annalisa Zecchin & Urs H. Langen

Energetic Materials

Exploiting Advances in Additively-Manufactured, Nano- and Non-Crystalline Materials, Synthetic Methods, Modeling and Simulation and In Situ Diagnostics for Energetic Materials

JUNE 3-8, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Betsy M. Rice

VICE CHAIR: Joseph M. Zaug

- **Rising Trends in Experimental Energetic Materials Research** *Steven Son,* Kyle Ramos, Alexander Tappan
- **Architected Energetic Materials** *C. Michael Lindsay,* H. Keo Springer, Alexander Mueller, Carole Rossi
- **Interweaving Energetic Materials Synthesis with Engineering** *Alexander Paraskos,* Klavs Jensen, Nathaniel Zuckerman, David Boruta
- **Frontiers in the Chemical Synthesis of Energetic Materials** *Jesse Sabatini,* Phil Baran, David Chavez, Colin Pulham
- **Modeling Challenges in Energetic Materials Research** *Scott Stewart,* John Reaugh, Brian Barnes, Edward Kober
- **Pushing the Boundaries: In Situ Studies of Energetic Materials Response** *Keith Nelson,* Trevor Willey, Katie Brown, Volkan Ortalan

- **Nano and Non-Crystalline Energetic Materials** *Nicholas Piekiel,* Denis Spitzer, Victor Stepanov, Stephen Tse
- **Emerging Predictive Methods for Energetic Materials Research** *William Mattson,* Evan Reed, Nir Goldman, Todd Martinez
- **Keynote Session: Perspectives on Future Directions and Frontiers in Energetic Materials Research** *Nick Glumac,* Ruth Doherty, David Moore, Craig Tarver

GRS Energetic Materials

Advances in Modeling, Experimental Developments and Synthesis of Energetic Materials

JUNE 2-3, 2018

CHAIRS: Leora Dresselhaus-Cooper & William Shaw

Environmental Endocrine Disruptors

Aiming for a Safe Chemical Environment: New Frontiers in the Comprehension of Endocrine Disrupting Chemicals Exposure, Effects and Specific Risk Assessment Requirements

JUNE 3-8, 2018 • LES DIABLERETS CONFERENCE CENTER, LES DIABLERETS, SWITZERLAND

CHAIR: Daniel Zalko

VICE CHAIRS: Susan Nagel & Jodi A. Flaws

- **Keynote Session: Increasing Exposure to Man-Made Chemicals Triggers Complex Responses in Living Organisms and Overthrows Established Dogmas** *Daniel Zalko,* Ana Soto, Andrea Gore
- **From Waters to Remote Terrestrial Ecosystems: New Evidences for EED Effects and Current Stakes** *Laura Vandenberg, Susan Nagel,* Dick Vethaak, Alan Vajda, Virginie Cuvillier, Sabrina Krief
- **Providing Evidence for Life-Span Effects of EEDs in the Complex Context of Human Exposure** *Andreas Kortenkamp, Barbara Demeneix,* Rémy Slama, Lidia Minguez-Alarcon, Vasantha Padmanabhan
- **Mechanisms of Effect of EED: Certainties, Hypotheses and Unexplored Shores** *Christopher Kassotis, Heather Patisaul,* Patrick Balaguer, Barbara Demeneix, Cristoforo Silvestri
- **Mechanisms of Effect of EED: Lots of Things Happen from "Nothing": Complex Mechanisms and Low Dose Exposure Effects** *Frederick Vom Saal, Jodi Flaws,* Lori Raetzman, Monica Lind, Paige Lawrence
- **EED Toxicology and Modes of Action: General and Specific Issues Raised by Endocrine Disruptors** *Alan Vajda, Pete Myers,* Andreas Kortenkamp, Vincent Laudet, Stephen Ferguson
- **EED Toxicology and Modes of Action: Mechanisms of Inheritence and Novel Paradigms** *Juliette Legler, Angel Nadal,* Bruce Blumberg, Martha Susiarjo, Serge Nef
- **Classical and Novel Approaches in Endocrine Disrupting Chemicals Toxicology** *Ana Soto, Rémy Slama,* Patience Browne, Christophe Rousselle, Nicolas Cabaton
- **Public Concerns and Public Health Policies** *Jane Muncke, Katie Pelch,* Cristina Fossi, Linda Giudice, Ninja Reineke

GRS Environmental Endocrine Disruptors

The Future of EDC Research: Cutting-Edge Techniques for Identifying Candidate EDCs and Novel Assays to Investigate Potential Health Outcomes

JUNE 2-3, 2018

CHAIRS: Katie E. Pelch & Christopher D. Kassotis

Environmental Sciences: Water

Innovations at the Intersections of the Aquatic Sciences: Water, Health, Materials and Technologies

JUNE 24-29, 2018 • HOLDERNESS SCHOOL, HOLDERNESS, NH

CHAIR: William A. Arnold

VICE CHAIR: Heileen Hsu-Kim

- **Water Nexus Issues: Real or Repackaged?** *Heileen Hsu-Kim,* Korneel Rabaey, Jeremy Guest
- **Molecular Scale Processes: Mega Trends** *Eric Pierce,* Kim Prather, Liane Benning, Brandy Toner
- **Impacts of Unconventional Gas and Oil Production** *William Burgos,* Avner Vengosh, Paula Mouser
- **Oxidative Processes and Contaminant Transformations** *Karl Linden,* Christina Remucal, Xiaohong Guan, Brian Chaplin
- **Reinventing the Toilet** *Alison Parker,* Tove Larsen, Michael Hoffmann
- **Antibiotic Resistance in Water Systems** *Diana Aga,* Amy Pruden, Michael Gillings, Tong Zhang
- **Microplastics** *Tamara Galloway,* Bart Koelmans, Chelsea Rochman
- **Toxicant Exposure** *Mark Strynar,* Kim Anderson, Kevin Thomas, Frank von der Kammer
- **Translating Aquatic Science Research to Practice** *Rula Deeb, Anh Pham,* Peter Fiske
- **Power Hour** *Jennifer Field*

GRS Environmental Sciences: Water

The Pristine, the Clean and the Filthy: Environmental Importance and Impact of Waters from Glacial Sources to Contaminated Runoff

JUNE 23-24, 2018

CHAIRS: Emily L. Marron & Brandon C. McAdams

Enzymes, Coenzymes and Metabolic Pathways

Advances in Enzymology: From Mechanism and Function to Therapeutic Applications

JULY 22-27, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIRS: Holly R. Ellis & Kay Ahn

VICE CHAIRS: Jennifer L. DuBois & Martin St. Maurice

- **Regulation of Protein Function** *Bo Li,* Hening Lin, Joan Hevel, Natalie Ahn
- **Mechanistic Features of Enzyme Cofactors** *Bruce Palfey,* Michael Marletta, Dennis Stuehr, Douglas Goodwin, Michael McLeish
- **Natural Product Biosynthesis** *Adrian Keatinge-Clay,* Satish Nair, Gavin Williams, Vahe Bandarian
- **Drug Discovery** *Randy Kipp,* Mario van der Stelt, Adam Johnson, Richard Miller
- **Emerging Methods** *Susan Miller,* Barry Honig, Richard Friesner, Neil Kelleher
- **Enzyme Mechanisms** *Keri Colabroy,* Brian Miller, Erika Taylor, Donald Becker, Andrew Murkin
- **Enzyme Inhibition** *Jessica Ward,* Kip Guy, Daniel Krosky, Craig Crews
- **Metabolic Pathways and Metabolomics** *Daniel Bachovchin,* Alexandre Zanghellini, Alan Saghatelian, Michael Fischbach
- **Structural Basis for Enzyme Mechanisms** *John Gerlt,* Karen Allen, Dagmar Ringe

GRS Enzymes, Coenzymes and Metabolic Pathways

How Enzymes Work: From Mechanism and Function to Therapeutic Applications

JULY 21-22, 2018

CHAIR: Tatiana V. Mishanina

NEW! Epigenomics of Diabetes and Other Metabolic Diseases

Epigenetic Mechanisms and Their Role in the Development of Diabetes

MAY 27 – JUNE 1, 2018 • REGAL RIVERSIDE HOTEL, HONG KONG, CHINA

CHAIRS: Assam El-Osta & Ronald C. Ma

VICE CHAIRS: Juliana C.N. Chan & Mark E. Cooper

- **Legacy Effects in Clinical Management of Diabetes** *Paul Zimmet,* Rury Holman, Trevor Orchard
- **Genome Wide Association Studies of Diabetic Complications** *Nelson Tang,* Leif Groop, Yuk-Lap Yip, Paul Franks
- **Cardiovascular Disease and Associated Network Analyses** *Simin Liu,* Mark McCarthy, Daniel Levy
- **Parental Transmission of Disease Risk to Offspring** *Mark Hanson,* Qing-Yuan Sun, Marika Charalambous
- **Noncoding RNAs in Diabetes** *Rama Natarajan,* Dongsheng Cai, Romano Regazzi
- **Epigenetics of Diabetic Complications** *George King,* Per-Henrik Groop, Charlotte Ling, Rama Natarajan

- **Preclinical and Human Epigenetics** *Stephan Beck,* John Pospisilik, Andrew Feinberg
- **Emerging Concepts of Epigenetic Memory in Metabolic Disease** *Peter Jones,* Francesco Cosentino, Rebecca Simmons, Niels Riksen
- **Therapeutic Strategies in Diabetic Complications** *Yu Huang,* Hui-Yao Lan, Patrick Collombat

Extracellular Vesicles

From Basic Research to Clinical Diagnostic and Therapeutic Applications of Extracellular Vesicles

AUGUST 19-24, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Giovanni Camussi

VICE CHAIRS: Paul D. Robbins & Kenneth W. Witwer

- **Keynote Session: Physio-Pathological Role of Extracellular Vesicles** *Jan Lotvall,* Alissa Weaver, Peter Quesenberry
- **Biogenesis, Composition and Characterization of Extracellular Vesicles** *Clotilde Thery,* Willem Stoorvogel, Xandra Breakefield, Stephen Gould
- **Extracellular Vesicles as Delivery Vehicles** *Anastasia Khvorova,* Samir El Andaloussi, Yong Gho, Steven Jay, Juliane Nguyen
- **Modulation of Inflammatory Response by Extracellular Vesicles** *Andrew Hill,* Camillo Ricordi, Adrian Morelli, Edit Buzas
- **The Role of Extracellular Vesicles in Infectious Diseases** *Amy Buck,* Vincent Bond, Esther Nolte-'t Hoen, Arturo Casadevall, Neta Regev-Rudzki
- **The Role of Extracellular Vesicles in Cancer Microenvironment and Metastasis** *Alissa Weaver,* Raghu Kalluri, Muller Fabbri, Benedetta Bussolati
- **Diagnostic and Therapeutic Applications of Extracellular Vesicles** *Raghu Kalluri,* Bernd Giebel, Alain Brisson, Randolph Corteling, Dana Larocca
- **The Role of Extracellular Vesicles in Neurobiology** *Xandra Breakefield,* Matthew Wood, Andrew Hill, Anastasia Khvorova
- **The Role of Extracellular Vesicles in Stem Cell Biology and Potential Clinical Applications** *Bernd Giebel,* Sai Lim, Bas van Balkom

GRS Extracellular Vesicles

The Latest Methods for Exploring Heterogeneity and Implications for Therapeutic EVs

AUGUST 18-19, 2018

CHAIRS: Scott W. Ferguson & Margerita Alba Carlotta Pomatto

Flow and Transport in Permeable Media

Flow and Transport in Permeable Media Across Scales: From Pore-Scale Physics to Geologic-Scale Processes

JULY 8-13, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Ruben Juanes

VICE CHAIR: Tanguy Le Borgne

- **Microfluidics and Wettability** *Martin Blunt,* David Weitz, Denis Bartolo
- **Wet Granular Physics** *Dani Or,* Daniel Bonn, Arshad Kudrolli, Bjornar Sandnes
- **Flow Instabilities and Chemical Reactions** *Insa Neuweiler,* Anne De Wit, Marco Dentz, Anthony Ladd
- **Digital Rock Physics** *Masa Prodanovic,* Cass Miller, Beatrice Riviere, Paal-Eric Oren
- **Geomechanics and Induced Seismicity** *Hamdi Tchelepi,* John Shaw, Pablo Sanz
- **Biophysics and Biological Porous Media** *Majid Hassanizadeh,* Ellen Kuhl, Sylvie Lorthois, Sujit Datta
- **Biogeochemistry and Reactive Transport** *Kathleen Smits,* Li Li, Jesus Carrera
- **Flow and Transport in Nanoscale Porous Media** *Steffen Berg,* Evelyn Wang, Farzam Javadpour, Franz-Josef Ulm
- **Geophysical Subsurface Flows** *Marc Hesse,* Jenny Suckale, Andrew Woods

GRS Flow and Transport in Permeable Media

Understanding Complexity for Prediction in Permeable Media

JULY 7-8, 2018

CHAIRS: Peter Kyungchul Kang & Joaquin Jimenez-Martinez

Forensic Analysis of Human DNA

Enhancing Human Identification Through Development of Novel Methods and Emerging Applications

JUNE 17-22, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIRS: Robin Cotton & Daniele Podini
VICE CHAIRS: Steven Lee & Sarah Seashols

- **Keynote Session: The Unexpected Outcomes of More Powerful Forensic Technologies** *Robin Cotton,* Pamela King, Peter Schneider
- **Analysis of Samples at the Crime Scene** *Joan Bienvenue,* Bruce Budowle, James Landers, Utkan Demirci
- **Novel Sample Preparation and Amplification Methods** *Todd Bille,* Jack Ballantyne, Hanlee P. Ji, Adrian Linacre
- **DNA Transfer and Human Activity** *R.A.H. van Oorschot,* Bianca Szkuta, Georgina Meakin, Bas Kokshoorn
- **Molecular Methods for Determination of Biological Fluids** *Titia Sijen,* Gerda Edelman, Rachel Fleming, David Saul
- **Novel Marker Discovery and Emerging Applications Using Massively Parallel Sequencing** *Niels Morling,* Peter de Knijff, Walther Parson, Glendon Parker
- **Probabilistic Genotyping-Advances and Concerns** *Catherine Grgicak,* Corina Benschop, Keith Inman, Duncan Taylor
- **Age, Ancestry and Appearance** *Susan Walsh,* David Ballard, Manfred Kayser, Christopher Phillips
- **Data Interpretation, Presentation of Evidence and the Future of Forensic DNA Analysis** *Michael Coble,* John Butler, Kristy Martire, Christophe Champod

Forensic Analysis of Human DNA
From Notebook to Case Report: The Translation of Research to Applications in Forensic Analysis
JUNE 16-17, 2018
CHAIRS: Rachel E. Wiley & Carolyn Lewis

Fragile X and Autism-Related Disorders

Convergence and Divergence Between Fragile X and Autism Spectrum Disorders

JUNE 10-15, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIR: Peter Kind
VICE CHAIR: Mustafa Sahin

- **Keynote Session: Rescue Studies from Genes to Drugs** *Louis Reichardt,* Mark Bear, Adrian Bird, Laura Mamounas, Tracy King
- **Convergence from Genes to Phenotype** *Emily Osterweil,* Jennifer Darnell, Daniel Geshwind, Eric Klann
- **Clinical Trials: In Search of Treatments for the ASDs** *Elizabeth Berry Kravis,* Linmarie Sikich, Pilar Trelles, Mustafa Sahin
- **Convergence of Cellular Pathophysiology** *Kimberly Huber,* Claudia Bagni, Peter Scheiffele, Emily Osterweil
- **Circuit Biology: Local Connectivity** *Carlos Portera-Cailliau,* Anis Contractor, Vitaly Klyachko, Qiao Zhou
- **Circuit Biology: Local and Long Range Connectivity** *Jennifer Darnell,* Kevin Pelphrey, Kimberly Huber, Carlos Portera-Cailliau
- **Behavioral Convergence Across Animal Models** *Alice Luo Clayton,* Shona Chattarji, Ype Elgersma, Lauren Orefice
- **Human Cellular Models: iPSC-Derived Neural Cells as a Preclinical Model** *Anis Contractor,* Stormy Chambrlain, Flora Vaccarino, David Wyllie
- **Innovative Approaches to Clinical Outcome Measures and Trial Design** *Michael Tranfaglia,* Brian Kaspar, Elizabeth Torres, Elizabeth Berry Kravis

Fragile X and Autism-Related Disorders
Technical and Conceptual Advances in Fragile X Syndrome and Neurodevelopmental Disorders: Towards New Biomarkers and Therapies
JUNE 9-10, 2018
CHAIRS: Sam A. Booker & Nisha Raj

Fuel Cells

Energizing the Future by Innovation in Fuel Cell Materials, Methods, Modeling and Manufacture

JULY 29 – AUGUST 3, 2018 • BRYANT UNIVERSITY, SMITHFIELD, RI

CHAIRS: Kunal Karan & Deborah J. Jones
VICE CHAIRS: Marc Secanell & Shanna D. Knights

- **The Future of Sustainable Transport with Fuel Cells** *Shanna Knights,* William Resende, Josef Kallo
- **Low PGM Catalysts: Shaping the Future** *Hubert Gasteiger,* Jeff Greeley, Peter Strasser
- **Non-PGM Catalysts: Opportunities and Challenges** *Kateryna Artyushkova,* Frederic Jaouen, Dustin Banham
- **Ionomers and Next Generation Membranes** *Thomas Zawodzinski,* Michael Guiver, Takeshi Hirai, Erik Kjeang
- **Young Investigator Presentations** *Roswitha Zeis,* Aliaksandr Bandarenka, David Zitoun, Iryna Zenyuk
- **Techniques and Diagnostics** *Anthony Kucernak,* Renate Hiesgen, Karl Mayrhofer, Deborah Myers
- **Late-Breaking Topics** *Madeleine Odgaard*
- **Catalyst Layer Structure and Transport and New Insights on Ionomer Thin Films** *Jon Pharoah,* Yu Seung Kim, Kensaku Kodama, Anusorn Kongkanand
- **Green Hydrogen** *Bryan Pivovar,* Thomas Schmidt, Katherine Ayers

Fuel Cells
Understanding First Principles and Exploring New Innovations in Fuel Cells
JULY 28-29, 2018
CHAIRS: John J. Slack & Tasleem Muzaffar

Genomic Instability

Chromosome Replication, Repair and Architecture

JULY 22-27, 2018 • THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY, HONG KONG, CHINA

CHAIRS: Anja Groth & Anindya Dutta
VICE CHAIRS: Lee Zou & Michael S.Y. Huen

- **Chromosome Replication** *Yuanliang Zhai,* Bruce Stillman, Bik Tye, John F. Diffley
- **Replication Fork Stability and Repair** *Yuh-Hwa Wang,* Karlene Cimprich, Kyungjae Myung, Michael Huen, Agata Smogorzewska, Robert Weiss
- **Telomere Maintenance** *Randy Poon,* Simon Boulton, Ming Lei
- **Histone Dynamics and Epigenome Maintenance** *Xiang David Li,* Dinshaw Patel, Shiv Grewal, Qing Li, Rui-Ming Xu
- **Nuclear Architecture and Chromosomal Stability** *Kui Ming Chan,* Susan Gasser, Clodagh O'Shea
- **DSB Repair Mechanisms** *Chun Liang,* Jo Murray, Yunje Cho, Shunichi Takeda, John Rouse
- **DNA Damage Signalling** *Ashby Morrison,* Li-Lin Du, Junjie Chen, Lee Zou
- **Genome Instability and Disease** *Karen Wing Yee Yuen,* Maria Jasin, Yossi Shiloh, Eva Hoffmann, Frederick Alt
- **Targeting Genome and Epigenome Maintenance in Cancer** *Rebecca Chin,* Mark O'Connor, Wei-Guo Zhu
- **Power Hour** *Agata Smogorzewska, Karlene Cimprich*

Genomic Instability
Chromosome Replication, Repair and Organization in the Maintenance of Genome Stability
JULY 21-22, 2018
CHAIRS: Giulia Saredi & Catalina Pereira

Geochemistry of Mineral Deposits

Mineralizing Processes Across All Scales

AUGUST 5-10, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIRS: David Cooke & Claire M. Chamberlain
VICE CHAIR: Sarah A. Gleeson

- **Geochemical Evolution of the Earth's Hydrosphere and Lithosphere** *Ross Large,* Peter Cawood, Jessica Whiteside, Timothy Lyons
- **Mineralizing Processes in the Oceans** *Thomas Monecke,* Cornel De Ronde, Mark Hannington, Susan Humphris
- **Constraining the Duration of Geochemical Processes** *Katy Evans,* Steven Reddy, Robert Creaser, Katja Deckart
- **Mineralizing Processes in Basins** *Steve Piercey,* Sophie Decree, Joe Magnall, Steve Roberts
- **Ore Deposit Preservation, Enhancement and Destruction** *Eduardo Campos,* Rodrigo Riquelme, Thomas Bissig, Laura Evenstar
- **Mineralizing Processes Associated with Deformation** *Sally Goodman,* Murray Allan, Ana Fonseca, Steffen Hagemann, Gloria Arancibia
- **Geochemical Detection of Ore Deposits** *Shaun Barker,* Jeremy Vaughan, Jamie Wilkinson, Paul Agnew
- **Mineralizing Processes Associated with Magmatism** *Isabelle Chambefort,* Sarah-Jane Barnes, Adam Simon, Zhaoshan Chang, Alison Rust
- **Future Directions: The Next Phase of Mineral Deposit Geochemistry Research** *John Thompson,* Jorge Carriedo, Chris Heinrich

Geochemistry of Mineral Deposits
Mineralizing Processes Across All Scales
AUGUST 4-5, 2018
CHAIRS: Ayesha Ahmed & Angela J. Escolme

Granular Matter

The Interdisciplinary Nature of Particulate Systems

JULY 22-27, 2018 • STONEHILL COLLEGE, EASTON, MA

CHAIRS: Devaraj Van Der Meer & Aparna Baskaran
VICE CHAIRS: Xiang Cheng & Nathalie M. Vriend

- **Forces in Granular Matter** *Roberto Zenit,* Daniel Goldman, Karen Daniels
- **Grains and Interfaces** *Ko Okumura,* Kathleen Stebe, Suzie Protiere
- **Gravity-Driven Flows** *Nathalie Vriend,* Kimberly Hill, Anthony Thornton, Justin Burton
- **Dense Granular Suspensions** *Eric Brown,* Elisabeth Guazzelli, Wiebke Drenckhan, Itai Cohen
- **Impact on Granular Beds** *Paul Umbanhowar,* Yoel Forterre, Felipe Pacheco
- **Phases in Granular Matter** *Melany Hunt,* Nicolás Mujica, Matthias Schroeter
- **Experimental Techniques** *Robert Behringer,* Ralf Stannarius, Axelle Amon
- **Structure in Solid Granular Matter** *Bulbul Chakraborty,* Matthieu Wyart, Xia Li
- **Granular Matter in Extreme Conditions** *Lou Kondic,* James Michaels, Daniel Lathrop

Granular Matter
The Interdisciplinary Nature of Particulate Systems
JULY 21-22, 2018
CHAIRS: Cacey Stevens Bester & Scott R. Waitukaitis

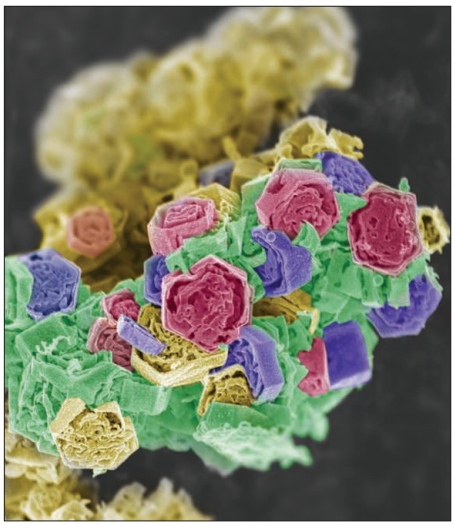
Green Chemistry

Addressing the Challenges at the Energy-Materials-Food-Water Nexus Through Green Chemistry

JULY 29 – AUGUST 3, 2018 • REY DON JAIME GRAND HOTEL, CASTELLDEFELS, SPAIN

CHAIRS: Bala Subramaniam & Anna Simpson
VICE CHAIRS: Walter Leitner & Emilio E. Bunel

- **Keynote Session: Advances Toward Renewable Energy and Chemicals** *Peter Licence, William Tumas,* Peter Wasserscheid, Daniel Nocera
- **Catalysis for Sustainability** *Cathy Tway,* Shu Kobayashi, Jurgen Klankermayer, Ive Hermans, Rafael Luque
- **Fundamentals of Catalysis for Renewables** *Karen Goldberg,* Susannah Scott, Johannes de Vries, Yong Wang



"Bouquet of flowers": False-colored scanning electron microscope image of MoS_2 catalyst, suitable for hydrogen evolution reaction and hydrodesulphurization of crude oil, illustrating chemistry flourishing green. CREATED BY GLEB VERYASOV. SUBMITTED BY THE 2018 GREEN CHEMISTRY GRS CHAIRS.

- **Renewable Chemicals and Materials from Biomass** *Mark Harmer,* Brent Shanks, Ning Yan, Bert Sels, Paul Dauenhauer
- **Biocatalysis Including Novel Enzymes** *Roger Sheldon, Joe Jump,* Gregg Beckham, Nicholas Turner, Ulf Hanefeld
- **Electrocatalysis for CO_2 and H_2O Conversion to Fuels and Chemicals** *James Blakemore,* Thomas Jaramillo, Atsushi Urakawa, Ryu Abe, Mich Hein
- **Novel Materials for Energy and Other Applications** *Thalappil Pradeep,* Audrey Moores, Jinlong Gong, Krista Walton
- **Sustainable Process Design and Metrics** *Mary Kirchhoff,* Helen Sneddon, Frank Roschangar, Richard Helling
- **Future Challenges in Green Chemistry and Engineering** *Paul Anastas, John Warner,* David Allen, Gabriele Centi, Philip Jessop

Green Chemistry
Green Chemistry and Its Relevance to Society
JULY 28-29, 2018
CHAIRS: Clement Camp & Tapish Saboo

Hemostasis

Defining the Interactions Between Blood, Cells and Vessels in Hemostasis and Disease

JULY 29 – AUGUST 3, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIR: Alisa S. Wolberg
VICE CHAIRS: Sidney W. Whiteheart & Alan E. Mast

- **Initiating Events in Hemostasis and Thrombosis** *Hartmut Weiler,* David Gailani, Santiago Di Pietro, James Morrissey
- **Contributions from the Blood and Vasculature** *Usha Pendurthi,* Charles Lowenstein, Douglas Fowler, Nicola Mutch, Andreas Greinacher, Randal Westrick
- **Molecular Interactions Between Blood and Platelets** *David Lillicrap,* Jorge Di Paola, Karen Vanhoorelbeke, Judith Cosemans
- **Cellular Contributions to Hemostasis and Thrombosis** *Gow Arepally,* Jose Lopez, Evi Stavrou, Marvin Nieman, James O'Donnell, Kellie Machlus
- **Advanced Models of Coagulation** *Owen McCarty,* Bart van Vlijmen, Scott Diamond, Karin Leiderman
- **New and Emerging Therapeutic Targets** *Maria Aleman,* Roland Herzog, Umesh Desai, Gallia Levy, Bruce Sullenger, Ashley Brown
- **Late-Breaking Topics** *Alan Mast*
- **Coagulation Mechanisms Beyond Hemostasis** *Andrew Weyrich,* Joseph Palumbo, Mari Kaartinen, Rafal Pawlinski, James Luyendyk, Weifei Zhu
- **Keynote Session: Hemostasis and Thrombosis: Bench to Bedside** *Sidney Whiteheart,* Jeffrey Weitz, Rodger McEver
- **Power Hour** *Karen Vanhoorelbeke*

Hemostasis
Defining the Interactions Between Blood, Cells and Vessels in Hemostasis and Disease
JULY 28-29, 2018
CHAIRS: James R. Byrnes & Jamie M. O'Sullivan

Heterocyclic Compounds

The Ubiquitous Use of Heterocycles in Modern Chemistry

JUNE 17-22, 2018 • SALVE REGINA UNIVERSITY, NEWPORT, RI

CHAIR: Julia M. Clay
VICE CHAIR: Eric M. Ferreira

- **The Connectivity Between Methodology Development and Total Synthesis** *Christa Chrovian,* Sarah Reisman, Doug Frantz
- **Improvements to the Synthesis of Heterocyclic Compounds** *Sarah Wengryniuk,* Jeff Kuethe, Eric Voight, Carolyn Anderson
- **Unique Applications of Heterocycles to Broad Biology Challenges** *Daniel Elbaum,* Matthew Shair, Cynthia Jesudason
- **Development of Methodology for Improved Heterocyclic Synthesis** *Jason Herr,* Jennifer Roizen, Corey Stephenson, Tehshik Yoon
- **The Use of Novel Approaches to the Synthesis of Biologically Active Compounds** *Corinna Schindler,* Jeffrey Johnson, Thomas Hoye, Angela Puchlopek-Dermenci
- **Heterocycles and Their Use as Biological Probes** *Mark Behnke,* Emily Balskus
- **The Use of Heterocycles in Catalysis** *Jennifer Howell,* Alison Frontier, Song Lin
- **New Strategies for the Synthesis of Heterocycles** *Cheryl Carson,* Laura Anderson, David Nagib, Jimmy Wu
- **Keynote Session: Nature Inspired Synthesis of Heterocyclic Natural Products** *Justin Lopchuk,* Phil Baran, Erik Sorensen

Human Genetic Variation and Disease

Human Genetics Research at the Intersection of Systems Biology, Computation, Medicine and Biophysics

JUNE 10-15, 2018 • UNIVERSITY OF NEW ENGLAND, BIDDEFORD, ME

CHAIRS: Rita Casadio & Rachel Karchin
VICE CHAIRS: Yana Bromberg & Olivier Lichtarge

- **Keynote Session: The Future of Human Variation and Disease Science** *Elizabeth Phimister,* Evan Eichler, Roderic Guigo
- **Emerging Classes of Variation and Disease** *Tychele Turner,* Angela Brooks, Ekta Khurana, Kai Tan, Michael Beer
- **Genetic Testing in the Age of Whole-Genome and Whole-Exome Sequencing** *Melissa Cline,* Robert Nussbaum, Heidi Rehm
- **Data-Driven Approaches for Precision Medicine** *Obi Griffith,* Wolfgang Huber, Ben Raphael, Alfonso Valencia, Joshua Denny
- **Biophysical Perspectives on Variation and Disease** *David Masica,* John Chodera, Anna Panchenko
- **New Directions: Ribosome Profiling, Microbiomes and Single Cell Technologies** *Christina Leslie,* Andrew Clark, Nicholas Ingolia, Smita Krishnaswamy, Cynthia Sears
- **Integrating Genomic Variation with Medical Records** *Brian Shirts,* Elmer Bernstam, Funda Meric-Bernstam
- **Genetic Variation in Cancer** *Mark Sausen,* Hannah Carter, Sharon Plon, Robert Scharpf, Luis Serrano
- **Common Variation and Disease** *Michael Hicks,* Francesco Cucca, Marcella Devoto
- **Power Hour** *Rachel Karchin, Anna Panchenko*

Human Genetic Variation and Disease
Genomic Data in Human Disease and Medicine: Emerging Opportunities and Challenges
JUNE 9-10, 2018
CHAIR: Vikas R. Pejaver

Hybrid Electronic and Photonic Materials and Phenomena

Electronic and Photonic Processes and Interfacial Phenomena in Organic/Inorganic Hybrid Materials and Their Applications in Optoelectronic Devices

JUNE 10-15, 2018 • REGAL RIVERSIDE HOTEL, HONG KONG, CHINA

CHAIRS: Deqing Zhang & Licheng Sun
VICE CHAIRS: Jian-Bin Xu & Thuc-Quyen Nguyen

- **Perovskite Solar Cells: Stability** *Thuc-Quyen Nguyen,* Nam-Gyu Park, Qingbo Meng
- **Perovskite Solar Cells: Structure and Dynamics** *Licheng Sun,* Tõnu Pullerits, David Ginger, Mohammad Nazeeruddin
- **Organic Semiconductors: Doping and Interface** *Zijian Zheng,* Karl Leo, Norbert Koch
- **Organic Semiconductors: Charge Transport and Thermoelectronics** *Lay Lay Chua,* Daoben Zhu, Henning Sirringhaus, Paul Blom
- **Organic and Hybrid Electronics** *Natalie Banerji,* Xinran Wang, Seth Darling
- **Organic Solar Cells: Materials and Interface** *Elizabeth Von Hauff,* Jean-Luc Bredas, Jianhui Hou, Fei Huang
- **Bioelectronics and Bioimaging** *Vivian Yam,* Luisa Torsi, Ben Zhong Tang
- **Organic Solar Cells: Device Physics** *Jianpu Wang,* Jenny Nelson, Dieter Neher, Lin Chen
- **Novel Photonic Phenomena and New Conjugated pi-Systems for Optoelectronics** *Jian-Bin Xu,* Chihaya Adachi, Shigehiro Yamaguchi, Henry Yan

Image Science

Creating Knowledge from Imaging Data

JUNE 17-22, 2018 • STONEHILL COLLEGE, EASTON, MA

CHAIR: Michael Insana
VICE CHAIR: Rafael Piestun

- **Imaging in Brain Science Discovery** *Bennett Landman,* Edward Boyden, Valentina Emiliani
- **Inverse Problems** *Mini Das,* Scott Carney, Carola Schoenlieb, Jinyi Qi
- **Imaging at the Physical Limits** *Harrison Barrett,* Sua Myong, Margaret Murnane
- **Observers, Perception and Computer Vision** *Elizabeth Krupinski,* David Stork, Craig Abbey, Vivek Goyal
- **Compressed Sensing and Machine Learning** *Michael Gehm,* Zhi-Pei Liang, Yonina Eldar
- **OCT and Adaptive Optics** *Chrysanthe Preza,* Martin Booth, Jannick Rolland, Zhongping Chen
- **Astronomical Imaging** *Joseph O'Sullivan,* David Hogg, Christian Marois
- **Imaging in Complex Media** *Sylvain Gigan,* Mark Anastasio, Allard Mosk, James Fienup
- **Computational Imaging** *Daniel Rueckert,* Gordon Wetzstein, Ravindra Athale
- **Power Hour** *Mary Lou Jepsen*

Image Science
Speed, Depth and Precision in Image Science
JUNE 16-17, 2018
CHAIRS: Lucas R. Borges & Hugo Defienne

Immunochemistry and Immunobiology

Advances in Immunology and Immunotechnology: Insights in the Regulation of Protective and Pathological Immune Responses

JUNE 10-15, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIR: Federica Sallusto
VICE CHAIR: Facundo Batista

- **Keynote Session: Initiation and Modulation of the Immune Response** *Federica Sallusto,* Ruslan Medzhitov, Ronald Germain, Michel Nussenzweig
- **Gene Programing of Immune Cells** *Bali Pulendran,* Sarah Teichmann, Ido Amit, Dan Littman, Vijay Kuchroo
- **Development, Function and Regulation of Innate Lymphoid Cells** *Annette Oxenius,* Albert Bendelac, Jim Di Santo, Henrique Veiga-Fernandes
- **Immune Repertoires** *Shane Crotty,* Marc Jenkins, Mark Davis, Donna Farber, Peter Savage
- **Cell-Cell Communications in Immunity** *Facundo Batista,* Morgan Huse, Shannon Turley, Carola Vinuesa
- **Inflammation and Immune Regulation** *David Artis,* Caetano Reis e Sousa, Sasha Rudensky, Marcia Haigis, Adrian Liston
- **Microbial Interactions at Barrier Surfaces** *Carola Vinuesa,* Kathy McCoy, David Artis, Bana Jabri
- **Immunity to Infections** *Antonio Lanzavecchia,* Matteo Iannacone, Annette Oxenius, Anne Puel
- **Antibodies, Vaccines and Immunotherapies** *Shannon Turley,* Bali Pulendran, Antonio Lanzavecchia, Shane Crotty

Immunochemistry and Immunobiology
Engineering the Immune System: Applications in Clinical and Technological Translation
JUNE 9-10, 2018
CHAIRS: Kaitlyn Sadtler & Todd M. Gierahn

"I remember my first GRC because I got to meet, often for the first time, many of my peers whose work I had read and been inspired by over the years."

DR. KEITH SILLAR
Neuroethology: Behavior, Evolution and Neurobiology GRC

In Vivo Magnetic Resonance

Challenging Assumptions About Magnetic Resonance Technology and Applications in a Changing World

JULY 15-20, 2018 • PROCTOR ACADEMY, ANDOVER, NH

CHAIR: Daniel K. Sodickson
VICE CHAIR: Jeff F. Dunn

- **Surprising Magnetic Resonance: New Paths to Polarization** *Mikhail Shapiro,* Ronald Walsworth, Wilson Miller
- **Challenging Assumptions in Data Acquisition and Image Reconstruction: Software** *Leslie Ying,* Debiao Li, Michael Lustig, Shanshan Wang
- **Challenging Assumptions in Data Acquisition and Image Reconstruction: Hardware** *Elena Kaye,* Orlando Simonetti, Bruno Madore
- **Challenging Assumptions in Data Interpretation: The Microstructure Revolution** *Jennifer McNab,* Daniel Topgaard, Dmitry Novikov
- **Challenging Assumptions in Data Interpretation: Artificial Intelligence Unleashed** *Yvonne Lui,* Jure Zbontar, Greg Zaharchuk
- **Building Networks Across Scales and Disciplines: Cells, Brains and Populations** *Jeff Dunn,* Elizabeth Hillman, Karla Miller
- **Seeing Differently: Emerging Contrast Agents and Mechanisms** *Zaver Bhujwalla,* Alan Jasanoff, Lucio Frydman
- **Changing the Value Proposition of Magnetic Resonance** *Jim Pipe,* Christopher Hess, Elizabeth Morris, Vikas Gulani
- **Leveraging MR Information for Therapy: Image Informed Intervention** *Craig Meyer,* Kim Butts Pauly, Rob Tijssen

In Vivo Magnetic Resonance
The Changing World of Magnetic Resonance: Old Physics, New Techniques
JULY 14-15, 2018
CHAIRS: Scott C. Beeman & Carson A. Hoffman

Industrial Ecology

The Role of Industrial Ecology in Reaching the Sustainable Development Goals

MAY 20-25, 2018 • LES DIABLERETS CONFERENCE CENTER, LES DIABLERETS, SWITZERLAND

CHAIR: Stefanie Hellweg
VICE CHAIR: Anu Ramaswami

- **Resource Use for a More Prosperous, Healthy and Equitable World** *Julia Steinberger,* Narasimha Rao, Thomas Graedel
- **Industrial Ecology's Contribution to Remain Within Planetary Boundaries and Achieve the Sustainable Development Goals (SDGs)** *Marina Fischer-Kowalski,* Gang Liu, Jooyoung Park, Heinz Leuenberger
- **Sustainable Use and Governance of Natural Resources** *Jo Dewulf,* Saleem Ali, Elias T. Ayuk
- **The Role of the Circular Economy in Creating Responsible Production and Consumption** *Anthony Shun Fung Chiu,* Janez Potocnik, Elsa A. Olivetti, Nancy Bocken
- **Life on Land and Below Water: Recent Developments in Assessing Biodiversity Loss** *Edgar Hertwich,* Francesca Verones, Michael Obersteiner
- **Data and Metrics to Inform Progress Toward Sustainable Development** *Ming Xu,* Heinz Schandl, Cássia Ugaya, Sybil Derrible
- **Clean Energy for All: The Role of Technology Innovation and Systems Thinking** *Valerie Thomas,* Claudia Binder, Rishee Jain
- **Sustainable Cities, Communities and Infrastructure Innovations in an Urban Planet** *Weiqiang Chen,* Karen C. Seto, Josephine Musango, Ajay Nagpure
- **Implementing Industrial Ecology Solutions in Practice** *Liselotte Schebek,* Urs Walter Schenker
- **Power Hour** *Anu Ramaswami*

Industrial Ecology
The Role of Industrial Ecology in Reaching the Sustainable Development Goals
MAY 19-20, 2018
CHAIRS: Mengya Tao & Morgan R. Edwards

Inorganic Chemistry

Innovative Advancements and Technical Challenges that Span the Periodic Table

JUNE 17-22, 2018 • UNIVERSITY OF NEW ENGLAND, BIDDEFORD, ME

CHAIR: Stosh A. Kozimor
VICE CHAIR: Amy L. Prieto

- **Keynote Session: At the Forefront of Inorganic Chemistry** *Stosh Kozimor,* Tobin Marks, Robert Crabtree
- **Bioinspired Inorganic Chemistry** *Rebecca Abergel,* Thomas Meade, Elisa Tomat, Claudia Turro, Andrew Borovik
- **Molecular Magnetism** *David Harris,* Muralee Murugesu, Michael Nippe, Matthew Shores
- **Catalysis and Devices** *Jeffrey Long,* Christopher Ackerson, Brent Melot, Nathan Neale, Jennifer Hollingsworth
- **Energetic Materials** *Alex Carpenter,* Jacqueline Veauthier, Kenneth Suslick, Karl Christe
- **Physical Inorganic Chemistry** *William Tolman,* Stefan Minasian, David Shultz, Serena Debeer, William Schneider
- **Organometallic Chemistry** *Smaranda Marinescu,* Christopher Cummins, Nilay Hazari, William Evans
- **Metal Organic Frameworks** *Mircea Dinca,* Omar Farha, Natalia Shustova
- **Novel Coordination Chemistry** *Amy Prieto,* Thomas Albrecht-Schmitt, Jonathan Sessler

Inorganic Chemistry
Bioinorganic, Organometallic and Materials Science: Applications for the Advancement of Fundamental Inorganic Chemistry
JUNE 16-17, 2018
CHAIRS: Tobias J. Sherbow & Xian B. Powers

Intermediate Filaments

Intermediate Filaments as the Platform to Underpin the "Social Network" of Cells and Tissues

JUNE 24-29, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIR: Milos Pekny
VICE CHAIRS: Jan Lammerding & Roy A. Quinlan

- **IFs as Critical Regulators in Health and Disease** *Milos Pekny, Clarissa Koch,* Bishr Omary, Valerie Weaver
- **CNS: IFs in Neurodegeneration, Neuroplasticity and Regeneration** *Sandrine Etienne-Manneville,* Elly Hol, Albee Messing, Ulrika Wilhelmsson, Robert Zorec
- **Intermediate Filaments, the Immune System and Repair** *Natasha Snider, Birgit Lane,* Andrei Gudkov, David Markovitz
- **Intermediate Filaments in Cell Differentiation, Adhesion, Migration and Senescence** *Karen Ridge, John Eriksson,* Sandrine Etienne-Manneville, Robert Goldman, Masaki Inagaki, Cecilia Sahlgren
- **Heart and Muscle Control in Human Diseases** *Elly Hol,* Gisele Bonne, Howard Worman
- **Regulating the Cell Microenvironment and Mechanotransduction** *Jan Lammerding,* Roy Beck-Barkai, Dennis Discher, Kristian Franze, Yosef Gruenbaum
- **From Intermediate Filament Structure to Diseases** *Gisele Bonne, Thomas Magin,* Pierre Coulombe, Roland Foisner, Ohad Medalia
- **Intermediate Filament Biology: Connecting the Laboratory with the Clinic** *Diana Tiavola, Yosef Gruenbaum,* John Eriksson, Birgit Lane, Karen Ridge, Natasha Snider, Pavel Strnad
- **Metabolic Regulation, Mitochondria and Intermediate Filaments** *Roy Quinlan,* Yassemi Capetanaki, Thomas Magin, Diana Tiavola
- **Power Hour** *Cecilia Sahlgren*

Intermediate Filaments
The Future of Intermediate Filament Research: Moving from Basic Science to Novel Technologies and Clinical Advances
JUNE 23-24, 2018
CHAIRS: Clarissa M. Koch & Oscar Stassen

Intrinsically Disordered Proteins

Transcending Scales of Protein Disorder from Molecules to Medicines

JULY 1-6, 2018 • LES DIABLERETS CONFERENCE CENTER, LES DIABLERETS, SWITZERLAND

CHAIRS: Vincent J. Hilser & Martin Blackledge
VICE CHAIRS: Philipp Selenko & Elizabeth Rhoades

- **Keynote Session: Evolution of IDPs and Function** *Philipp Selenko,* Raul Andino, Thomas Boothby, Ashutosh Chilkoti, Keith Dunker, Monika Fuxreiter, Debora Marks
- **The Emergent Properties of Disordered Ensembles** *Madan Babu,* Pau Bernado, Sigrid Milles, John Orban, Benjamin Schuler
- **The Roles of IDPs in Membraneless Organelles** *Rohit Pappu,* Simon Alberti, Yves Gaudin, Tanja Mittag, Richard Young
- **Ensembles and Conformational Dynamics of IDPs** *Gary Daughdrill,* Roderick Lim, Sua Myong, Malene Ringkjobing-Jensen, Andrew Baldwin, Elizabeth Rhoades
- **Post-Translational Modifications of IDPs** *Peter Tompa,* Elisar Barbar, Mart Loog, Michal Sharon
- **The Physical Basis of Phase Transitions in Cells** *Richard Kriwacki,* David Allan Drummond, Edward Lemke, Rohit Pappu, Avinash Patel
- **Membrane Interactions with IDPs and Transport** *Monika Fuxreiter,* Ashok Deniz, David Eliezer, Birthe Kragelund, Jeanne Stachowiak
- **IDP Interactions and Allosteric Regulation** *Vincent Hilser,* Sarah Bondos, Remy Loris, Andrei Lupas, Per Jemth, Sarah Shammas
- **Keynote Session: The Role of IDPs in Function and Disease** *Martin Blackledge,* Patrick Chene, Richard Kriwacki, Peter Wright

Intrinsically Disordered Proteins
Disordered but Not Disorganized: How IDPs Drive Spatial and Temporal Cellular Regulation
JUNE 30 – JULY 1, 2018
CHAIRS: Alex S. Holehouse & Shana Elbaum

Ion Channels

Excitable Membranes in the Era of Precision Biology

JULY 8-13, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA

CHAIR: Chris A. Ahern
VICE CHAIR: Brad S. Rothberg

- **Keynote Session: Excitability at High Resolution** *Gary Yellen,* Nieng Yan, Frances Ashcroft
- **Channel Gating Up Close** *Baron Chanda,* Youxing Jiang, Sudha Chakrapani, Crina Nimigean, Show-Ling Shyng, Jian Yang
- **Ion Channel Design Elements** *Teresa Giraldez,* Vera Moiseenkova-Bell, Liz Carpenter, Kallol Gupta, Henry Colecraft
- **Voltage Sensing and Gating Mechanisms** *Kenton Swartz,* Adam Cohen, Lucie Delemotte, Indira Raman
- **Evolution of Electrical Signaling, Emergent Properties and Ion Channel Frontiers** *Sebastian Brauchi,* Peter Hegemann, Joshua Rosenthal, Gurol Suel, Harold Zakon, Brad Rothberg
- **Ion Channels in Organelles and Within Physiological Contexts** *Richard Lewis,* Elena Oancea, Yuriy Kirichok, Murali Prakriya, Dejian Ren
- **Anion Channels and Confused Channel-Transporters** *Merritt Maduke,* Raimund Dutzler, Jue Chen, Randy Stockbridge, László Csanády
- **Chemical Biology at the Synapse** *Andrew Plested,* Isabelle Baconguis, Alex Sobolevsky, Vasanthi Jayaraman
- **Keynote Session: The Synthesis of Structure, Function and Physiology** *Christopher Miller,* Yifan Cheng, Ardem Patapoutian

Ion Channels
Excitable Membranes in the Era of Precision Biology
JULY 7-8, 2018
CHAIRS: Timothy Lynagh & Claudia P. Alvarez Baron

Ionic Liquids

Ionic Liquids as a Critical Enabling Technology for Meeting Current and Future Needs in Energy, Materials and Living Systems

AUGUST 12-17, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Jim Davis
VICE CHAIR: Paul C. Trulove

- **Ionic Liquids as a Key Element of Batteries and Other Energy Applications** *Robert Mantz,* Daniel Buttry, Stefano Passerini, Wesley Henderson
- **The Future of Ionic Liquids in Devices: Moving from Lubricants for Machines to Circulatory Systems in Robotics** *John Newberg,* Maria Forsyth, Timothy Minton, Rui Qiao
- **Ionomers: Putting Ionic Liquids into Polymers and Making Polymers out of Them** *Rhett Smith,* Norman Wagner, Alexei Sokolov, Timothy Lodge
- **Advancing Analytic Technologies Through Ionic Liquids** *Jared Anderson,* Scott Shaw, Ana Afonso, C. Daniel Frisbie
- **Quo Vadis: Ions for Ionic Liquids from Inexpensive or Renewable Sources** *Boyan Iliev,* Jason Hallett, Patrik Johansson, Aaron Scurto

- **Ionic Liquids in the Manipulation of Naturally Occurring Materials** *Robin Rogers,* Luke Haverhals, Gabriela Gurau, Chieu Tran, Dimitris Argyropoulos
- **All About Synthesis: Making Ionic Liquids and Making Other Materials in Them** *Jamie Ferguson,* Jindal Shah, Tamar Greaves
- **What Computation, Spectroscopy and Physicochemical Studies Tell Us About How to Make Better Ionic Liquids** *Stephen Paddison,* Oleg Borodin, Patricia Hunt, Olga Russina
- **Under Duress: Ionic Liquids and Molten Salts for Utilization in Extreme Conditions** *Rasmus Fehrmann,* Donald Sadoway, Ilya Shkrob, Kevin West

GRS Ionic Liquids
Ionic Liquids as a Critical Enabling Technology for Meeting Current and Future Needs in Energy, Materials and Living Systems
AUGUST 11-12, 2018
CHAIRS: Paula Berton & Betul Uralcan

Lasers in Medicine and Biology

Unmet Needs and New Directions in Translational Biophotonics

JULY 8-13, 2018 • BATES COLLEGE, LEWISTON, ME
CHAIRS: Anita Mahadevan-Jansen & Paul M.W. French
VICE CHAIRS: Kristen C. Maitland & David Sampson

- **Pathways to Success in Biophotonics Research** *Bruce Tromberg,* Rajesh Naik, Robert Nordstrom, Rainer Pepperkok
- **Translational Methods in Cancer Care** *Samuel Achilefu, Javier Jo,* Gerard Cote, Rohit Bhargava, Tayabba Hasan
- **Novel Global Health Applications** *Aydogan Ozcan,* David Bell, Chetan Patil, Bayden Wood
- **Using Light for Drug Discovery, Delivery and Resistance** *Kin Chang, Cristina Zavaleta,* Beverley Isherwood, Adela Ben-Yakar, Conor Evans
- **Transforming Forensic Science with Light** *Maurice Aalders, Lise Randeberg,* Claude Roux, Ravi Kalyanaraman
- **Infectious Diseases and Immunology** *Audrey Ellerbee,* Ronald Germain, Stephen Boppart
- **Improving Our Understanding of Maternal/Fetal Medicine** *Christine Hendon, Jessica Ramella-Roman,* James Wynn, Xingde Li
- **New Directions in BRAIN Research** *Elizabeth Hillman,* Peter Konrad
- **Human Performance and Wellness** *Ton Van Leeuwen, Jerry Wilmink,* Cleber Ferraresi
- **Power Hour** *Kristen Maitland*

GRS Lasers in Medicine and Biology
Improving the Optical Toolbox of Clinicians and Researchers
JULY 7-8, 2018
CHAIRS: Sam Osseiran & Anouk L. Post

NEW! Lasers in Micro, Nano and Bio Systems

Integration of Laser Physics, Photonics, Materials, Nanotechnology, Biochemistry and Biomedicine

JUNE 17-22, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH
CHAIRS: Xudong Fan & Seok-Hyun Andy Yun
VICE CHAIRS: Teri W. Odom & Axel Scherer

- **Keynote Session: History, Challenge and Potential of Micro/Nano/Biolasers** *Axel Scherer,* Federico Capasso, Vladimir Shalaev
- **Bio-Integrated and Bio-Inspired Lasers** *Vladimir Zharov,* Sven Höfling, Matjaz Humar, Yu-Cheng Chen
- **Opto-Mechanical Lasers and Their Applications in Biochemical Analysis** *Hong Tang,* Gaurav Bahl, Ivan Favero
- **Novel Bio-Materials for Lasers** *Geoffrey Waldo,* Malte Gather, Sivaraj Sivaramakrishnan, Huajie Liu
- **Nano/Micro Lasers for Sensing** *Yong-Hee Lee,* Toshihiko Baba, Ren-Min Ma
- **Micro/Nanofluidic Devices** *Yeshaiahu Fainman,* Jason Smith, Hui Cao, Anders Kristensen
- **Plasmonic Lasers and Their Biomedical Applications** *Shang-Jr Gwo,* Henri Lezec, Teri Odom
- **Laser-Based Probes and Imaging** *Mark Stockman,* Vladimir Zharov, Ji-Xin Cheng, Nicola Martino
- **Parity-Time Symmetric Lasers** *Demetrios Christodoulides,* Lan Yang, Boubacar Kantu

NEW! Lignin

Towards Viable Solutions for Lignin Valorization

AUGUST 5-10, 2018 • STONEHILL COLLEGE, EASTON, MA
CHAIRS: Gregg T. Beckham & Lindsay D. Eltis
VICE CHAIRS: Ana Gutiérrez & Yuriy Román

- **Keynote Session: The Need for Sustainable Approaches to Lignin Valorization** *Blake Simmons,* John Ralph, Bert Sels
- **Understanding and Tailoring Lignin Biosynthesis In Planta** *Laura Bartley,* Wout Boerjan, Daniele Werck-Reichhart, Clint Chapple, José Del Río, Richard Dixon
- **Designing Lignin for Deconstruction in Energy Crops** *Arthur Ragauskas,* Gerald Tuskan, Claire Halpin, Shawn Mansfield
- **Towards Selective Catalytic Lignin Depolymerization** *R. Tom Baker,* Nicholas Westwood, Feng Wang, Corey Stephenson, Katalin Barta, Jeremy Luterbacher
- **Catalytic Production of Chemicals from Lignin** *Robert Brown,* Shannon Stahl, Pieter Bruijnincx, Yuriy Román
- **Elucidating Lignin Structure with Emerging Analytical and Computational Methods** *Robert Henry,* Yuki Tobimatsu, Antje Postthast, Linda Broadbelt, Claudia Crestini
- **Designing New Lignin-Based Polymeric Materials** *Mojgan Nejad,* Florian Graichen, Dimitris Argyropoulos, Thomas Epps
- **Microbial Conversion of Lignin** *Tim Bugg,* Eiji Masai, Aindrila Mukhopadhyay, Ellen Neidle, Timothy Donohue
- **Enzymatic Lignin Depolymerization** *Emma Master,* Angel Martinez, Miguel Alcalde, Elizabeth Sattely

Lipoprotein Metabolism

Lipoprotein Metabolism in the Brain and Circulation and Its Role in Disease

JUNE 10-15, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH
CHAIRS: Alan Remaley & Cheryl Wellington
VICE CHAIRS: Mahmood Hussain & Kiran Musunuru

- **Keynote Session: New Pathways in Cellular Lipid Homeostasis in the Brain and Other Tissues** *Kiran Musunuru,* Peter Tontonoz
- **Lipoprotein Metabolism in the Brain** *Joachim Herz,* Oleg Butovsky, Gayathri Ramaswamy, Maki Tsujita, Jason Ulrich, Melissa Beton
- **Gut Microbiota and Intestinal Lipid Metabolism** *Rebecca Haeusler,* Mark Brown, Marc-Emmanuel Dumas, Thomas Vallim
- **Tissue Engineering: New Human Experimental Platforms for the Study of Metabolic Disease** *Marlys Koschinsky,* Alison Kohan, Jerome Robert, Takanori Takabe, Sara Vasconcelos
- **Genomics of Dementia and Cardiovascular Disease** *Katey Rayner,* Haiming Cao, Muredach Reilly, Jose Vargas, Szilard Voros
- **HDL Structure and Function** *Mary Sorci-Thomas,* Sean Davidson, Amy Shah, Jonathan Smith, Scott Gordon
- **ApoB-Containing Lipoprotein Metabolism and Cellular Uptake Pathways** *Mahmood Hussain,* Gabor Csanyi, Gordon Francis, Saskia Neher, Gissette Reyes-Soffer
- **Novel Therapies and Diagnostic Approaches for Vascular Lipoprotein Disorders** *Sudha Biddinger,* James Otvos, Anna Schwendeman, Norman C. Wong, Sam Wright
- **Selected Poster Presentations and Late-Breaking Topics** *Alan Remaley*

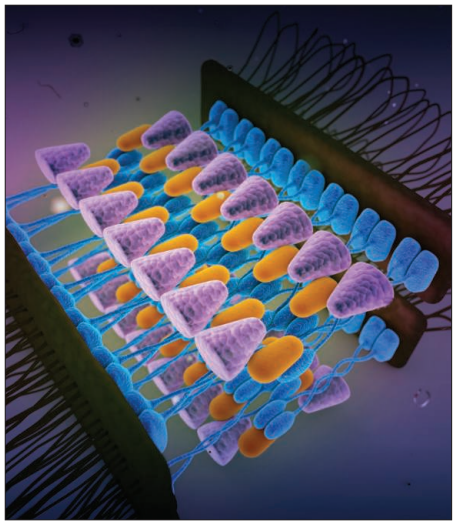
GRS Lipoprotein Metabolism
Genetic Regulation of Lipoprotein Metabolism in Disease and Lipoprotein Structure-Function and Kinetics
JUNE 9-10, 2018
CHAIRS: Swapnil V. Shewale & Allison Andraski

Liquid Biopsy for Cancer

Circulating Tumor Cells, ctDNA and Extracellular Vesicles

AUGUST 5-10, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA
CHAIRS: Shannon Stott & Stefanie Jeffrey
VICE CHAIRS: Klaus Pantel & Shana O. Kelley

- **Keynote Session: Liquid Biopsy: New Opportunities and Challenges in the Field** *Klaus Pantel,* Mehmet Toner, Caroline Dive
- **Isolation Technologies** *Anthony Dickherber,* Dino DiCarlo, Sunitha Nagrath, David Issadore
- **Phenotyping and Genotyping** *Viktor Adalsteinsson,* Evi Lianidou
- **Liquid Biopsy: Exploring Tumor Biology** *Shana Kelley,* Andrew Rhim, Catherine Alix-Panabieres
- **Liquid Biopsy: Exploring the Biology of Metastasis** *Marsha Rosner,* Min Yu
- **Additional Tumor-Educated Products in Circulation** *Bakhos Tannous,* Thomas Wurdinger, Wilfred Ngwa



Artist's rendering of the three-dimensional architecture of the *Drosophila* synaptonemal complex, a multiprotein meiotic structure, based on images acquired by combining structured illumination with expansion microscopy. CREATED BY RYAN KRAMER IN CONSULTATION WITH CORI K. CAHOON. SUBMITTED BY THE 2018 MEIOSIS GRC CHAIRS.

- **Technologies for Characterization and Analysis** *Brian Kirby,* Scott Manalis
- **Incorporating Liquid Biopsy into Clinical Trials** *Stefanie Jeffrey,* Howard Scher, Allison Welsh
- **Steps Towards Clinical Integration** *George Sledge,* Michail Ignatiadis

GRS Liquid Biopsy for Cancer
Advancements and Discoveries in Biological Fluid Interrogation for Detecting and Monitoring Cancer
AUGUST 4-5, 2018
CHAIRS: Erica D. Pratt & Karla Williams

Lysosomes and Endocytosis

Molecules, Pathways and Physiology of Endosomes, Lysosomes and Lysosome-Related Organelles

JUNE 17-22, 2018 • PROCTOR ACADEMY, ANDOVER, NH
CHAIR: Lois S. Weisman
VICE CHAIR: Christopher G. Burd

- **Lysosomes: Metabolism, Lipids and Lysosomal Diseases** *Andrea Ballabio, Gillian Griffiths,* Rosa Puertollano-Moro, Anne Simonsen, Suzanne Pfeffer
- **Lysosomal Biogenesis and Autophagy: Normal Pathways and Contributions to Neurological Disease** *Victor Faundez, Amy Kiger,* Antonella De Matteis, Alexey Merz, Shawn Ferguson, Gilbert DiPaolo, Tamotsu Yoshimori
- **Endocytosis: Basic Mechanisms, Signaling and Diabetes** *Julie Donaldson, Amira Klip,* Marko Kaksonen, Jeanne Stachowiak, Mark Von Zastrow, Timothy McGraw
- **Autophagy, Endocytosis and Exosomes: The Ins and Outs of Cancer and Immunity** *Norma Andrews, Michael Marks,* Katja Simon, Randy Schekman, Alexander Sorkin, Sandra Schmid
- **Roles of the Endosomal Network in Organismal Physiology** *Graca Raposo, Liz Miller,* Xiaochen Wang, Roberto Weigert, Frances Brodsky
- **Cellular Integration via Organelle Contact Sites and Phosphoinositide Signaling** *Peter Cullen, Fred Maxfield,* Benoit Kornmann, Karin Reinisch, Sergio Grinstein, Pietro De Camilli, Heidi McBride
- **Late-Breaking Topics** *Mary Munson, Judith Klumperman,* Tomas Kirchhausen
- **Sorting in the Endosomal Network** *Phyllis Hanson, Christopher Burd,* Scott Emr, Robert Piper, Benjamin Glick, James Hurley, Carole Parent
- **Keynote Session: Mechanisms of Membrane Fusion** *Lois Weisman,* William Wickner
- **Power Hour** *Liz Miller, Christopher Burd*

GRS Lysosomes and Endocytosis
Endosomes, Lysosomes and Trafficking in Health and Disease
JUNE 16-17, 2018
CHAIR: Mengxiao Ma

Mammalian Reproduction

Pathways from Gametogenesis to Pregnancy

JULY 29 – AUGUST 3, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIRS: Humphrey H. Yao & Jon Oatley

VICE CHAIRS: Margaret Petroff & Kyle Orwig

- **Stem Cells and Reproductive Diseases** *Amander Clark,* Magdalena Zernicka-Goetz, Barbara Vanderhyden, Mana Parast
- **Making Golden Eggs** *Richard Anderson,* Shoukhrat Mitalipov, Lei Lei, Richard Freiman
- **Domestic Animal Models for Reproductive Research** *Gregory Johnson,* Bruce Whitelaw, Eric Pailhoux, Thomas Spencer
- **Cross-Talk at the Maternal-Fetal Interface** *James Pru,* Carlos Simon, Hongmei Wang, Indrani Bagchi
- **Making Golden Sperm** *Massimo De Felici,* Paula Cohen, Tony De Falco, Tessa Lord
- **Reproduction on Steroids** *Julie Kim,* Francesco Demayo, Lee Smith, Jeffrey Pollard
- **Fate Determination of Reproductive Cell Lineages** *Joan Jorgensen,* Josephine Bowles, Marie-Christine Chaboissier, Takashi Shinohara
- **Extrinsic/Intrinsic Influences on Reproductive Processes** *Wipawee Winuthayanon,* Anne Goriely, Tracy Bale, Yang Xia
- **Keynote Session: Reproductive Biology Research** *Margaret Petroff, Kyle Orwig,* Fuller Bazer, John McCarrey
- **Power Hour** *Margaret Petroff*

Mammalian Reproduction
Novel Tools and Technologies Applied to Mammalian Reproduction
JULY 28-29, 2018
CHAIRS: Pablo I. Hurtado Gonzalez & Francesca Soncin

Mammary Gland Biology

Mammary Gland Development and Breast Cancer from Systems Biology to Single Cell

MAY 27 - JUNE 1, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIRS: Christina Scheel & Renee Van Amerongen

VICE CHAIRS: Weston Porter & Kaylee Schwertfeger

- **Keynote Session: Establishing Complex Tissue Architecture by Integrating Mechanical and Biochemical Cues** *Christine Watson,* Celeste Nelson
- **Transcriptional and Translational Control of Mammary Gland Development and Breast Cancer** *Maria Vivanco,* Andrew Ewald, Camila dos Santos, Clare Davies
- **Emerging Aspects of Metastasis** *Eva Gonzalez-Suarez,* Christoph Klein, Nicola Aceto
- **Mammary Gland Biology Beyond Mice and Women** *Russell Hovey,* Dagmar Iber, Helena Richardson, Kathleen Arcaro
- **Breast Cancer Heterogeneity and Precision Medicine** *Tan Ince,* Nicholas Navin, Khalil Zaman
- **Physiological and Environmental Factors that Influence Lactation and Breast Cancer Risk** *Robert Clarke,* Hector Peinado, Rebecca Riggins, Donna Geddes
- **(Immune) System Interactions in Development and Disease** *Kaylee Schwertfeger,* Jennifer Richer, Geoffrey Lindeman
- **Developmental Signaling and Tumor Resistance Mechanisms** *Weston Porter,* Thorarinn Gudjonnson, Benjamin Spike, Johanna Ivaska
- **Keynote Session: Stem Cells in Mammary Gland Development and Breast Cancer** *Mohamed Bentires-Alj,* Cedric Blanpain
- **Power Hour** *Maria Vivanco*

Mammary Gland Biology
Branching Out: Exploring the Cellular Processes Driving Mammary Gland Development and Disease
MAY 26-27, 2018
CHAIRS: Nathan J. Godde & Johanna Wagner

Marine Microbes

Elucidating Microbial Processes Across Spatial and Temporal Scales

JULY 1-6, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIR: Kay Bidle

VICE CHAIR: Corina Pd. Brussaard

- **Evolution of Microbial Genomes and Metabolic Pathways** *Marco Fondi,* Oded Beja, Donato Giovannelli, Simonetta Gribaldo
- **Linking Microbial Diversity and Interactive Processes to Ecological and Biogeochemical Function** *Sonya Dyhrman,* Anne Dekas, Brook Nunn, Alyson Santoro
- **Microbial Mediation of Elemental Cycling and Nutrient Transformation** *Mak Saito,* Brett Baker, Kimberlee Thamatrakoln, Phoebe Lam
- **Physical Structuring of Microbial Processes and Ecosystems** *Roman Stocker,* Martin Ackermann, Thomas Kiorbe, Katharina Ribbeck
- **Microbial Sensing, Cell Signaling and Infochemicals** *Angela Falciatore,* Angelo Fontana, Jon Todd, Maria Immacolata Ferrante
- **Flow and Connectivity of Microbial Ecosystems** *Katherine McMahon,* Stefan Bertilsson, Xose Anxelu Moran, Alexis Pasulka
- **Interpreting Microbial Processes from Automated Observations and Platforms** *Heidi Sosik,* John Breier, Kristen Hunter-Cevera, Julie Robidart
- **Integrating Big Data and Computational Approaches** *Shinichi Sunagawa,* A. Murat Eren, Rob Finn, Patrick Wincker
- **Developing New Approaches to Model Microbial Processes** *Victoria Coles,* Andrew Barton, Daniele Iudicone, David Talmy
- **Power Hour** *Heidi Sosik, Brook Nunn*

Marine Microbes
Marine Microbial Strategies for Survival in a Changing Environment
JUNE 30 – JULY 1, 2018
CHAIRS: Flora J. Vincent & Kyle R. Frischkorn

Mechanisms of Epilepsy and Neuronal Synchronization

Translating Mechanisms into Therapies for Epilepsies

AUGUST 19-24, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIRS: Christophe Bernard & Amy Brooks-Kayal

VICE CHAIRS: Jeffrey L. Noebels & Chris G. Dulla

- **Keynote Session: Harnessing Complexity to Better Understand Epilepsies and Improve Their Treatments** *Christophe Bernard, Amy Brooks-Kayal,* Fabrice Bartolomei, Ivan Soltesz
- **Large Scale Networks** *Akio Ikeda,* Viktor Jirsa, Dimitri Kullmann, Atul Maheshwari, John Terry
- **Behavioral and Cognitive Dysfunction** *Asla Pitkanen,* Kathryn Davis, Edward Boyden
- **Astrocytes and Metabolism** *Tallie Z. Baram,* Amy Brewster, Manisha Patel, Karen Wilcox
- **Blood Brain Barrier and Inflammation** *Aristea Galanopoulou,* Shelley Russek, Alon Friedman
- **Cellular Dysfunction** *Helen Scharfman,* Omar Ahmed, Heinz Beck, Igor Pavlov, Kevin Staley, Philippa Karoly
- **Genetics/Epigenetics** *Katja Kobow,* Jeannie Chin
- **Stem Cells and iPSCs** *Jack Parent,* Kyung-Ok Cho, Jenny Hsieh, Lori Isom, Steve Danzer
- **Novel Translational Models** *Scott Baraban,* Richard Baines, Aliesha Griffin

Mechanisms of Epilepsy and Neuronal Synchronization
Insights into Mechanisms and Therapies for Epilepsy
AUGUST 18-19, 2018
CHAIRS: Tristan Shuman & Amanda E. Hernan

Medicinal Chemistry

Recent Advances in Drug Discovery: Using Innovations in Technology, Screening and Synthesis to Identify Novel Treatments for Unmet Medical Needs

AUGUST 5-10, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIR: Carolyn D. Dzierba

VICE CHAIR: Robert W. Marquis

- **Non-Oral Drug Delivery** *Christopher Plummer,* Mark Zak, Kevin Dack, Izzat Raheem
- **Immuno-Modulation for the Treatment of Cancer: Recent Medicinal Chemistry Advances** *Michael Ellis,* Wes Trotter, Michelle Lamb, Emily Cherney, Mikhail Zibinsky
- **New Paradigms in SBDD: Understanding Ligand Conformation to Aid Molecular Design** *Ashley Jarvis,* Elisabetta Chiarparin, Tom Heightman, Thorsten Nowak
- **Emerging Approaches for the Treatment for Non-Alcoholic Steatohepatitis (NASH)** *Ralf Glatthar,* Dieter Hamprecht, Valentina Molteni, Brian Raymer, Arun Sanyal
- **Novel Solutions to ADME Challenges** *Julia Haas,* Nandini Patel, Michael Wiley, Rui Xu
- **Hijacking the Ubiquitin Proteasome System: Recent Progress in the Development of Targeted Protein Degraders** *Matthew Bourbeau,* Alessio Ciulli, Christopher Nasveschuk, Steven Staben, John Harling
- **Targeting RNA with Small Molecules** *Darby Schmidt,* Russell Petter, Hasane Ratni, Justin Ernst
- **Late-Breaking Topics: First Disclosures of Clinical Candidates** *Joshi Ramanjulu*
- **Keynote Session: Molecular Complexity: The Challenge of Modern Clinical Candidates** *Carolyn Dzierba,* Martin Eastgate

Medicinal Chemistry
Strategies for Optimizing Pharmacological, Metabolic and Toxicological Profiles of Drug Leads
AUGUST 4-5, 2018
CHAIR: Amy B. Dounay

Meiosis

Molecular Mechanisms and Regulation of Meiosis Across Species

JUNE 10-15, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIR: Monica P. Colaiacovo

VICE CHAIR: Paula E. Cohen

- **Chromosome Synapsis: Organization, Regulation and Functions** *Jinmin Gao,* Scott Hawley, Kevin Corbett, Amy MacQueen, Ricardo Benavente
- **Meiotic Recombination: Regulation of Initiation and Progression of Recombination** *Luke Berchowitz,* Scott Keeney, Douglas Bishop, Neil Hunter, Bernard De Massy, R. Daniel Camerini-Otero, Maria Jasin, Franz K. Klein
- **Aneuploidy: New Emerging Technologies and Health Implications** *Ewelina Bolcun-Filas,* Eva Hoffmann, Melina Schuh, David Page, Patricia Hunt
- **Chromosome Segregation: Spindle Assembly and Cohesion** *Karen Schindler,* Adele Marston, Tomoya Kitajima, Iva Tolic, Joanne Engebrecht, Akira Shinohara, Raphael Mercier, Elcin Unal
- **Epigenetics, Expression and Germ Cells** *Yonatan Tzur,* Barbara Meyer, Satoshi Namekawa, Andreas Hochwagen, Gloria Brar
- **Meiotic Recombination: Regulation of Frequency and Distribution** *Philip Jordan,* Michael Lichten, Francesca Cole, Jeff Sekelsky, Nancy Kleckner, Anne Villeneuve, Paula Cohen, Gerald Smith
- **Checkpoints and Regulation of Cell Cycle Progression** *Yumi Kim,* James Turner, Attila Toth, John Schimenti, Ignasi Roig, Abby Dernburg
- **Chromosome Dynamics and Chromatin Organization** *Sadie Wignall,* Matthew Neale, Enrique Martinez-Perez, Denise Zickler, Monica Pradillo
- **Evolution: Diversity and Conservation of Meiosis** *Sarah Zanders,* Mary Ann Handel, Jesus Page, Sean Burgess
- **Power Hour** *Needhi Bhalla, Andreas Hochwagen*

Meiosis
Mechanisms and Regulation of Gametogenesis Through Meiosis
JUNE 9-10, 2018
CHAIRS: Jessica L. Hopkins & Carla M. Abreu

Membrane Transport Proteins

Transmembrane Transporters in Health to Disease

JUNE 10-15, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Harald H. Sitte

VICE CHAIR: Aurelio Galli

- **Brain Matters: Membrane Transporters in Glia and Their Relationship to Disease** *Jeffrey Rothstein,* Rebecca Seal, Michael Robinson, Rajini Rao, Renae Ryan
- **Insights into Transporter Function: State-of-the Art Approaches** *Ulrik Gether,* Satinder Kaur Singh, Peter Hinterdorfer, Thorben Cordes, Dimitrios Stamou, Avner Schlessinger, Simon Scheuring, Claus Loland
- **Protein Trafficking: Chaperoning Services** *Michael Freissmuth,* Suzanne Pfeffer, Habibeh Khoshbouei, Imogen Coe, Nancy Leidenheimer
- **Plasma Membrane as a Regulator of Transport** *Aurelio Galli,* Gerhard Schütz, Ai Yamamoto, Sharona Gordon, Gregory Fairn
- **Sex as a Biological Variable in Transport Processes** *Gaia Novarino,* Erin Calipari, Theresa Powell, Alicia McDonough, Sandra Hewett

- **Transporters in the Brain and Their Role in Disease** *Haley Melikian,* Steven Kushner, Gonzalo Torres, Susan Ingram, Randy Blakely
- **Transporters in Disease: CFTR and ABC Transporters** *David Hepworth,* Ina Urbatsch, Igor Stagljar, Show-Ling Shyng
- **Diabetes and Beyond: Transporters Are Key** *Lydia Aguilar-Bryan,* Michael Czech, Timothy Ryan, Natascia Vedovato, Mauricio DiFulvio
- **Keynote Session: Transporters: Clinically Relevant Targets of Licit and Illicit Drugs** *Harald Sitte,* Kathleen Giacomini, Hanne Poulsen, Francisco Bezanilla
- **Power Hour** *Imogen Coe*

Membrane Transport Proteins
Membrane Proteins: From Structure to Disease
JUNE 9-10, 2018
CHAIRS: Alice Verchre & Aparna Shekar

Membranes: Materials and Processes

Translating Molecular Scale Discoveries to Commercial-Scale Membrane Operations

AUGUST 12-17, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIRS: Mary L. Lind & Manish Kumar
VICE CHAIRS: Isabel Escobar & William A. Phillip

- **Keynote Session: Membrane Design Informed by Applications at Scale** *Maria Coleman,* Peter Pohl, Harry Seah
- **Molecular Components of Membranes: Bioinspired Design** *Dibakar Bhattacharyya, Young-hye Na,* Aleksei Aksimentiev, Mihail Barboiu
- **Molecular Components of Membranes: Synthetic Polymers** *Ruilan Guo, Matthew Green,* Marc Hillmyer, Nitash Balsara
- **Membranes, Mesoscale Devices with Controlled Nanostructures** *Miao Yu, Geoffrey Geise,* Chinedum Osuji, Ivo Vankelecom, Orlando Coronell
- **Membranes, Antifouling Strategies** *Abhishek Roy,* Hans Vrouwenvelder, Ayse Asatekin
- **Modules, Design, Packing and Operation** *Shihong Lin,* Raja Ghosh, Tequila Harris, Christopher Stafford
- **Modules, Novel Designs and Insights** *Avner Ronen, Zachary Smith,* David Jassby, Mou Paul
- **Emerging Ideas and Systems** *Laura Arias Chavez, Jessica Schiffman,* Cristiana Boi, Wanqin Jin, Jay Kniep
- **Keynote Session: Recent Discoveries Pushing Membranes into the Future** *Bradley Ladewig,* Kitty Nijmeijer, Richard Noble
- **Power Hour** *Maria Coleman*

Membranes: Materials and Processes
From Molecules to Modules: A Journey from Molecular Designs of Membranes to High-Performance Membrane Modules
AUGUST 11-12, 2018
CHAIRS: Yuexiao Shen & Morten Logemann

NEW! Mesophotic Coral Reef Ecosystems

The Functional Roles of Mesophotic Coral Reefs in the Anthropocene

JUNE 17-22, 2018 • BATES COLLEGE, LEWISTON, ME

CHAIR: Michael P. Lesser
VICE CHAIR: Marc Slattery

- **Hyperbaric Medicine and Technical Diving Advances Relevant to Mesophotic Coral Reef Research** *Elizabeth Kintzing,* Simon Mitchell, John Clarke

- **Diversity, Ecophysiology and Community Structure of Mesophotic Coral Reef Ecosystems** *Tom Bridge,* Sonia Rowley, Tracy Ainsworth, Celia Smith
- **The Geology and Physical Environment of Mesophotic Coral Reefs** *James Leichter,* Clark Sherman, Curtis Mobley
- **Genetic Connectivity Within and Between Mesophotic Coral Reef Ecosystems** *Robert Toonen,* Pedro Frade, Gretchen Goodbody-Gringley, Joshua Voss
- **Reproductive Ecology of Mesophotic Coral Reef Organisms** *Tali Mass,* Daniel Holstein, Saki Harii
- **Mesophotic Reefs and the Deep Reef Refuge Hypothesis** *Pim Bongaerts,* Frederic Sinniger, Tyler Smith, Gal Eyal
- **Fish Communities and Their Ecology on Mesophotic Coral Reefs** *Luiz Rocha,* Christina Bradley, Hudson Pinheiro
- **Anthropogenic Change and the Future of Mesophotic Coral Reefs** *Yossi Loya,* Richard Appeldoorn, Peter Etnoyer, Tsuyoshi Watanabe
- **Conservation Challenges and Future Directions in Mesophotic Coral Reef Ecosystem Research** *Michel Pichon,* Bernhard Riegl, Marjorie Reaka

Metallocofactors

Essential Metal-Based Reactions Transforming Hydrogen, Carbon, Nitrogen, Sulfur and More

JUNE 10-15, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA

CHAIR: Sean J. Elliott
VICE CHAIR: Serena Debeer

- **Frontiers of Metallocofactor-Based Reduction** *Patrick Holland,* Oliver Einsle, Edward Solomon
- **Redox Transformations of Carbon** *Hannah Shafaat,* Russ Hille, Christophe Leger, Jose Moura, Stephen Ragsdale
- **Iron-Sulfur Clusters and Molybdenum Enzymes** *Kenichi Yokoyama,* Sharon Burgmayer, Martin Kirk, Silke Leimkuehler
- **Metallocofactor Biogenesis** *Daniel Suess,* David Barondeau, Yilin Hu, Steven Mansoorabadi
- **Hydrogenase Chemistry: Native and (Semi)Synthetic** *Alison Parkin,* Marcetta Darensbourg, Paul King, Wendy Shaw
- **Novel Bonds and Novel Redox Reactions** *Neal Mankad,* Alison Fout, Connie Lu, Jenny Yang
- **Oxidations of Carbon and Nitrogen: The Anaerobic Way** *Kyle Lancaster,* Thomas Barends, Jennifer Glass, Nicolai Lehnert
- **AdoMet Radical Enzymes** *Nozomi Ando,* Vahe Bandarian, Olivier Berteau, Joan Broderick
- **Bringing Metallocofactor Mechanisms to Life** *Maria-Eirini Pandelia,* Carsten Krebs, Jonas Peters

Metals in Medicine

The Indispensable Role of Metals in Medical Diagnostics, Therapeutics and Beyond

JUNE 24-29, 2018 • PROCTOR ACADEMY, ANDOVER, NH

CHAIRS: Seth M. Cohen & Kenneth Kam-Wing Lo
VICE CHAIRS: Edith (Phoebe) P. Glazer & Angela Casini

- **Inorganic Nanomaterials in Medicine** *Chad Mirkin,* Patricia Horcajada, Vincent Rotello, Michael Sailor
- **Recent Developments in Metallodrugs** *Maria Contel,* Jonathan Sessler, Valentina Gandin, James McKerrow, Celine Marmion
- **From Chemistry to Clinic** *Jonathan Sessler,* Chad Mirkin, David Puerta, Christine Brennan
- **Metal Homeostasis in Health and Disease** *David Giedroc,* Chuan He, Anne-Kathrin Duhme-Klair, Amy Palmer, Raphael Rodriguez
- **Metalloglycomics** *Susan Berners-Price,* Jeremy Turnbull, Mauro Pavao, Nicholas Farrell
- **New Agents for Imaging Applications** *Christoph Fahrni,* Roger Alberto, Carolyn Anderson, Xiaogang Liu
- **Case Studies in Translational Research** *Nicholas Farrell,* Walter Berger, Petra Heffeter, Christian Kowol
- **Analytical Techniques for Metals in Biological Systems** *Christian Hartinger,* Victoria DeRose, Peter Lay, Ryszard Lobinski
- **Young Investigator Presentations** *Angela Casini,* Loi Do, Bo Li, Anthony Grillo

Microbial Stress Response

Microbial Control of Homeostasis in Extreme, Hostile and Unpredictable Environments

JULY 15-20, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA

CHAIRS: Petra A. Levin & William W. Navarre
VICE CHAIRS: Michael Laub & Jade Wang

- **Keynote Session: Bacteriophage Related Stress: Killers or Masterminds** *Daniel Haeusser,* Ryland Young, Karen Maxwell, Blake Wiedenheft
- **Stress and the Cell Envelope** *Natividad Ruiz,* Angelika Grundling, Kevin Young, Dennis Claessen, Gemma Reguera
- **Microbial Survival in Host and Non-Host Environments** *Amy Schmid,* Christopher Yost, Barbara Kunkel
- **Stress and Metabolism** *Daniel Stoebel,* John Kirby, Kim Lewis, Anthony Richardson
- **Antimicrobial Stress** *Joan Slonczewski,* Michael Baym, Elizabeth Harry, Eduardo Groisman, Kornelia Smalla
- **Intermicrobial Interactions: The Stress of Living Together** *Frederico Rey,* John Whitney, Aniek Ivens, Elizabeth Sockett
- **Symbiosis: A Community Approach to Dealing with Stress** *Paul Price,* Silvia Bulgheresi, Joel Griffitts, John McCutcheon, Corrie Moreau
- **Developmental Responses to Stress** *Julia van Kessel,* Pamela Brown, Marie Elliot, Kumaran Ramamurthi, Amy Gehring, Gilles van Wezel
- **Using Big Data to Understand Microbial Stress Response** *Michael Ibba,* Jay Hinton, K.C. Huang, Paul Wiggins, Jie Xiao

Microbial Stress Response
New Insights into Bacterial Adaptation in Response to Fluctuating Environments
JULY 14-15, 2018
CHAIRS: Saumya Gopalkrishnan & Emily K. Crispell

Microbial Toxins and Pathogenicity

Bacterial Pathogenesis: From Pathogen Physiology to Interactions with Host Microbiota and Immune System

JULY 8-13, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIR: Andrew Camilli
VICE CHAIR: Heran Darwin

- **Keynote Session: Host Microbiota in Infection and Disease** *Heran Darwin,* Walter Adams, Andreas Baumler, Samuel Miller, Jeannette Tenthorey
- **The Dynamics of Pathogens** *Mary O'Riordan,* Robert Abramovitch, Alan Hauser, Tammy Kielian, Stephen Trent
- **Physiology and Virulence of Bacterial Pathogens** *Marvin Whiteley,* Jenifer Coburn, Erin Gaynor, Stefan Schild, James Slauch
- **Toxins and Effector Proteins Pave the Way** *Peggy Cotter,* James Bliska, Juliane Bubeck Wardenburg, Alex Esminger, Victor Torres, Joseph Vogel
- **Toxins: Action, Targeting and Structure** *Daniel Portnoy,* Joseph Barbieri, Steven Blanke, Sam Light, Peter Sebo
- **Pathogenesis and New Approaches** *James Slauch,* Timothy Cover, Deborah Hung, Christopher Sassetti, Hank Steven Seifert, Marvin Whiteley
- **Close Encounters with the Host Cell** *Juliane Bubeck Wardenburg,* Peggy Cotter, Kelly Doran, Vanessa Sperandio, Jun Zhu
- **Immune Responses and Pathogenesis** *Tammy Kielian,* Lee-Ann Allen, John Brumell, Ivan Dikic, Mary O'Riordan, Christina Stallings
- **Keynote Session: Host-Pathogen Biochemistry** *Walter Adams,* Matthias Machner, Kim Orth

Microbial Toxins and Pathogenicity
Exploring the Molecular Conflicts Between Host and Pathogen
JULY 7-8, 2018
CHAIRS: Jeannette Tenthorey & Walter I. Adams

NEW! Microbiology of the Built Environment

Integrating Human Health with Building Microbiomes

JULY 15-20, 2018 • UNIVERSITY OF NEW ENGLAND, BIDDEFORD, ME

CHAIR: Jordan Peccia
VICE CHAIR: Jessica L. Green

- **How the Built Environment Microbiome Impacts the Human Microbiome** *Jessica Green,* Jack Gilbert
- **Building Design and Operation Impact Microbial Diversity and Exposure** *Kerry Kinney,* Rachel Adams, Martin Taubel
- **Viruses in Buildings** *Maosheng Yao,* Linsey Marr
- **Building Microbes, Allergies and Asthma** *Karen Dannemiller,* Elizabeth Matsui, Juha Pekkanen
- **Mold in Buildings** *Jean Cox-Ganser,* Christine Rogers
- **Pathogens in Premise Plumbing** *Charles Haas,* Nicholas Ashbolt, Joe Falkinham
- **Surface and Airborne Pathogens in Buildings** *Jordan Peccia,* Noah Fierer
- **Control of Pathogen Transmission in Buildings** *Mark Hernandez,* Sarah Haig
- **New Tools for Understanding Microbial Exposure** *Lynn Schriml,* Andrew Persily

Mitochondria and Chloroplasts

Fundamental Processes in Organelle Biology: Evolution, Biogenesis, Dynamics and Quality Control

JULY 8-13, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIR: Johannes M. Herrmann
VICE CHAIR: Katherine W. Osteryoung

- **Late-Breaking Topics** *Thomas Fox,* Silvia Ramundo, Nils-Goran Larsson
- **Evolution of Organelles** *Andreas Weber,* Thijs Ettema, Eva Nowack, Patrick Keeling
- **Gene Expression in Organelles** *Alice Barkan,* Ian Small, Bob Lightowlers
- **Protein Import into Mitochondria and Chloroplasts** *Carla Koehler,* Nikolaus Pfanner, Diana Stojanovski, Danny Schnell, Rong Li
- **Assembly of Organellar Protein Complexes: Proteins, Lipids and Cofactors** *Antoni Barrientos,* Eric Shoubridge, Elena Rugarli, Shu-Ou Shan
- **Signaling to and from Organelles** *Ophry Pines,* Christine Foyer, Jared Rutter, Sebastian Hiller, Jesse Woodson
- **Large Scale Organelle Biology** *Sabeeha Merchant,* Trevor Lithgow, Bettina Warscheid, Klaas Van Wijk
- **Organelle Dynamics** *Benedikt Westermann,* Laura Lackner, Heidi McBride, Joerg Nickelsen
- **Organelle Autophagy and Aging** *Richard Youle,* Masanori Izumi, Konstanze Winklhofer

GRS Mitochondria and Chloroplasts
Fundamental Processes in Organelle Biology: Evolution, Biogenesis, Dynamics and Quality Control
JULY 7-8, 2018
CHAIRS: Felix Boos & Cheng Chen

Molecular and Cellular Neurobiology

Recent Discoveries and Technological Advances in the Study of the Nervous System During Development, Health and Disease

JULY 1-6, 2018 • THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY, HONG KONG, CHINA

CHAIR: John J. Ngai
VICE CHAIR: Aaron Gitler

- **Keynote Session: Development of the Nervous System** *Yishi Jin,* Larry Zipursky, Kang Shen, Tomomi Shimogori
- **Synapses and Synaptic Development** *Xiang Yu,* Shernaz Bamji, Mu-ming Poo, Cagla Eroglu, Lu Chen, Thomas Sudhof
- **Neural Stem Cells and the Specification of Neuronal Cell Fates** *Elva Diaz,* Marius Wernig, Christopher Walsh, Samantha Butler
- **Circuits and Behavior** *Jun Ding,* Stephen Liberles, Zhigang He, Claire Wyart, Yang Dan
- **Visualization and Analysis of the Connectome** *Yimin Zou,* Hongwei Dong, Ann-Shyn Chiang, Tianyi Mao, Qingming Luo
- **Genetic and Epigenetic Basis of Neuronal Identity** *Yi Sun,* Hongkui Zeng, Jens Hjerling Leffler, Joseph Ecker, Ed Lein, Stavros Lomvardas
- **Sensory Systems** *Nirao Shah,* Kristin Scott, Sandeep Robert Datta, Ardem Patapoutian
- **Disease Models of the Nervous System** *Louis Reichardt,* Jonah Chan, Susan Ackerman, Eric Huang, Hailan Hu, James Bibb
- **Keynote Session: Advanced Imaging Technologies in Neuroscience** *Liqun Luo,* Xiaowei Zhuang, Jin Hyung Lee, Na Ji

GRS Molecular and Cellular Neurobiology
Molecular and Cellular Dynamics of Neural Function
JUNE 30 – JULY 1, 2018
CHAIR: Anita A. Thambirajah

Molecular Basis of Microbial One-Carbon Metabolism

Dynamic One-Carbon Use on a Changing Planet

JULY 29 – AUGUST 3, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Victoria J. Orphan
VICE CHAIR: Seigo Shima

- **Putting C1 Metabolism to Work** *Thomas Hanson,* Steven Mansoorabadi, Annette Rowe, Lisa Stein, Stephane Vuilleumier
- **New Microbial Players and Metabolic Functions in the C1 Cycle** *Ronald Oremland,* Gene Tyson, Fengping Wang, Gunter Wegener, J. Colin Murrell
- **Regulation and Genetics of C1 Microorganisms** *William Metcalf,* Dipti Nayak, Michael Rother, Paula Welander

GRC is introducing three new conference venues in Castelldefels, Spain, Hong Kong, China and Newry, Maine this summer. Visit www.grc.org for information about all our conference venues.

- **C1 Metabolism and Environmental Implications at High Latitudes** *Mandy Joye,* Virginia Rich, Kelly Wrighton, Katey Walter Anthony, Alexander M Anesio
- **Symbiosis of C1** *Kathleen Scott,* Jillian Petersen, Michiko Taga, Amelia-Elena Rotaru
- **Microbially-Inspired C1 Processes in Industry** *Tobias Erb,* Doris Haffenbradl, Cheryl Kerfeld, Ramon Gonzalez, Ching Leang
- **C1 Cycling in the Ocean** *J. Colin Murrell,* Fumio Inagaki, Alfred Spormann, Orit Sivan
- **Structure and Function of C1 Enzymes** *Rolf Thauer,* Oliver Mueller-Cajar, F. Robert Tabita, John Coates
- **C1 Metabolism: Implications for Early Earth and Astrobiology** *Tori Hoehler,* Alexis Templeton, Shino Suzuki
- **Power Hour** *Paula Welander*

GRS Molecular Basis of Microbial One-Carbon Metabolism
C1 Metabolism: From Fundamental Discoveries to Their Biotechnological Applications
JULY 28-29, 2018
CHAIRS: Benjamin M. Woolston & Tristan P.A. Wagner

Molecular Interactions and Dynamics

Exploring the Molecular Interactions and Dynamics in Complex Systems: Isolated Molecules to Atmospheric Aerosols

JULY 8-13, 2018 • STONEHILL COLLEGE, EASTON, MA

CHAIR: Richard A. Loomis
VICE CHAIR: Hua Guo

- **Atmospheric Reaction Dynamics** *Craig Murray,* Veronica Vaida, Jesse Kroll, Mitchio Okumura
- **Dynamics of Intermediates and Competing Pathways** *Lawrence Harding,* Kopin Liu, Robert Continetti, Jeremy Hutson, Craig Taatjes
- **Photochemistry and Nonadiabatic Systems** *Nancy Levinger,* David Manolopoulos, Christopher Elles, Spiridoula Matsika
- **Dynamics at Interfaces** *Arthur Utz,* Ruth Signorell, Kenneth McKendrick, Heather Allen, Franz Geiger
- **Catalytic Reactions** *Etienne Garand,* Donald Truhlar, Robert Baker, Joseph Francisco
- **Interactions Within Clusters** *Hanna Reisler,* Anne Zehnacker-Rentien, Stuart MacKenzie, Hui Li, J. Mathias Weber
- **Reactivity and Dynamics in Aerosols** *Margaret Greenslade,* Miriam Freedman, Nicole Riemer, Jonathan Reid
- **Molecular Interactions** *Gary Douberly,* Stuart Althorpe, William Hase, Floyd Davis, Donghui Zhang
- **Keynote Session: Bimolecular Dynamics** *Mark Johnson,* Carl Lineberger, Daniel Neumark, Ian Sims

GRS Molecular Interactions and Dynamics
Dynamics of Energy Transfer and Chemical Reactions in Challenging Systems: From Isolated Molecules to Condensed Phases
JULY 7-8, 2018
CHAIRS: Barak Hirshberg & Daniel T. Kwasniewski

Molecular Structure Elucidation

Enabling Development of Novel Therapeutics Through Innovative Analytical Technologies and Methods

AUGUST 12-17, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIRS: Yong Liu & Zheng Ouyang
VICE CHAIRS: Graham Cooks & Roy Helmy

- **Biomolecular Processes** *Yong Liu,* Joachim Frank
- **Protein Structure** *Gaetano Montelione,* Jingke Weng, Michael Rossmann
- **Computational Chemistry in Structural Elucidation** *Edward Sherer,* Nina Gonnella, Rainer Wilcken, Gaetano Montelione
- **Advances in Crystallography and Cryo-EM** *Nina Gonnella,* Phoebe Stewart, Makoto Fujita, Angela Gronenborn
- **Separation Sciences** *Mohammad Alsayah,* Susan Olesik, Daniel Armstrong, Nelu Grinberg
- **Mass Spectrometry in Biological/Biomarker Characterization** *Abraham Badu-Tawiah,* Yu Xia, Lingjun Li, David Russell
- **Advancing Pharmaceutical Discovery/Development Through Molecular Structural Elucidation** *Gaurav Chopra,* Karin Briner, Peter Wuelfing, David Stirling
- **NMR in Advancing Small Molecule Drug Development** *Gary Martin,* Yizhou Liu, Kirk Gustafson, Ann McDermott
- **Molecular Spectroscopic Imaging** *Matthew Lamm,* Garth Simpson, Ji-Xin Cheng, Laurence Nafie

Multiferroic and Magnetoelectric Materials

Effects in Multiferroics Beyond the Coupling of Magnetic and Electric Order

AUGUST 5-10, 2018 • BATES COLLEGE, LEWISTON, ME

CHAIRS: Manfred Fiebig & Nicola A. Spaldin
VICE CHAIR: Ramamoorthy Ramesh

- **Coupled and Competing Instabilities** *Daniel Khomskii,* Tsuyoshi Kimura, Alexander Balatsky, Andrew Millis
- **New Tools for Calculating and Characterizing Multiferroics** *Jens Kreisel,* Jorge Iniguez, Istvan Kezsmarki, Markus Raschke, Urs Staub
- **Post-Modern Multiferroic Composites** *Nian Sun,* Kathrin Doerr, Judith Driscoll, Julia Mundy
- **Dynamical Multiferroic Processes** *Roman Pisarev,* Steven Johnson, Stanislav Kamba, Naoto Nagaosa, Paolo Radaelli
- **Exploiting Point Defects: The Chemical Potential as a Conjugate Field** *Nicola Spaldin,* Sergei Kalinin, James Rondinelli, Sverre Selbach
- **Domain Walls as Functional Interfaces** *Sang-Wook Cheong,* Andrea Bencan, Beatrice Noheda, Marta Rossell, Jan Seidel
- **Multiferroic Devices** *Ramamoorthy Ramesh,* Salvador Pané i Vidal, Jacobo Santamaria, Christian Binek
- **Order Parameters Beyond Magnetoelectric Coupling** *Pierre Toledano,* Nicole Benedek, Venkatraman Gopalan, Michel Kenzelmann, Karin Rabe
- **Keynote Session: Multiferroics Permeate Condensed Matter** *Janice Musfeldt,* Paul C. Chu, Yoshinori Tokura

GRS Multiferroic and Magnetoelectric Materials
Emerging Phenomena in Multiferroics: Novel Insights and Applications
AUGUST 4-5, 2018
CHAIRS: Urko Petralanda & Kishan K. Sinha

Multiphoton Processes

Attosecond and Strong-Field Dynamics, Ultrafast Imaging of Multiphoton Processes and Controlling Light and Matter

JUNE 24-29, 2018 • BRYANT UNIVERSITY, SMITHFIELD, RI

CHAIR: Itzik Ben-Itzhak
VICE CHAIR: Caterina Vozzi

- **Keynote Session: Multiphoton Science** *Itzik Ben-Itzhak,* Peter Lambropoulos
- **Attosecond Dynamics** *Nirit Dudovich,* Andreas Becker, Matthias Kübel, Samuel Beaulieu
- **Ultrafast Imaging** *Kenneth Schafer,* Daniel Neumark, Peter Baum
- **High-Harmonic Spectroscopy** *Smirnova Olga,* Pascal Salieres, Lars Madsen, Carlos Trallero-Herrero
- **New Laser Sources** *Francois Legare,* Sergei Kühn, Gil Porat
- **Controlling Light and Matter** *Eric Wells,* Johan Mauritsson, Thomas Weinacht
- **Molecular Dynamics in Strong Fields** *Joe Sanderson,* Jochen Mikosch, Michael Spanner, Jian Wu
- **Multiphoton Processes at Free-Electron Lasers** *Daniel Rolles,* Kiyoshi Ueda, Oliver Gessner
- **Multiphoton Phenomena** *Carla Figueira de Morisson Far,* Reinhard Dörner, Misha Ivanov, Gerhard Paulus

Multiscale Plant Vascular Biology

Plasticity in Plant Vascular Systems: Roles, Limits and Consequences

JUNE 17-22, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIRS: Barbara Lachenbruch & Jarmila Pittermann
VICE CHAIRS: Brent Helliker & Jeannine Cavender-Bares

- **Subcellular Development** *Andrew Groover,* Nathaniel Street, Enrico Scarpella
- **Development of Cells to Individuals** *Lenka Plavcova,* Cyrille Rathgeber, Giai Petit, Anna Jacobsen

- **Phloem** *Fulton Rockwell,* Michael Knoblauch, Kathy Steppe
- **Xylem** *Kate McCulloh,* Mark Olson, Gretchen North, Teemu Holtta
- **Microevolution** *Thomas Givnish,* Lisa Donovan, Frederic Lens
- **Whole-Plant Responses** *Anna Sala,* Maciej Zwieniecki, Thomas Kolb, Daniel Johnson
- **Macroevolution** *Brendan Choat,* Scott McAdam, Adrienne Nicotra
- **Communities, Ecosystems and the Water Cycle** *Rafael Oliveira,* Sally Thompson, Shabtai Cohen, Adam West
- **Ecosystems of the Future: Looking Forward** *Todd Dawson,* Walid Sadok, William Anderegg
- **Power Hour** *Jeannine Cavender-Bares*

Multiscale Plant Vascular Biology
Knowns and Unknowns of Plant Vascular Responses to Environmental Change
JUNE 16-17, 2018
CHAIRS: Jess T. Gersony & Jennifer L. Teshera-Levye

Musculoskeletal Biology and Bioengineering

The Coordinated Continuum of Biological Systems Supporting Human Motion

AUGUST 5-10, 2018 • PROCTOR ACADEMY, ANDOVER, NH
CHAIR: Peter Johnson
VICE CHAIR: Tamara Alliston

- **The Biological Genesis of Motion** *Kim Cooper,* Otger Campas, Ralph Marcucio, Marian Ros
- **Molecular Energetics and Control** *Clifford Rosen,* Jennifer Elisseeff, Stavroula Kousteni, Fanxin Long, Bruce Spiegelman
- **Cellular Organization and Behavior** *Elizabeth G. Loboa,* David Hoey, Vicki Rosen, Martin Stoddart
- **Macrostructural Musculoskeletal Elements** *Michael Yaszemski,* Tammy Donahue, Rita Kandel, Kenton Kaufman, Xiaowei Liu
- **Central and Peripheral Neurological Control Systems** *Susanne Graessel,* Paul Baldock, Florent Elefteriou, Jason McDougall
- **Diseases of Mobility** *Frank Beier,* Teresita Bellido, Theresa Guise, Christopher Little, Cheryle Seguin
- **The Restoration of Musculoskeletal Function** *Louis Defrate,* Robert Guldberg, Martha Murray, Gregory Sawicki
- **Perfecting Musculoskeletal Coordination** *Scott Levin,* Paul Cederna, Laurie Goodrich, Richard Lieber, Robert Mauck
- **Keynote Session: The Musculoskeletal System and the Machine** *Peter Johnson,* Dean Kamen

Musculoskeletal Biology and Bioengineering
Insight into Musculoskeletal Tissue Interfaces in Homeostasis and Disease
AUGUST 4-5, 2018
CHAIRS: Brian O. Diekman & Brianne K. Connizzo

Mutagenesis

Mechanisms of Intrinsic and Induced Genome Instability

JUNE 24-29, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME
CHAIR: Karlene Cimprich
VICE CHAIR: Julian E. Sale

- **Keynote Session: The Mechanistic Origins of Mutagenesis** *Karlene Cimprich,* Wei Yang, Johannes Walter
- **RNA-Dependent Mutagenesis** *Simon Boulton,* Andrés Aguilera, Philippe Pasero, Houra Merrikh
- **Mutagenesis Due to Environmental and Endogenous Sources of DNA Damage** *Serena Nik-Zainal,* Ketan Patel, Reuben Harris, Titia Sixma

- **Damage Avoidance: Lesion Bypass and Template Switching** *Johannes Walter,* Dana Branzei, Thomas Kunkel, Helle Ulrich, Aidan Doherty
- **Mutagenesis in Low Complexity and Repetitive Sequences** *Madalena Tarsounas,* Eric Brown, Agnel Sfeir, Sergei Mirkin
- **Genome Instability and Mutagenesis in Disease** *Ketan Patel,* Simon Boulton, Madalena Tarsounas, Peter McKinnon
- **Replication Stress and the Consequences of Failure to Complete Replication** *Eric Brown,* Batsheva Kerem, David Pellman, Massimo Lopes
- **Understanding the Origins of Mutagenesis in Cancer** *Reuben Harris,* Steve Jackson, Serena Nik-Zainal, Anna Malkova, Georgios Karras
- **Emerging Themes in Mutagenesis: From Concept to Clinic** *Julian Sale,* Daniel Jarosz, Roger Greenberg, Josep Forment
- **Power Hour** *Madalena Tarsounas, Wei Yang*

Mutagenesis
The Mechanisms of Mutagenesis and the Changing Genetic Landscape
JUNE 23-24, 2018
CHAIR: Gregory M. Williams

Nanoscale Science and Engineering for Agriculture and Food Systems

Nano-Enabled Technologies to Improve Efficiency, Quality and Health in Food and Agriculture

JUNE 3-8, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA
CHAIRS: Cristina Sabliov & David W. Britt
VICE CHAIRS: Antje Baeumner & Julie M. Goddard

- **Keynote Session: The Nano-Nexus in Food, Agriculture, Energy and Water** *Cristina Sabliov, David Britt,* Greg Lowry, Jason White
- **Nano-Enabled Approaches for Food and Nutrition from a Biomedical Perspective** *Pingfan Rao,* Esther Chang, Ke Lijing, Yoav Livney
- **Sustainable Deployment of Nano-Enabled Agrochemicals: Nano-Impact in Environmental and Agricultural Fate and Transport** *Jorge Gardea-Torresdey,* Enzo Lombi, Juan Giraldo, Arturo Keller
- **Nano-Enabled Sensing for Food and Agriculture** *Antje Baeumner,* Jan Schnorr, Junhong Min, Ciara O'Sullivan
- **Nano-Microbiome: Nano Effects on the Second Genomes of Plants, Animals and Humans** *Hang Xiao,* Sangeeta Khare, Patricia Holden, Theodore Henry
- **Nano Implications in Human Health** *Philip Demokritou,* Joachim Loo, Gretchen Mahler, Shirley Ho
- **Young Investigator Presentations** *Julie Goddard,* Nuria Acevedo, Laurene Tetard, Leanne Gilbertson
- **Regulation and Policy: Influence on Entrepreneurship and Industry in Nano-Food and Agriculture** *Ricky Yada,* John Dutcher, Swadeshmukul Santra, Lekh Juneja
- **Bio-Inspired, Targeted and Intelligent Nano-Carriers** *Maria DeRosa,* Eijiro Miyako, Neena Mitter, Sam Nugen
- **Power Hour** *Melanie Kah, Maria DeRosa*

Nanoscale Science and Engineering for Agriculture and Food Systems
Nano-Enabled Technologies to Improve Efficiency, Quality and Health in Food and Agriculture
JUNE 2-3, 2018
CHAIRS: Verena Muhr & Sean Swetledge

Nasopharyngeal Carcinoma

New Perspectives on the Virus-Host Interplay in Nasopharyngeal Carcinoma and Their Impact on Diagnosis and Therapeutic Interventions

JUNE 24-29, 2018 • THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY, HONG KONG, CHINA
CHAIRS: George S. Tsao & Fei-Fei Liu
VICE CHAIRS: Kwok Wai Lo & Quynh-Thu Le

- **Keynote Session: Viruses, Cancer and Stem Cell** *Alan Rickinson,* Patrick Moore, Irving Weissman
- **EBV Infection and NPC Pathogenesis** *Alan Chiang,* Paul Farrell, Bill Sugden, Rebecca Skalsky, Bo Zhao
- **Regulation of Lytic and Latent EBV Infection** *Mei-Ru Chen,* Shannon Kenney, Lori Frappier, Mu Sheng Zeng
- **Risk Factors and Novel Markers for NPC** *Jin-Xin Bei,* Wei-Hua Jia, Jin-Ching Lin, Dennis Lo, Maria Lung, Shana Kelley
- **Molecular Profiling of NPC** *Andrew Futreal,* Daniel De Carvalho, Wei Dai, Kwok Wai Lo
- **Tumor Microenvironment of NPC** *Eric Stanbridge,* Maria Massucci, Pierre Busson, Paul Robson
- **Challenges and Novel Approaches in NPC Treatment** *Brian O'Sullivan,* Danny Rischin, Jun Ma, Anne Lee, Troy Messick
- **Immunotherapy of NPC** *Dora Kwong,* Lillian Siu, Rajiv Khanna, Graham Taylor, Han Chong Toh, Brigette Ma
- **Keynote Session: Future Perspectives in NPC Research and Treatment** *Quynh-Thu Le,* Tak Mak, Lawrence Young
- **Power Hour** *Quynh-Thu Le, Maria Lung*

Natural Products and Bioactive Compounds

Research at the Leading Edge of Synthesis, Drug Discovery and Biosynthesis

JULY 29 – AUGUST 3, 2018 • PROCTOR ACADEMY, ANDOVER, NH
CHAIR: Christopher N. Boddy
VICE CHAIR: Matthew J. LaMarche

- **Frontiers in Catalysis** *Sophie Rousseaux,* Bill Morandi, Corey Stephenson
- **Aggressive Bond Disconnections in Total Synthesis** *Louis Barriault,* Michael Sherburn, David Sarlah, Sergey Pronin
- **Chemical Probes for Characterizing Biology** *Danielle Dube,* John Pezacki, Daniel Harki
- **Synthetic Biology for Natural Products** *Fern McSorley,* Christopher Voigt, Emily Parker
- **Advances in Drug Discovery** *Eric Brown,* Kip Guy
- **Natural Product Discovery and Biosynthesis** *David Stevens,* Sandra Loesgen, Carole Bewley
- **Combining Synthesis and Biosynthesis to Construct Complex Molecules** *Bradley Moore,* Tobias Gulder, Rebecca Goss, David Sherman
- **New Directions in Antibiotic Discovery and Development** *Clarissa Sit,* Eric Brown, Sylvie Garneau-Tsodikova, Suzanne Walker, Nadine Ziemert
- **The State-of-the-Art in Accessing Complex Molecules** *Michael Sherburn,* Bradley Moore

Natural Products and Bioactive Compounds
Frontiers in Natural Products: Synthesis, Biosynthesis and Drug Discovery
JULY 28-29, 2018
CHAIR: Graham Heberlig

Neural Development

Generating Diverse Cells and Networks in the Nervous System

JULY 29 – AUGUST 3, 2018 • SALVE REGINA UNIVERSITY, NEWPORT, RI
CHAIR: Rosalind A. Segal
VICE CHAIR: Claude R. Desplan

- **Keynote Session: From Stem Cells to Networks** *Rosalind Segal,* Andrea Brand, Christopher Walsh
- **Epigenetic Regulation of Neural Development** *Claude Desplan,* Azad Bonni, Michael Dyer, Kristen Kroll, Jessica Tollkuhn
- **Glial Cell Differentiation and Biology** *Thomas Schwarz,* Jonah Chan, Benjamin Deneen, Marc Freeman, Christian Klambt
- **Formation of Synapses and Circuits** *Roy Sillitoe,* Carina Hanashima, Kang Shen, Irene Aliaga, Matthew Pecot
- **Regulating Translation in Neural Development: Spatial Challenges of Axons and Dendrites** *Azad Bonni,* Vivian Budnick, Yan Song, Avraham Yaron, Florence Besse
- **Stem Cells and Neural Precursors that Form Neurons and Glia** *Corinne Houart,* Paola Arlotta, Ronald Parchem, Debby Silver
- **Cell Fate and Differentiation** *Chris Doe,* Chenghua Gu, Maria Lehtinen, Roy Sillitoe
- **Axons and Dendrites: Pathfinding and Establishing Connections** *Matthew Pecot,* Lisa Goodrich, Corinne Houart, Thomas Schwarz, Yimin Zou
- **Computing Development** *Marc Freeman,* Thomas Clandinin, Eva Marie Collins, John Huguenard
- **Power Hour** *Lisa Goodrich*

Neural Development
Generating Diverse Cell Types and Networks in the Nervous System
JULY 28-29, 2018
CHAIRS: Simone Mayer & Andrea Yung

Neurobiology of Brain Disorders

The Role of Innate Immunity, Glia, Neurons and the Blood-Brain Barrier in the Pathogenesis of Neurodegeneration

AUGUST 5-10, 2018 • REY DON JAIME GRAND HOTEL, CASTELLDEFELS, SPAIN

CHAIRS: David M. Holtzman & Cheryl Wellington
VICE CHAIRS: Leonard Petrucelli & Alison Goate

- **Keynote Session: Chance, Risk and Breakthroughs in Neurobiological Disease** *David Holtzman, Cheryl Wellington,* Bart De Strooper, Huda Zoghbi
- **The Brain's Innate Immune System in Health and Disease** *Robyn Klein,* Oleg Butovsky, Marco Colonna, Sarkis Mazmanian
- **Apolipoprotein E and Other Metabolic Factors: Role in Brain Function and Disease** *Joachim Herz,* Guojun Bu, Shannon Macauley, Jerome Robert
- **Frontotemporal Dementia and Amyotrophic Lateral Sclerosis: Pathogenesis and Implications for Treatment** *Leonard Petrucelli,* Chris Shaw, Judith Steen, J. Paul Taylor
- **Traumatic Brain Injury and Neurodegeneration** *Danielle Sandsmark,* Ramon Diaz-Arrastia, Victoria Johnson, Barry Jordan
- **Blood-Brain Barrier, Brain Fluid Flow and Neurodegeneration** *Robert Bell,* Christer Betsholtz, Jonathan Kipnis, Maiken Negergaard
- **Novel Experimental Models to Study Normal Brain Function and Disease** *Celeste Karch,* Karen Duff, Molly Shoichet, Andrew Yoo
- **Biomarkers: Use in Diagnostics and Therapeutics for Neurodegeneration** *Erik Portelius,* Randal Bateman, Kaj Blennow, Tania Gendron
- **The Role of Different Brain Cell Types in Protein Aggregation, Homeostasis and Metabolism** *Alison Goate,* Ana Maria Cuervo, Mathias Jucker, David Rubinsztein

Neurobiology of Brain Disorders
Molecular and Cellular Mechanisms of Neurodegenerative Diseases
AUGUST 4-5, 2018
CHAIRS: Heather Rice & Peter J. Chung

Neurobiology of Cognition

Neural Circuits Supporting Cognitive Function

JULY 22-27, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIRS: David Leopold & Jennifer M. Groh
VICE CHAIRS: David J. Freedman & Ila Fiete

- **Communicating Brains** *Charles Schroeder,* Stanislas Dehaene, Doris Tsao
- **Networks and Areal Interactions in Neural Circuits** *Earl Miller,* Matteo Carandini, Charles Gray, Alex Huth, Sabine Kastner, Mala Murthy
- **Evolution of Cognitive Circuits** *Jon Kaas,* Suzana Herculano, Hans Hofmann, Leah Krubitzer, Mary Raghanti
- **Frontotemporal Circuits for Learning and Memory** *Rony Paz,* Alison Adcock, Daniel Foster, Tatiana Pasternak, Rodrigo Quian Quiroga, Misha Tsodyks, Kay Tye
- **Natural Behavior and Embodied Cognition** *Michael Graziano,* Marina Bedny, Jody Culham, Krish Sathian, Anil Seth
- **Machine Learning in Neuroscience** *Adrienne Fairhall,* James Dicarlo, Alyson Fletcher, Bruno Olshausen, Nicole Rust, Joshua Tenenbaum, Xiao-Jing Wang
- **Sensorimotor Control of Action** *Bijan Pasaran,* Aaron Batista, Kathleen Cullen, John Krakauer, Marc Sommer
- **Neural Mechanisms of Decision Making** *Joni Wallis,* Bruno Averbeck, Timothy Behrens, Anne Churchland, Rui Costa, Yael Niv, Erin Rich
- **Sound and Language** *Stanislas Dehaene,* Edward Chang, Ingrid Johnsrude, David Poeppel, Sarah Woolley

Neurobiology of Cognition
Neural Circuits and Systems for Perception and Action
JULY 21-22, 2018
CHAIRS: Rodrigo M. Braga & Valeria C. Caruso

NEW! Neuroplasticity of Sensory Systems

Neuroplasticity and Maladaptation of Sensory Systems

JUNE 3-8, 2018 • REGAL RIVERSIDE HOTEL, HONG KONG, CHINA

CHAIRS: Jufang He & Josef P. Rauschecker
VICE CHAIRS: Anna Wang Roe & Jan Schnupp

- **Homeostatic Neuroplasticity** *Jun Xia,* Shaowen Bao, Mark Hübener
- **Neuroplasticity in the Thalamocortical System** *Michael Stryker,* Ming-fai Fong, Patrick Kanold
- **Tinnitus and Auditory Maladaptive Neuroplasticity** *Richard Salvi,* Arnaud Noreña, Richard Tyler, Berthold Langguth
- **Cross-Modal Plasticity** *Xiang Yu,* Mark Wallace, Robert Zatorre
- **Cortical Synaptic Plasticity** *Anthony Holtmaat,* Guoqiang Bi, Alfredo Kirkwood, Colin Blakemore, Frank Sengpiel
- **Malplasticity in the Cerebral Cortex** *Wing Ho Yung,* Xiao-Ming Li, Liping Wang
- **Sensory Perception** *Ying-Shing Chan,* Xiao-hui Zhang
- **Attention and Neuroplasticity in the Neocortex** *Christoph Schreiner,* Minmin Luo, Tania Pasternak
- **Neuroprostheses and Neuroplasticity** *Gregg Recanzone,* Ruth Litovsky

Noble Metal Nanoparticles

From Fundamentals to Applications of Collective Excitations in Nanostructured Materials

JUNE 17-22, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA

CHAIR: Stephan Link
VICE CHAIR: Sara E. Skrabalak

- **Plasmons Supported by Non-Noble Metals** *Stephan Link,* Peter Nordlander, Teri Odom
- **Hybrid Nanostructures** *Jingyi Chen,* Svetlana Neretina, Dong Qin, Miguel Yacaman, Yugang Sun
- **The Impact of Shape on Noble Metal Nanoparticles** *Amanda Haes,* Catherine Murphy, Cecilia Noguez, Mostafa El-Sayed
- **Hot Electron Chemistry** *Matthew Sheldon,* Renee Frontiera, Sebastian Schlucker, Bin Ren, Richard Van Duyne
- **Nanoparticle Superstructures** *Hui Wang,* Tim Liedl, Qian Chen, George Schatz
- **Nanomedicine: Detection and Treatment** *Denis Boudreau,* Rizia Bardhan, Laura Sagle, Francesco Stellacci, Michael Natan
- **Mechanics of Noble Metal Nanoparticles** *Gregory Hartland,* Fabrice Vallee, John Sader, Michel Orrit
- **Strong Coupling to Particles, Molecules, Photons and Electrons** *Kallie Willets,* Gilad Haran, Jon Camden, Jeremy Baumberg, Hiroaki Misawa
- **Selected Poster Presentations** *Sara Skrabalak,* Naomi Halas
- **Power Hour** *Sara Skrabalak*

Noble Metal Nanoparticles
From Fundamentals to Applications of Collective Excitations in Nanostructured Materials
JUNE 16-17, 2018
CHAIRS: James L. Brooks & Dayne F. Swearer

Notch Signaling in Development, Regeneration and Disease

Integrating Dynamics, Mechanisms and Consequences to Understand Notch Signaling Specificity and Disease Implications

JULY 22-27, 2018 • BATES COLLEGE, LEWISTON, ME

CHAIRS: Sarah J. Bray & Christian Siebel
VICE CHAIRS: Ivan Maillard & Freddy Radtke

- **Keynote Session: Setting Notch in Context** *Christian Siebel,* Leonard Zon, Mariann Bienz
- **Transcriptional Dynamics and Regulation** *Sarah Bray,* Ellen Rothenberg, Raphael Kopan, Rhett Kovall, Juan Carlos Zuniga-Pflucker
- **Signaling Interactions and Modulations** *Pamela Stanley,* Stephen Blacklow, Susan Lea, Susan Cole, Robert Haltiwanger
- **Notch and Disease Mechanisms** *Adolfo Ferrando,* Joseph Arboleda-Velasquez, Yibin Kang, Stacey Rentschler, Urban Lendahl, Qi Yang
- **Tissue Dynamics and Cellular Organization** *David Sprinzak,* Andrew Oates, Nancy Papalopulu, Francois Schweisguth, Christopher Chen
- **Stem Cell and Niche Interactions** *Anna Bigas,* Verdon Taylor, Shahragim Tajbakhsh, Maria Dominguez Castellano, Benjamin Ohistein, Linda Samuelson
- **Late-Breaking Topics** *Ivan Maillard*
- **Notch, Cancer and Therapeutics** *Lucio Miele,* Warren Pear, Jon Aster, Julien Sage, Rajwinder Lehal
- **Environmental Influences and Signaling Cross-Talk** *Freddy Radtke,* Kim Dale, Andreas Fischer
- **Power Hour** *Kim Dale*

Notch Signaling in Development, Regeneration and Disease
Integrating Dynamics, Mechanisms and Consequences to Understand Notch Signaling Specificity and Disease Implications
JULY 21-22, 2018
CHAIRS: Daniel Lafkas & Rachel K. LoPilato

NOX Family NADPH Oxidases

NOX as Center of Redox Communication in Health and Disease

MAY 27 – JUNE 1, 2018 • LES DIABLERETS CONFERENCE CENTER, LES DIABLERETS, SWITZERLAND

CHAIR: Ulla Knaus
VICE CHAIR: Albert Van Der Vliet

- **Intracellular Communication via ROS: Insights into Mitochondria** *Robert Clark,* Alicia Kowaltowski, Fabio Di Lisa, Valentin Cracan
- **NOX Back to Basics: Bridging Knowledge for the Future** *William Nauseef,* Susan Smith, Hideki Sumimoto, Edgar Pick, Vincent Jaquet, Becky Diebold, Katrin Schroder
- **From Structural Mechanisms to NOX Drug Development** *Susan Smith,* Andrea Mattevi, Marie Erard, Franck Fieschi, Philippe Wiesel
- **ROS Signaling and Networking** *Miklos Geiszt,* Harald Schmidt, Melissa Kemp, Nancy Hynes
- **Hallmarks of NOX Function: Immunity and Inflammation** *Nancy Hynes,* Yun Soo Bae, Rikard Holmdahl
- **ROS as Key Player in Interkingdom Crosstalk at Barriers** *Marie Jose Stasia,* Gerard Clarke, Helmut Grasberger, Kim Orth
- **Redox Signals in Cancer: From NOS to NOX** *David Lambeth,* Douglas Thomas, Jean-Luc Perfettini, James Doroshow, Thomas Leto
- **NOXes in Disease Pathophysiology** *Isabel Fabregat,* David Brenner, Louise Hecker, Karl-Heinz Krause, Simone Di Giovanni
- **NOX-Mediated ROS Signaling in Metabolism and Cardiovascular Disease** *Rhian Touyz,* Jun Sadoshima, Ajay Shah, Lev Becker

NOX Family NADPH Oxidases
Biological Roles of NADPH Oxidases: Insights into Fundamental Mechanisms and Therapeutic Potential
MAY 26-27, 2018
CHAIRS: David E. Heppner & Aikaterini Anagnostopoulou

Ocean Biogeochemistry

Biogeochemistry of Marine Interfaces

JULY 8-13, 2018 • THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY, HONG KONG, CHINA

CHAIRS: Louis Legendre & Sylvia Sander
VICE CHAIRS: Chuanlun Zhang & Susanne Neuer

- **Socioeconomic Aspects of Ocean Biogeochemistry** *DanLing Tang,* Andrea Koschinsky, Jean-Luc de Kok
- **Atmosphere to Ocean** *Linn Hoffmann,* Markus Weinbauer, Maria Kanakidou, Miri Trainic
- **Ocean to Atmosphere** *Hongbin Liu,* Wei-Jun Cai, Lucy Carpenter
- **Surface and Mesopelagic Ocean** *Fei Chai,* Nianzhi Jiao, Raphaëlle Sauzède, Svenja Christiansen
- **Oxygen Minimum Zones** *Douglas Wallace,* Zouhair Lachkar, Osvaldo Ulloa
- **Deep Ocean** *Deborah Steinberg,* Gerald Haug, Bruce Robison, Jingping Xu
- **Young Investigator Presentations** *Jihua Liu, Bethanie Edwards*
- **Bottom Water and Sediment** *Adina Paytan,* Morgan Raven, Pinghe Cai, Alexandra Turchyn
- **Hydrothermal and Deep Seafloor Systems** *Satoshi Mitarai,* Brandy Toner, Antje Boetius
- **Power Hour** *M. Robin Anderson, Qian Li*

Ocean Biogeochemistry
Biogeochemistry of Marine Interfaces
JULY 7-8, 2018
CHAIRS: Jihua Liu & Bethanie R. Edwards

Ocean Global Change Biology

Integrative Research Addressing Responses, Refuges and Rescue in Marine Ecosystems

JULY 15-20, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIR: Gretchen E. Hofmann
VICE CHAIR: Sinead Collins

- **Keynote Session: A Horizon Scan for Ocean Global Change Biology** *Martina Doblin,* Philip Munday, Debora Iglesias-Rodriguez, Kristy Kroeker
- **New Perspectives on the Response to Multiple Interacting Stressors in the Marine Environment** *Mary Sewell,* Hannes Baumann, Katherine Mackey, Karen Chan
- **Adaption, Evolution and Phenotypic Plasticity** *Thorsten Reusch,* Luis-Miguel Chevin, Morgan Kelly, Elisa Schaum
- **Emerging Insight from the Study of Ecological Processes** *Francis Chan,* Jarrett Byrnes, Joshua Lord, Jennifer Sunday
- **A Diverse Look at the Response to Multiple Stressors at the Population-Level** *Daniela Schmidt,* Naomi Levine, Malin Pinsky, Samantha Gibbs
- **Climate Refuges and Rescue Strategies** *Piero Calosi,* Ruth Gates, Catriona Hurd, Dustin Marshall
- **Epigenetics: Providing New Insights in Ocean Global Change Biology** *Sinead Collins,* Jose Eirin-Lopez, Mikhail Matz, Lisa Shama
- **Modeling and Experimental Design** *Jonathan Havenhand,* Rebecca Asch, Curtis Deutsch, Cristian Vargas
- **New Developments in "Many-Traits" Research** *Andrew Barton,* Jorn Bruggeman, Zoe Finkel, Mridul Thomas

GRS: Ocean Global Change Biology
Spatial and Temporal Scales of Biological Response in Ocean Global Change Biology
JULY 14-15, 2018
CHAIRS: Grace E. Kim & Umihiko Hoshijima

NEW! Ocean Mixing

Towards a Global Representation of the Impact of Ocean Mixing Processes on Large Scale Circulation

JUNE 3-8, 2018 • PROCTOR ACADEMY, ANDOVER, NH

CHAIRS: Matthew Alford & Jennifer A. Mackinnon
VICE CHAIRS: Jonathan Nash & Kurt Polzin

- **Impacts of Ocean Mixing** *Matthew Alford, Jennifer Mackinnon,* Robert Hallberg, Lynne Talley
- **The Geography of Mixing, Implications to Large-Scale Circulation Patterns and the Energetics of Regional Through Climate-Scale Dynamics** *Amy Waterhouse,* Ali Mashayek, Caitlin Whalen, Sabine Mecking
- **Mixing at High Latitude: Cool Observations** *Mary-Louise Timmermans,* Ilker Fer, Yueng Lenn
- **Internal Waves: Generation, Propagation and Dissipation, Wave-Wave Interactions and the Cascade to Turbulence** *Eric Kunze,* Mattias Green, Harper Simmons, Stephanie Waterman
- **Mixing at the Bottom: Entrainment and Wave Radiation in Density Currents, Overflows and Other Frictional Boundary-Layer Flows in the Deep and Abyssal Ocean** *Brian Arbic,* Jody Klymak, Lars Umlauf
- **Mixing and the Top and Lateral Processes: Controls on the Rates of Isopycnal Stirring and Mixing at Sub-Mesoscales** *Randolph Watts,* Eric D'Asaro, Helen Phillips, John Taylor, Leif Thomas
- **Frontiers of Technique: Validity of Assumptions in Finescale Parameterizations, Mixing Efficiency and Other Inferred Estimates** *Jonathan Nash,* Michael Gregg, Lou St. Laurent
- **Frontiers of Technique: Innovations in Observational Methods for Measuring, Modeling and Parameterizing Mixing** *Kurt Polzin,* Ann Gargett, James Ledwell, James Moum
- **Frontiers and Next Directions in Ocean Mixing Research** *Sonya Legg,* Raffaele Ferrari, Alberto Naveira Garabato
- **Power Hour** *Stephanie Waterman, Ann Gargett*

Optogenetic Approaches to Understanding Neural Circuits and Behavior

Optogenetics and Imaging: Technology Development, Novel Applications and Closing the Loop Between Models and Experiments

JULY 15-20, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Kay M. Tye
VICE CHAIR: Bernardo Sabatini

- **Keynote Session: Development and Application of Optogenetic Tools** *Christian Luscher,* Karl Deisseroth, Alice Ting
- **Sensorimotor Integration, Decision-Making and Memory** *David Anderson,* Massimo Scanziani, Attila Losonczy, Sonja Hofer, Fan Wang
- **Imaging Approaches and Analyses** *Mark Schnitzer,* Peyman Golshani, Na Ji, Laura Waller, Xiaowei Zhuang
- **Psychiatric Disease** *Ofer Yizhar,* Gul Dolen, Stephan Lammel, Byungkook Lim, Mazen Kheirbek
- **Novel Neurotechnology** *Edward Boyden,* Valentina Emiliani, Ehud Isacoff, Markita Landry, Eric Schreiter
- **Neurological Disorders and Motor Function** *Veronica Alvarez,* Ivan Soltesz, Li-Huei Tsai, Joshua Dudman, Takaki Komiyama
- **Homeostatic Systems and Circuits** *Garret Stuber,* Mark Andermann, Yeka Aponte, Zachary Knight, Dragana Rogulja
- **Addiction, Reward and Aversion** *Antonello Bonci,* Patricia Janak, Mario Penzo, Vanessa Ruta, Nadine Gogolla
- **Late-Breaking Topics** *Sheena Josselyn, I-han Chou,* Michael Halassa

GRS: Optogenetic Approaches to Understanding Neural Circuits and Behavior
From Synapses to Behavior: Using the Optogenetic Toolbox to Study Neural Circuits
JULY 14-15, 2018
CHAIRS: Laura M. McGarry & Sage R. Aronson

Organic Geochemistry

Scientific Insights and Economic Value from State-of-the-Art Organic Geochemistry

JULY 29 – AUGUST 3, 2018 • HOLDERNESS SCHOOL, HOLDERNESS, NH

CHAIR: Lloyd R. Snowdon
VICE CHAIR: Richard D. Pancost

- **(Geo)Chemistry on the Edges of Space, Time and Consciousness** *Steve Larter,* Paul Mahaffy, Matthew Collins, David Gold
- **Stable C, H, S, O Isotope Geochemistry** *Robert Dias,* Alon Amrani, Max Lloyd, Elise Wilkes, Renzo Silva
- **Biogeochemistry/Aquatic Geochemistry Along the Aquatic Continuum** *Elizabeth Canuel,* Kristen Boye, Andrew Steen, Jan-Hendrik Hehemann
- **Oxygen in the Ocean and Carbon in the Mud: OM Input and Preservation** *Richard Pancost,* Sarah Myhre, Fanny Monteiro, Morgan Raven, Thorsten Bauersachs
- **Exploration and Development of Unconventional Resources** *Jennifer Adams,* Martin Elsner, Mathew Fay, Eric Michael
- **Lipid Biosynthesis and Novel Methods** *Laura Villanueva,* Benjamin Van Mooy, Diana Sahonero, Paula Welander, Alexander Bradley
- **Catastrophic to Chronic Introduction of OM into the Environment** *Mark Yunker,* Steve Mattingly, Christoph Aeppli, Peter Ross
- **HMW and Polar Fraction Geochemistry** *Sabine Lengger,* Zhirong Zhang, Artur Stankiewicz, Florence Schubotz
- **Late-Breaking Topics** *Loes van Bree*

GRS: Organic Geochemistry
The Future of Organic Geochemistry: Advances in Organic Proxies and Analytical Techniques
JULY 28-29, 2018
CHAIR: Loes van Bree

Organic Reactions and Processes

Progress in Organic Synthesis and Understanding Reaction Mechanisms

JULY 15-20, 2018 • STONEHILL COLLEGE, EASTON, MA

CHAIRS: Jeremy A. May & Jennifer Albaneze-Walker
VICE CHAIRS: Mitchell P. Croatt & Yi Hsiao

- **Discoveries in Organic Synthesis** *Chulbom Lee,* Scott Rychnovsky, Alison Frontier, Brian Stoltz
- **Methods in Organofluorine Chemistry** *Jeremy May,* Qilong Shen
- **Modern Heterocycle Chemistry** *Jennifer Roizen,* Vladimir Gevorgyan
- **Theory in Catalytic Mechanisms** *Franziska Schoenebeck,* Kaori Ando, Mimi Hii, Steven Wheeler
- **Functionalization of Aromatic Systems** *Pamela Tadross,* David Sarlah, Robert Maleczka, Milton Smith
- **Advances in Process Chemistry** *Yi Hsiao,* Haiming Zhang
- **Novel Catalytic Methods** *Andrew Harned,* Michelle Chang, Corinna Schindler, Scott Schaus
- **Organometallic Catalytic Mechanisms** *Jean Suffert,* Laurence Grimaud, Valentine Ananikov
- **Organometallic Catalytic Methods** *Mitchell Croatt,* Jan Backvall, Robert H. Grubbs

Organometallic Chemistry

Conceptual Advances, Innovative Discoveries and Interdisciplinary New Directions in Organometallic Chemistry

JULY 8-13, 2018 • SALVE REGINA UNIVERSITY, NEWPORT, RI

CHAIR: Christine Thomas
VICE CHAIR: Alfred A. Barney

- **Young Investigator Presentations** *Milton Smith,* Ian Tonks, Alexander Radosevich
- **Organometallic Chemistry of Earth-Abundant Metals** *Theodore Betley,* Neal Mankad, Liang Deng, Alison Fout, Xile Hu
- **Main Group Chemistry** *T. Don Tilley,* Nathaniel Szymczak, Rebecca Melen, Makoto Yamashita
- **Transition Metal-Mediated Bond Activation and Formation Processes** *Clifford Kubiak,* Mu-Hyun Baik, Nathan West, Joseph Sadighi, Elizabeth Papish
- **Organometallic Approaches to the Synthesis of Polymers and Solid State Materials** *Alex Carpenter,* Adam Hock, Jeff Greco
- **Organometallic Chemistry of the Early Transition Metals, Lanthanides and Actinides** *Paula Diaconescu,* Andrew Gaunt, Adam Veige, Richard Layfield
- **Ligand Design** *Aaron Appel,* Chip Nataro, Brandi Cossairt, Mark Gandelman
- **Applications of Organometallics to Organic Synthesis** *Bernadette Donovan-Merkert,* Jennifer Love, Patrick Hanley, Alison Campbell
- **Keynote Session: New Strategies in Catalysis** *Alfred Barney,* Maurice Brookhart, Kenneth Caulton
- **Power Hour** *Jennifer Love, Bernadette Donovan-Merkert*

GRS: Organometallic Chemistry
New Advances in Organometallic Synthesis, Structure and Reactivity
JULY 7-8, 2018
CHAIRS: Benjamin R. Reiner & Mark D. Levin

Oscillations and Dynamic Instabilities in Chemical Systems

Decrypting and Controlling Self-Organized Structures Through Theories and Experiments

JULY 8-13, 2018 • LES DIABLERETS CONFERENCE CENTER, LES DIABLERETS, SWITZERLAND

CHAIR: Istvan Z. Kiss
VICE CHAIR: Satoshi Nakata

- **Oscillations and Patterns in Electrochemistry** *Vilmos Gaspar,* Katharina Krischer, Hamilton Varela
- **Network Structure and Dynamics** *Marcus Hauser,* Jordi Garcia-Ojalvo, Yannick Rondelez
- **Control and Design of Self-Organized Structures** *Satoshi Nakata,* Harald Engel, Peter Tass
- **Biological Oscillators** *Alexander Aulehla,* Hiroshi Kori, Lev Tsimring, Stanislav Shvartsman
- **Tuning Interactions Using Encapsulated Media** *Irving Epstein,* Kenneth Showalter, Seth Fraden
- **Theory: Connecting Microscopic Mechanisms to Macroscopic Observations** *Agota Toth,* Yannick de Decker, Gregory Yablonsky, Istvan Lengyel
- **Patterns with Mass Transfer** *Oliver Steinbock,* Dezso Horvath, Hideki Nabika
- **Active Matter** *Raymond Kapral,* Karsten Kruse, Daniela Wilson
- **Collective Behavior** *Carsten Beta,* Hiroyuki Kitahata, Shashi Thutupalli

Oscillations and Dynamic Instabilities in Chemical Systems
Emergent Phenomena in Chemical Systems Across Multiple Scales
JULY 7-8, 2018
CHAIRS: Jan Frederik Totz & Delora Gaskins

Personalized Medicine

Exploring the New Era of Individualized Treatment Through Science, Technology and Integrated Medicine

JULY 29 – AUGUST 3, 2018 • THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY, HONG KONG, CHINA

CHAIRS: Yen Yun & Edward J. Benz

VICE CHAIRS: Steven T. Rosen & Hsing-Jien Kung

- **Phenotyping and Genotyping** *Chih-Ming Ho,* Xianting Ding, Dean Ho, Ali Zarrinpar, Stephen Quake, Edward Kai-Hua Chow
- **Integrated Genomics and Therapy** *Mien-Chie Hung,* Hongyang Wang, Wei Zhang, Joshua Schiffman, Chuan He
- **Stem Cell and Cell Therapy in Human Diseases** *Rita Yen-Hua Huang,* Kenneth Kun-Yu Wu, Max Wicha, Ye-Guang Chen, Bradley Cairns
- **Tumor Metabolism and Therapy** *Wei Jia,* Van-Dang Chi, Lenny Dang, Neal Rosen, Craig Thompson
- **Personalized Therapy in Cancer** *Tony S.K. Mok,* Patrycja Nowak-Sliwinska, Hong Wu, Jonathan J. Keats
- **Precision Medicine and Novel Technology** *Priscilla N. Kelly,* Pui-Yan Kwok, Sridhar Mani, Christiane Querfeld, Irene O.L. Ng
- **Pharmacogenomics** *Richard Weinshilboum,* Edward Chu, Steven Offer, Liewei Wang
- **Personalized Immunotherapy** *Chien-Tsun Kuan,* Arjan Griffioen, John Williams
- **Late-Breaking Topics** *Yiwu He*

Phosphorylation and G-Protein Mediated Signaling Networks

Regulation and Inter-Connectivity of Kinases, Phosphatases and G-Protein Mediated Signaling Pathways in Health and Disease

JUNE 3-8, 2018 • UNIVERSITY OF NEW ENGLAND, BIDDEFORD, ME

CHAIR: Anton Bennett

VICE CHAIR: Rebecca Berdeaux

- **Metabolism: Yin and Yang of Metabolic Signaling Networks** *Carol Williams,* Stefan Offermanns, Matthew Spite, Rebecca Berdeaux
- **Lipids Linking Signaling** *Kun-Liang Guan,* Jonathan Backer, Lloyd Trotman
- **Cardiovascular and Vascular Signaling Networks** *Gregory Tall,* Alan Smrcka, Carol Williams
- **Visualization and Models Systems in Signaling** *Carmen Dessauer,* Henrik Dohlman, Jin Zhang, Roger Sunahara
- **Cyclic Nucleotide and G-Protein Coupled Receptor Signaling** *Henrik Dohlman,* Gregory Tall, Mark von Zastrow, Venetia Zachariou
- **Nexus of Phosphorylation and G-Protein Signaling** *Natalie Ahn,* Aashish Manglik, Nicholas Tonks
- **Cancer Biology: Protein Phosphorylation-G-Protein Signaling Connections** *Jin Zhang,* Natalie Ahn, Kun-Liang Guan, Silvio Gutkind
- **Wiring the Neuron by Phosphorylation and G-Proteins** *Venetia Zachariou,* Carmen Dessauer, Linda Van Aelst
- **Keynote Session: The Hub of Signal Integration: Mitogen Activated Protein Kinases** *Anton Bennett,* Melanie Cobb

GRS: Phosphorylation and G-Protein Mediated Signaling Networks

Discoveries in G Protein Signaling Biochemistry and Therapeutic Potential

JUNE 2-3, 2018

CHAIR: Taylor J. Moon

Photonuclear Reactions

From Quarks to Nuclei in Photonuclear Reactions

AUGUST 5-10, 2018 • HOLDERNESS SCHOOL, HOLDERNESS, NH

CHAIRS: Julie Roche & Nicole D'Hose

VICE CHAIR: Huey-Wen Lin

- **Late-Breaking Topics** *Jen-Chieh Peng*
- **Nucleons in Nuclei** *Ian Cloet,* Raphael Dupre, Will Detmold, Cynthia Keppel
- **QCD for Neutrino Physics** *Kendall Mahn,* Saori Pastore, Omar Benhar
- **Movement of Partons in the Proton** *Elke Aschenauer,* Emanuele Nocera, Andrea Bressan, Jaroslav Adam
- **Innovative Tools for the Study of Hadrons** *Jian-Ping Chen,* Dipangkar Dutta, Jin Huang
- **Hadron Spectrum and QCD** *Reinhard Beck,* David Ireland, Andrey Sarantsev
- **Imaging the Proton in 3D** *Cédric Lorcé,* Barbara Pasquini, Silvia Niccolai, Michael Engelhardt
- **Long Range Structure of Hadrons** *Evangeline Downie,* Phil Martel, Guy Ron, Ralf Gothe
- **Origin of the Proton Mass** *Zein-Eddine Meziani,* Jianwei Qiu, Martha Constantinou
- **Power Hour** *Evangeline Downie*

Physics Research and Education

Novel Research in Energy Topics and Transformative Methods for Teaching Undergraduate Students About Energy Concepts

JUNE 10-15, 2018 • BRYANT UNIVERSITY, SMITHFIELD, RI

CHAIRS: Nancy Ruzycki & Dawn C. Meredith

VICE CHAIRS: Shane L. Larson & Sean P. Robinson

- **Keynote Session: Energy as a Subtle Concept** *Michael Wittmann,* Robert Jaffe, Tamer Amin
- **Bringing Kinematics into the 21st Century** *Mehri Fadavi,* Lauren Barth-Cohen, Tom Krupenkin, Benedikt Harrer
- **Energy in Fields** *Shane Larson,* Justin Khoury, Beth Lindsey
- **Energy as a Cross Cutting Topic Across Disciplines** *Laura Sinclair,* Melanie Cooper, Leslie Schoop, Ben Geller
- **Dynamic Systems** *David Kumar,* Sharon Chou, Ben Dreyfus
- **Energy Harvesting** *Nancy Ruzycki,* Svetlana Boriskina, Knut Neumann, Canan Dagdeviren
- **Matter-Energy Interactions** *Sean Robinson,* Amy Robertson, Alicia Soderberg
- **Energy Transformations** *Dawn Meredith,* Jose Banuelos, Eugenia Etkina, Peter Ciesielski
- **Keynote Session: The Future of Energy Research and Education** *Eugenia Etkina,* Mara Prentiss, Stamatis Vokos
- **Power Hour** *Laura Sinclair*

GRS: Physics Research and Education

Using Energy Models to Teach and Understand Complex Physics Problems in the Research Lab and Classroom

JUNE 9-10, 2018

CHAIRS: Serena M. Eley & Daryl McPadden

Plant and Microbial Cytoskeleton

Cytoskeletal Organization, Dynamics and Function

AUGUST 12-17, 2018 • PROCTOR ACADEMY, ANDOVER, NH

CHAIR: David R. Kovar

VICE CHAIRS: Erin D. Goley & Geoffrey O. Wasteneys

- **Keynote Session: Frontiers in Cytoskeletal Regulation** *Geoffrey Wasteneys,* Magdalena Bezanilla, Sophie Martin
- **Regulation of Cytoskeletal Polymers** *Chris Staiger,* Jan Lowe, Luke Rice, Andrei Smertenko
- **Regulation of Cytoskeletal Dynamics and Polarity** *Kathy Gould,* Mohan Balasubramanian, Yves Brun, Thomas Pollard
- **Cell Division** *Carolyn Rasmussen,* Pamela Brown, Fred Chang, Martine Pastuglia, Jie Xiao
- **Selected Poster Presentations** *Erin Goley*
- **Cytoskeletal Motors, Movement and Forces** *Bruce Goode,* Wei-Lih Lee, Sabine Mueller, Einat Sadot
- **Cytoskeletal Self-Organization** *David Kovar,* Farhah Assaad, Jane Kondev, Anthony Vecchiarelli
- **Cellular Signaling and Morphogenesis** *Petra Levin,* Daniel Lew, Chad Pearson, Daniel Szymanski
- **Membrane Organization and Dynamics** *Scott Dawson,* Federica Brandizzi, Lillian Fritz-Laylin, Alexander Paredez

Plant Molecular Biology

Dynamic Plant Systems

JUNE 10-15, 2018 • HOLDERNESS SCHOOL, HOLDERNESS, NH

CHAIR: Gloria M. Coruzzi

VICE CHAIR: C. Robertson McClung

- **Keynote Session: (Epi)genomic Dynamics and Gene Regulatory Networks** *Gloria Coruzzi,* Joseph Ecker, Olivia Wilkins
- **Dynamics of Epigenetic Modifications** *Rebecca Mosher,* Robert Schmitz, Julie Law
- **Transcriptional Networks and Dynamics** *Rodrigo Gutierrez,* Gabriel Krouk, Philip Benfey
- **Abiotic and Hormone Signaling Dynamics** *Julia Bailey-Serres,* Malcolm Bennett, Jose Dinneny
- **Nutrient Transport and Sensing in Time** *David Mendoza-Cozatl,* Marie Barberon, Mary Lou Guerinot
- **Cell Biology Dynamics** *Natasha Raikhel,* George Bassel, Magdalena Bezanilla, Xu Chen
- **Responses in Circadian Time** *C. Robertson McClung,* Colleen Doherty, Stacey Harmer, Dawn Nagel
- **Development in Space and Time** *Miltos Tsiantis,* Ken Birnbaum, Alexander Jones
- **Genome Dynamics and Evolution** *Ana Caicedo,* Ben Blackman, Detlef Weigel
- **Power Hour** *Natasha Raikhel, Julia Bailey-Serres, Mary Lou Guerinot*

GRS: Plant Molecular Biology

Dynamic Plant Systems

JUNE 9-10, 2018

CHAIRS: Matthew Brooks & Amanda Schrager Lavelle

Plasma Processing Science

Fundamental Insights in Plasma Processes

AUGUST 5-10, 2018 • BRYANT UNIVERSITY, SMITHFIELD, RI

CHAIR: Peter Bruggeman

VICE CHAIR: Anthony B. Murphy

- **Plasma-Material Interaction** *Rebecca Anthony,* Jane Chang, Vincent Donnelly, Lorenzo Mangolini
- **Plasma Agriculture and Medicine** *Alexander Fridman,* Georg Bauer, Masaru Hori, Endre Szili
- **Multiphase Plasmas** *R. Mohan Sankaran,* Davide Mariotti, Javad Mostaghimi, Naoki Shirai
- **Plasma-Catalysis** *Hyun-Ha Kim,* Kristof Ball, Dae Hoon Lee
- **Plasma Assisted Combustion and Flow Control** *Christophe Laux,* Igor Adamovich, Armelle Cessou
- **Exploring New Plasma Regimes** *Francoise Massines,* Jeff Hopwood, Yi-Kang Pu, Pierre Tardiveau
- **Challenges in Diagnostics** *Richard Engeln,* Edward Barnat, Uwe Czarnetzki
- **Challenges in Modeling** *John Verboncoeur,* Anne Bourdon, Juan Trelles
- **Late-Breaking Topics** *Anthony Murphy*
- **Power Hour** *Rebecca Anthony, Katharine Hunter*

GRS: Plasma Processing Science

Understanding and Controlling Plasmas for Future Industries

AUGUST 4-5, 2018

CHAIRS: Adam Obrusnik & Amanda M. Lietz

Plasmonics and Nanophotonics

Harvesting, Generating and Manipulating Light at the Nanoscale

JULY 8-13, 2018 • GRAND SUMMIT HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIR: Peter Nordlander

VICE CHAIR: Jennifer A. Dionne

- **Keynote Session: Novel Concepts in Plasmonics and Nanophotonics** *Naomi Halas,* Harald Giessen, John Pendry, Sergey Bohzevolnyi
- **Hot Carriers and New Materials** *Prineha Narang, Luke Sweatlock,* Stephan Link, Anatoly Zayats, Delia Milliron, Alexandra Boltasseva
- **Active Plasmonics** *Maiken Mikkelsen,* Thomas Ebbesen, Jianfang Wang, Reuven Gordon
- **Terahertz Photonics and Quantum Effects** *Javier Garcia de Abajo, Uriel Levy,* Richard Averitt, Antoinette Taylor, Javier Aizpurua, Vincenzo Giannini
- **Metasurfaces** *Din Ping Tsai,* Laura Na Liu, Nader Engheta, Shang-Jr Gwo
- **Plasmon-Enabled Chemistry and Dielectric Photonics** *Hiroaki Misawa, Arseniy Kuznetsov,* Phillip Christopher, Renee Frontiera, Yuri Kivshar, Michal Lipson
- **Biotechnology Applications** *Christy Landes,* Jwa-Min Nam, Romain Quidant, Hatice Altug
- **Spectroscopy and Late-Breaking Topics** *Vahid Sandoghdar, Mark Brongersma,* Albert Polman, Olivier Martin
- **Keynote Session: What Is Next in Plasmonics and Nanophotonics** *Jennifer Dionne,* Harry Atwater

GRS: Plasmonics and Nanophotonics

Harvesting, Generating and Manipulating Light at the Nanoscale

JULY 7-8, 2018

CHAIRS: Lisa V. Poulikakos & Justus C. Ndukaife

Polymer Physics

New Developments in Hierarchical Structure and Dynamics of Polymers

JULY 22-27, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA

CHAIR: Amalie L. Frischknecht
VICE CHAIR: Sanat K. Kumar

- **Polymer Dynamics** *Jay Schieber,* Daniel Read, Julia Kornfield
- **Ion and Electron-Conducting Polymers** *Monica Olvera de la Cruz, Rachel Segalman,* Louis Madsen, Zhen-Gang Wang, Natalie Stingelin
- **Hierarchical Structure in Polymers** *Juan de Pablo,* Lilo Pozzo, Eugenia Kumacheva
- **Industrially Motivated Research** *Marc Couty, Jeffrey Weinhold,* Sudhin Datta, Ludwik Leibler, Peter Olmsted
- **Block Copolymers/Polymer Phase Behavior** *August Bosse,* Glenn Fredrickson, Ulrich Wiesner
- **Young Investigator Presentations** *Jodie Lutkenhaus, Mahesh Mahanthappa,* Andrew Ferguson, Michael Hore, Bryan McClosky, Sarah Perry, Michelle Seitz, Charles Sing
- **Biopolymers** *LaShanda Korley,* Andrew Spakowitz, Renko De Vries
- **Polymer Nanocomposites** *Russell Composto, Arthi Jayaraman,* Guruswamy Kumaraswamy, Richard Vaia
- **Mechanochemistry** *Andrey Dobrynin,* Stephen Craig, Sergei Sheiko
- **Power Hour** *Connie Roth, Laura Clarke*

Polymer Physics
Connecting Fundamentals to Broad Applications in Polymer Physics
JULY 21-22, 2018
CHAIRS: Michael F. Thees & Danielle J. Mai

Post-Transcriptional Gene Regulation

Integrating Technology and Mechanisms to Illuminate Function in RNA Biology

JULY 15-20, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIRS: Tracy L. Johnson & Brenton Graveley
VICE CHAIRS: Tom A. Cooper & Kristen W. Lynch

- **Keynote Session: Spliceosome Structure** *John Abelson,* Reinhard Luhrmann, Kiyoshi Nagai
- **Splicing Mechanisms** *Christine Guthrie,* Soo-Chen Cheng, Aaron Hoskins, Anna Marie Pyle, Charles Query, Jonathan P. Staley
- **Technologies to Study RNA Biology** *Jennifer Doudna,* Gene Yeo, L. Stirling Churchman
- **Translation Regulation** *Harry Noller,* Gloria Brar, Stephen Floor, Rachel Green, C. Joel McManus
- **Non-Coding RNAs** *Lynne Maquat,* Mitch Guttman, Jeannie Lee, Amy Pasquinelli, Oliver Rando
- **RNA and Disease** *Joan Steitz,* Angela Brooks, Adrian Krainer, Melissa Moore, Peter Smith, Benjamin Blencowe, Matthew Disney
- **Interesting RNA Biology in Weird Biological Settings** *Tom Cech,* Peter Baumann, Julia Salzman, Jin Billy Li
- **RNA Modification and Localization** *Anita Hopper,* Nick Conrad, Wendy Gilbert, Daniel Larson, Tao Pan, Geraldine Seydoux
- **Splicing Regulatory Mechanisms** *Douglas Black,* Manuel Ares, Karla Neugebauer, Tom Cooper, Kristen Lynch

Post-Transcriptional Gene Regulation
Post-Transcriptional RNA Processing: Surveys, Mechanisms and Disease
JULY 14-15, 2018
CHAIRS: Daniel I. Dominguez & Boxuan Zhao

Protein Processing, Trafficking and Secretion

Molecular Mechanisms and Translational Approaches to Cancer, Diabetes, Dyslipidemia, Cardiovascular and Neurodegenerative Disorders

JULY 15-20, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIR: Klaudia Brix
VICE CHAIR: Alan D. Attie

- **New Takes on Transport Along the Secretory Pathway** *Betty Eipper,* Spencer Freeman, Benjamin Glick, Alan Attie
- **Endocytic Pathway Trafficking and Connections to the Secretory Pathway** *Peter Arvan,* Juan Bonifacino, Judith Klumperman, Gary Thomas
- **Updates on Processing (and Beyond) in the Secretory and Endocytic Pathways** *Richard Mains,* Iris Lindberg, Eleanor Raffan, Nabil Seidah
- **Novel Treatment Mechanisms Targeting Diabetes, Obesity and Metabolic Syndrome** *John Creemers,* Melanie Cobb, Daniel Kirchhofer, Timo Müller
- **Significance of Intramembrane Proteolysis** *Regina Fluhrer,* Carl Blobel, Sinisa Urban
- **Protein Processing in Development, Reproduction and Aging** *Lloyd Fricker,* Jan Christian, James Whisstock
- **Secretory Proteases and Inhibitors in Health and Disease** *Stefan Lichtenthaler,* Judith Clements, Bonnie Sloane
- **Challenges in Defining Therapeutic Approaches Targeting Protein Processing** *Robert Day,* Ashley Buckle, Amantha Thathiah
- **Systems Biology Approaches in Protein Processing in Signaling** *Matthijs Verhage,* Christopher Overall, Paul Taghert
- **Power Hour** *Iris Lindberg*

Protein Processing, Trafficking and Secretion
Novel Techniques to Identify Molecular Mechanisms of Protein Processing and Trafficking
JULY 14-15, 2018
CHAIRS: Stephanie Duval & Stephen C. Ireland

Proteoglycans

Proteoglycans in Homeostasis and Disease: Cracking the PG Code

JULY 8-13, 2018 • PROCTOR ACADEMY, ANDOVER, NH

CHAIRS: Anthony J. Day & Carol De La Motte
VICE CHAIR: Liliana Schaefer

- **Late-Breaking Topics** *Jeffrey Esko, Marion Kusche-Gullberg*
- **Proteoglycan Homeostasis** *Edward Harris, Kirsi Rilla,* Thomas Dierks, Lena Kjellen, Barbara Triggs-Raine
- **Proteoglycans in Cell Metabolism, Autophagy and Oxidative Stress** *Paul Bollyky, Liliana Schaefer,* Naoki Itano, Maura Poli
- **Proteoglycan-Based Technologies and Treatments** *Clare Hughes, Toshihiko Toida,* Paul DeAngelis, Tannin Schmidt, Joseph Zaia
- **Proteoglycans in Development, Musculoskeletal and Aging Biology** *Linda Troeberg, Christine Kern,* Suneel Apte, Hannes Buelow
- **Proteoglycans in Fibrosis, Inflammation and Infectious Disease** *Charles Frevert, Pyong Woo Park,* Tracy Handel, David Jackson, Robert Steadman
- **Proteoglycans in Cell Signalling and Trafficking** *Ralf Richter, Larry Sherman,* John Couchman, Paraskevi Heldin
- **Proteoglycans in Tissue Engineering and Regenerative Medicine** *Megan Lord, Carsten Werner,* Kamil Godula, Catherine Merry, Scheffer C. G. Tseng
- **Proteoglycans in Cancer and Neural Biology** *Martin Gotte, Melanie Simpson,* Jessica Kwok, Fabio Melo
- **Power Hour** *Liliana Schaefer, Tabea Dierker*

Proteoglycans
Structure, Mechanisms and Applications of Proteoglycans in Health and Disease
JULY 7-8, 2018
CHAIRS: Aaron C. Petrey & Rogier M. Reijmers

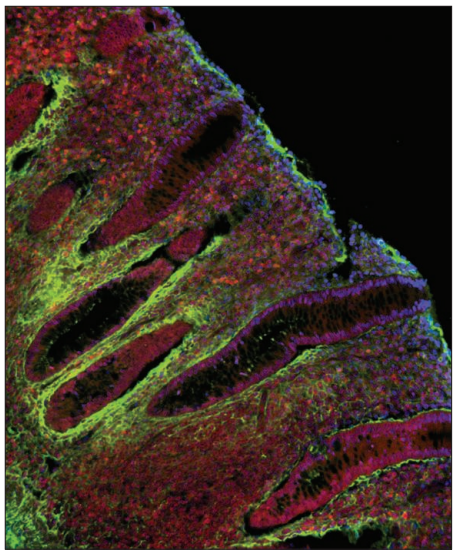
Proteolytic Enzymes and Their Inhibitors

Understanding Proteases and Their Roles as Regulators of Health and Disease

JUNE 3-8, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY

CHAIR: Matthew S. Bogyo
VICE CHAIR: James A. Huntington

- **Keynote Session: Proteases in Oncology** *Leila Akkari, Ingrid Wertz,* Peter Friedl, Vicki Plaks
- **Proteases as Cellular Signaling Molecules** *Margarete M.S. Heck, Christopher Overall,* Nigel Bunnett, Joanne Lemieux, Guy Salvesen
- **Proteases as Regulators of Immunity and Inflammation** *Jeanne Hardy, Benedikt Kessler,* Hidde Ploegh, Martijn Verdoes
- **New Technologies to Monitor Protease Activity and Function** *Jan Konvalinka, Thomas Reinheckel,* Marcin Drag, Galia Blum, Herman Overkleeft
- **Approaches to Modulate and Regulate Protease Activity and Function** *Laura Edgington-Mitchell, Kvido Strisovsky,* David Liu, Daniel Bachovchin
- **Proteases as Regulators of Pathogen Function** *Tim Clausen, Anthony O'Donoghue,* Jan Potempa, Jyothi Rengarajan, Stephan Sieber



During inflammation, matrices comprised of proteoglycans participate in disease progression or resolution, as seen in inflammatory bowel disease. Here, the glycosaminoglycan hyaluronan (green) and the receptor CD44 (red) foster inflammatory leukocyte recruitment in colon tissue from a Crohn's disease patient. CREATED BY AARON C. PETREY. SUBMITTED BY THE 2018 PROTEOGLYCANS GRS CHAIRS.

- **Therapeutic and Diagnostic Potential of Proteases** *Regina Fluhrer, Michael Wiener,* Yasuteru Urano, Jesus Gonzalez
- **Protease Structure and Function** *Sheena McGowan, James Whisstock,* David Komander, Michael Groll, Aimee Shen
- **Late-Breaking Topics in Proteolysis** *Antoine Dufour, Barbara Fingleton*

Proteolytic Enzymes and Their Inhibitors
Exploring the Opportunities and Confronting the Challenges Surrounding Protease-Targeted Therapies
JUNE 2-3, 2018
CHAIRS: Laura E. Edgington-Mitchell & Jaideep S. Dudani

Quantum Science

Non-Equilibrium Quantum Matter and Scalable Quantum Computing

JULY 29 – AUGUST 3, 2018 • STONEHILL COLLEGE, EASTON, MA

CHAIRS: Ana Maria Rey & Andrew Houck
VICE CHAIRS: Markus Greiner & Eugene Demler

- **Connecting Quantum Systems** *Jun Ye,* Cindy Regal, Shyam Shankar, Jelena Vuckovic
- **Progress in Quantum Computing Technology** *Shyam Shankar,* Rainer Blatt, Jay Gambetta, John Martinis, Chris Monroe
- **Quantum Information and Condense Matter** *Liang Jiang,* Susan Coppersmith, Kathryn Moler, Frank Verstraete
- **Quantum Sensing** *James Thompson,* Nathalie De Leon, Benjamin Lev, Jun Ye, Paola Cappellaro
- **Non-Equilibrium Quantum Matter** *Jonathan Simon,* Immanuel Bloch, Wojciech De Roeck, Jens Koch
- **Quantum Computation Algorithms and Error Correction** *Frank Verstraete,* Sergey Bravyi, Aram Harrow, Liang Jiang, Stephanie Wehner
- **Late-Breaking Topics** *Cindy Regal,* Daniel Greif, Jonathan Simon, Ahmed Omran
- **Light Matter Interactions and Many-Body Quantum Optics** *Jens Koch,* Gil Refael, Monika Schleier-Smith, Susanne Yelin, James Thompson
- **Connections Between Quantum Science and Other Fields** *Gil Refael,* Fernando Pastawski, Subir Sachdev, Adam Brown
- **Power Hour** *Julia Cline*

Quantum Science
Non-Equilibrium Quantum Matter and Scalable Quantum Computing
JULY 28-29, 2018
CHAIRS: Michael L. Goldman & Edward H. Chen

Research at High Pressure

Bridging Timescale, Temperature and Pressure Gaps in High-Pressure Compressed-Matter Science

JULY 15-20, 2018 • HOLDERNESS SCHOOL, HOLDERNESS, NH

CHAIR: Jon H. Eggert

VICE CHAIR: Sakura Pascarelli

- **Deep Earth, Super Earths and Exoplanets** *Thomas Duffy,* Agnès Dewaele, Ryuichi Nomura, Luke Shulenburger
- **Hydrogen** *Stanley Tozer,* Carlo Pierleoni, Eugene Gregoryanz, Peter Celliers, Mohamed Zaghoo
- **High-Pressure Biology and Pharmaceuticals** *Filip Meersman,* Nick Brooks, Elena Boldyreva, Karyn Rogers
- **Pressure-Induced Chemistry and Highly-Correlated Materials** *Fernando Rodriguez,* Choong-Shik Yoo, Kuo Li, Suchitra Sebastian, Daniel Haskel
- **The Approach to Equilibrium: Phase Transitions** *Raymond Smith,* Lorin Benedict, Sally Tracy
- **The Approach to Equilibrium: Planets** *Jon Eggert,* Ronald Redmer, Hauke Marquartd
- **Complementing Nature: Pressure-Synthesis of New Phases** *Chris Pickard,* Mao-Sheng Miao, Danae Polsin
- **Improving the Old and Building the New: Techniques and Facilities** *Cynthia Bolme,* Helen Maynard-Casely, Richard Sandberg
- **Keynote Session: Recent Advances in High-Pressure Research** *Sakura Pascarelli,* Shanti Deemyad

Research at High Pressure
Bridging Experimental Gaps in High-Pressure Condensed-Matter Science
JULY 14-15, 2018
CHAIR: Audrey D. Grockowiak

Rock Deformation

Integrated Approaches to Rock Deformation: Observations, Experiments and Models

AUGUST 19-24, 2018 • PROCTOR ACADEMY, ANDOVER, NH

CHAIR: Julia Morgan

VICE CHAIR: Daniel Faulkner

- **Earthquake Precursors and Prediction** *Andre Niemeijer,* Paul Johnson, Francois Renard
- **Experimental Constraints on Fault Slip and Slip Behavior** *Melodie French,* Cristiano Collettini, Christine McCarthy, Yannick Caniven
- **Slow and Fast Slip in the Rock Record** *Jamie Kirkpatrick,* Ake Fagereng, Alexis Ault
- **Earthquakes Physics from Seismology and Geodesy** *Susan Schwartz,* Greg Beroza, Sylvain Barbot, Jessica Hawthorne
- **Role of Sediments at Subduction Zones** *Maria Ask,* Frederick Chester, Matt Ikari
- **Ductile Shear Zones and Deformation Mechanisms** *David Goldsby,* Philip Skemer, Matej Pec, Whitney Behr
- **Geofluids, Geothermics and Geohazards** *Peter Eichhubl,* Jenny Suckale, Nicholas Davatzes
- **Fracture, Fragmentation and Granular Mechanics** *David Sparks,* Thomas Mitchell, Mai-Linh Doan, H. Jay Melosh
- **Young Investigator Presentations** *Daniel Faulkner*
- **Power Hour** *Julia Morgan*

Rock Deformation
Combined Approaches to Investigating Rock Deformation Across Vast Temporal and Spatial Scales
AUGUST 18-19, 2018
CHAIRS: Johanna M. Nevitt & Katrina M. Sauer

Salt and Water Stress in Plants

Abiotic Stress and the Future of Agriculture

JUNE 3-8, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIRS: Melvin J. Oliver & Jill Farrant

VICE CHAIRS: Jose R. Dinneny & Christa Testerink

- **Dealing with a Changing Environment** *Michael Nuccio,* Jian-Kang Zhu, Julia Bailey-Serres, Frank Dohleman
- **Root Responses to Abiotic Stress** *Jose Dinneny,* Robert Sharp, Robert Hill, Christopher Topp, Simon Gilroy
- **Shoot Responses to Abiotic Stress** *Julie Gray,* Helmut Kirchhoff, Christine Foyer, Michael Blatt
- **Abiotic Stress Signalling** *Julian Schroeder,* Jeffrey Harper, Honghong Hu, Ron Mittler, Erwin Grill
- **Metabolic Consequences of Abiotic Stress** *Diana Santelia,* Andrew Hanson, Joshua Blakeslee, Ruth Welti
- **Genome Level Responses to the Environment** *Henk Hilhorst,* Olivia Wilkins, Maria Costa, Julia Buitink
- **Living in Extreme Environments** *Sagadevan Mundree,* Dorothea Bartels, John Cheeseman, Xin Deng, Brett Williams
- **Making Use of Natural and Engineered Variation** *Tuan-Hua Ho,* Leonie Bentsink, Jonathan Lynch, Dirk Inze
- **Crop Productivity Under Abiotic Stress** *Stuart Roy,* Francois Tardeu, Felix Fritschi, Amelia Henry
- **Power Hour** *Jill Farrant*

Salt and Water Stress in Plants
Integrating Molecular Mechanisms, -Omics and Imaging to Develop Abiotic Stress Tolerant Crops
JUNE 2-3, 2018
CHAIRS: Sandra M. Schmöckel & Lidor Shaar-Moshe

Scientific Methods in Cultural Heritage Research

Leading Edge Applications of Data Science, Degradation Science and Conservation Strategies for Cultural Heritage

JULY 22-27, 2018 • REY DON JAIME GRAND HOTEL, CASTELLDEFELS, SPAIN

CHAIRS: C. Richard Johnson & Robert Van Langh

VICE CHAIRS: Julie Arslanoglu & Loic Bertrand

- **Keynote Session: Cultural Heritage Research: The Big Picture** *Jennifer Mass,* Barbara Berrie, Laurens van der Maaten
- **Data Science for Cultural Heritage** *John Delaney,* Robert Erdmann, Paul Messier, David Donoho
- **Computational Modeling for Cultural Heritage** *Warren Warren,* Alessandra Satta, Linda Broadbelt
- **Advanced Analytical Techniques: Biological Applications** *Admir Masic,* James Weaver, Maria Colombini, Johannes Krause
- **Advanced Analytical Techniques: Tracing the Origin of the Object** *Ina Reiche,* Manako Tanaka, David Thurrowgood
- **Detecting, Quantifying and Predicting Degradation Phenomena: Experimental Approaches** *Marco Leona,* Haida Liang, Costanza Miliani, Philippe Walter
- **Detecting, Quantifying and Predicting Degradation Phenomena: Theoretical Approaches** *Francesca Casadio,* Serge Cohen, Dominique Derome, Catherine Patterson
- **New Strategies for Treatment-Based Conservation** *Tom Learner,* Bronwyn Ormsby, Thomas Wurdinger, Bill Wei
- **New Strategies for Preventive Conservation** *Matija Strlic,* David Thickett, Ulderico SantaMaria

Scientific Methods in Cultural Heritage Research
From Studios to Laboratories: Scientific Innovations for Art and Archeology
JULY 21-22, 2018
CHAIRS: Marc Vermeulen & Zachary E. Voras

Signal Transduction by Engineered Extracellular Matrices

Designing Cell-Material Interactions to Achieve Regenerative Medicine Therapies and In Vitro Disease Models

JULY 22-27, 2018 • PROCTOR ACADEMY, ANDOVER, NH

CHAIR: Sarah C. Heilshorn

VICE CHAIRS: David V. Schaffer & Matthias Lutolf

- **Keynote Session: 3D Models to Diagnose, Understand and Treat Cancer** *Sarah Heilshorn,* Jeffrey Hubbell, Mina Bissell
- **Materials and Matrices for Tissue Regeneration** *Treena Arinzeh,* Paula Hammond, Tatiana Segura, George Muschler
- **New Methods to Evaluate Cell-Matrix Interactions** *Debra Auguste,* Alexander Dunn, Jan Lammerding
- **Materials and Matrices to Guide Stem Cell Biology** *Jason Burdick,* William Murphy, Linda Griffith, Mark Powers
- **The Microenvironment and Cell Fate** *Penney Gilbert,* William Keyes, Eduardo Moreno
- **Materials and Matrices for Disease Modeling** *David Belair,* Alison McGuigan, Sharon Gerecht, Sam Wadsworth

> *"The small size and everyone-in-one-room setting allows scientific stories to build throughout the week, creating an immersive experience."*
>
> DR. JULIA KUBANEK
> Marine Natural Products GRC

- **3D Cultures to Guide Organoid and Tissue Morphogenesis** *Andres Garcia,* Zev Gartner, Anne Grapin-Botton
- **New Approaches to Biomaterials Design** *Widya Mulyasasmita,* Kristopher Kilian, April Kloxin, Wilfried Weber
- **Materials for Immunomodulation** *Anjelica Gonzalez,* Edward Botchwey, Joel Collier

Signal Transduction by Engineered Extracellular Matrices
Engineering the Microenvironment to Direct Cellular Behavior
JULY 21-22, 2018
CHAIRS: Ana M. Porras & Cassady E. Rupert

Signaling by Adhesion Receptors

Connecting Structure, Mechanics and Function in Cells and Tissues

JUNE 24-29, 2018 • UNIVERSITY OF NEW ENGLAND, BIDDEFORD, ME

CHAIR: Christopher S. Chen

VICE CHAIR: Ann L. Miller

- **Keynote Session: New Insights on Old Pathways** *Christopher Chen,* Joan Brugge, Nicole King
- **Cell-Cell Adhesion Assembly and Disassembly** *Douglas Desimone,* Alpha Yap, Kathleen Green, Ronen Zaidel-Bar
- **Cell-Matrix Adhesion Assembly and Disassembly** *Martin Schwartz,* Bernhard Wehrle-Haller, Jonathan Cooper, Margaret Gardel
- **Mechanical Regulation of Adhesion** *Pere Roca-Cusachs,* Martin Schwartz, Alexander Dunn, Deborah Leckband
- **Orchestrating Adhesion and Migration** *Wesley Legant,* Michael Sixt, Mark Peifer, Peter Friedl
- **Adhesion and Tissue Remodeling** *Edna Cukierman,* Ann Miller, Kris DeMali, Celeste Nelson
- **Cell-Matrix, Cell-Cell and Growth Factor Receptor Cross-Talk** *Richard Assoian,* Johanna Ivaska, Andrea McClatchey, Boris Hinz
- **Evolving Concepts of Adhesion Signaling and Cancer Progression** *Madeleine Oudin,* Andrew Ewald, Weilan Ye, Gaudenz Danuser
- **Clinical Applications of Adhesion Modulation** *Albert Reynolds,* Simon Goodman, David Schlaepfer, Dean Sheppard

Signaling by Adhesion Receptors
Multi-Scale Adhesion Mechanics and Signaling
JUNE 23-24, 2018
CHAIRS: Karin Wang & Carlos Perez Gonzalez

Single Molecule Approaches to Biology

Uncovering Fundamental Mechanisms in Biology and Beyond, One Molecule at a Time

JULY 15-20, 2018 • MOUNT SNOW, WEST DOVER, VT

CHAIRS: Julie Biteen & Antoine Van Oijen

VICE CHAIRS: Erwin J.G. Peterman & Olga K. Dudko

- **Keynote Session: Understanding Life at a Higher Resolution** *Julie Biteen, Antoine Van Oijen,* W.E. Moerner, Jennifer Lippincott-Schwartz
- **Fundamental Cellular Processes** *Ethan Garner,* Ahmet Yildiz, David Rueda, Samara Reck-Peterson, Scott Blanchard
- **Single Molecule Approaches in Chemistry** *Steven Lee,* Christy Landes, Randall Goldsmith, Laura Kaufman
- **Photosynthesis and Energy Transfer** *Randall Goldsmith,* Gabriela Schlau-Cohen, Yousoo Kim, Richard Hildner, Rienk Van Grondelle
- **Single Molecules in Living Cells** *Johan Elf,* Bianxiao Cui, Jin Zhang, Ethan Garner
- **Super-Resolution Imaging** *Erwin Peterman,* Samuel Hess, Yujie Sun, Steven Lee, Suliana Manley
- **Single Molecule Nanophotonics and Plasmonics** *Christy Landes,* Michel Orrit, Katherine Willets, Niek Van Hulst
- **Single Molecule Mechanics** *Bianxiao Cui,* Steven Block, Madhavi Krishnan, Wesley Wong, Sabrina Leslie
- **From Single Molecules to Complex Systems** *Olga Dudko,* Frederick MacKintosh, Mark Wallace, Xiaoliang Sunney Xie

Single Molecule Approaches to Biology
Uncovering Fundamental Mechanisms in Biology and Beyond: One Molecule at a Time
JULY 14-15, 2018
CHAIRS: Xiaoyu Shi & Jorine M. Eeftens

Solar Energy Conversion

Pathways for Solar Energy Conversion and Storage: Electricity, Thermal and Fuel

JUNE 17-22, 2018 • THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY, HONG KONG, CHINA

CHAIR: Jia Zhu

VICE CHAIRS: Can Li & Anders Hagfeldt

- **Theory and Mechanism** *Philip Earis,* Shanhui Fan, Alex Zunger
- **Thermal Energy** *Peng Wang,* Naomi Halas, Andrej Lenert, Xiaobo Yin
- **Solar Electricity and Fuel** *Duoduo Liang,* Harry Atwater, Xiaolin Zheng
- **Photon Management and Structural Design** *Vivian Ferry,* Mark Brongersma, Din Ping Tsai, Erik Garnett
- **Industry Perspective: Materials and Processes** *Jian-Bin Xu,* Baosheng Zhong, Dirk Weiss
- **Solar Fuel** *Zhiyong Fan,* Nathan Lewis, Akihido Kudo, Dunwei Wang
- **Characterizations** *Elsa Couderc,* Xiaoyang Zhu, Fengtao Fan
- **Polymers, Small Molecules and Hybrids** *Vivian Yam,* Ben Zhong Tang, Yang Yang, Zenggi Xie
- **Perovskite Solar Cells** *Hairen Tan,* Shihe Yang, Jinsong Huang

Solar Energy Conversion
Materials, Physics and Devices for Advanced Solar Energy Conversion
JUNE 16-17, 2018
CHAIR: Ning Xu

Solid State Chemistry

Designing, Discovering and Understanding the Functional Materials of the Future

JULY 22-27, 2018 • COLBY-SAWYER COLLEGE, NEW LONDON, NH

CHAIR: Patrick M. Woodward

VICE CHAIR: Shiv Halasyamani

- **Energy Conversion Materials** *Shiv Halasyamani,* David Mitzi, Ram Seshadri
- **Computational Approaches to Materials Discovery** *Nicole Benedek,* Gerbrand Ceder, Richard Dronskowski, Bryce Meredig, James Rondinelli
- **Advanced Structural Characterization Methods** *Joke Hadermann,* John Evans, Katharine Page
- **Energy Storage Materials** *Seung-Tae Hong,* Boniface Fokwa, Yan Yan Hu, Linda Nazar
- **Thermoelectrics** *Franck Gascoin,* Sven Lidin, Eric Toberer, Li-Dong Zhao
- **The Science of Synthesis** *Anja Mudring,* David Johnson, James Neilson, Alexander Norquist, Paul Salvador
- **Perovskite Oxides** *Joshua Goldberger,* Michelle Dolgos, Susana Garcia-Martin
- **Quantum Materials** *Yuichi Shimakawa,* Simon Clarke, Danna Freedman, Je-Geun Park, Tanusri Saha-Dasgupta
- **Extreme Materials** *Patrick Woodward,* Thomas Albrecht-Schmitt, Timothy Strobel
- **Power Hour** *Michelle Dolgos*

Solid State Chemistry
Tomorrow's Materials for Energy Conversion and Storage: From Rational Design to Application
JULY 21-22, 2018
CHAIR: Miles A. White

Solid State Studies in Ceramics

Exploiting Defects and Interfaces in Paradigm-Shifting Processing and Extreme Environments

AUGUST 12-17, 2018 • MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MA

CHAIR: Jian Luo

VICE CHAIR: Ivar E. Reimanis

- **Additive Manufacturing of Ceramics** *Yiquan Wu,* Tobias Schaedler, Rebecca Dylla-Spears
- **Fundamentals of Interfaces and Defects** *Ming Tang,* I-Wei Chen, Wayne Kaplan, Edwin Garcia
- **Electric Field Assisted Ceramic Processing: Defects and Microstructures** *Antti Makinen,* Richard Todd, Haiyan Wang
- **"Ceramics and Defects Genome": From Theories and Modeling to Machine Learning and Data-Driven Discovery** *James Warren,* Krishna Rajan, Kristin Ceder-Persson, Wenqing Zhang
- **Ultra-Low Temperature Processing: The Roles of Interfaces and Defects** *Alexis Lewis,* Jon-Paul Maria, B. Reeja Jayan
- **Defects and Interfaces in Ceramics for Energy Applications** *Monika Backhaus-Ricoult,* Sossina Haile, Miaofang Chi, Sung-Yoon Chung
- **New Materials: High-Entropy Ceramics ("All Defective") and 2-D Ceramics ("Interfacial Materials")** *Eric Wuchina,* Yury Gogotsi, Don Brenner, Elizabeth Opila
- **Ceramics for Extreme Environments** *Vann Heng,* Nitin Padture, William Fahrenholtz, Randall Hay
- **Late-Breaking Topics** *Gregory Rohrer,* Maria Loi
- **Power Hour** *Tabbetha Dobbins, Diletta Giuntini*

Solid State Studies in Ceramics
Defects and Interfaces for New Functionalities in Ceramics
AUGUST 11-12, 2018
CHAIRS: Diletta Giuntini & Elias H. Penilla

Stereochemistry

The Many Dimensions of Stereochemistry: Catalysis, Chemical Biology, Macromolecules and Synthesis

JULY 22-27, 2018 • SALVE REGINA UNIVERSITY, NEWPORT, RI

CHAIRS: Gregory C. Fu & Cameron J. Cowden

VICE CHAIRS: Varinder K. Aggarwal & Eric Ashley

- **Stereochemistry: Structure and Function** *Varinder Aggarwal,* Squire Booker, Ben L. Feringa
- **Stereoselective Catalysis** *Hosea Nelson,* Christina White, Jin-Quan Yu, Cathleen Crudden
- **Stereochemistry of Macromolecules** *Julia Kalow,* Kyoko Nozaki, Michinori Suginome
- **Biocatalysis and Chemical Biology** *Todd Hyster,* Frances Arnold, Emily Balskus, Suzanne Walker
- **Asymmetric Synthesis in Industry** *Alison Narayan,* John Ragan, Rebecca Ruck
- **Enantioselective Reactions** *Kimberly Petersen,* Scott Denmark, Vy Dong, Michael Krische, David Sarlah
- **Understanding Stereoselectivity** *Daniel O'Leary,* Kendall Houk, Matthew Sigman
- **Enantioselective Synthesis of Natural Products** *Sarah Wengryniuk,* Tanja Gaich, Seth Herzon, Thomas Maimone
- **Stereochemistry in Two and Three Dimensions** *Eric Ashley,* Robert H. Grubbs, Eric Jacobsen
- **Power Hour** *Rebecca Ruck*

NEW! Streptococcal Biology

Molecular Mechanisms at the Streptococcal-Host Interface

AUGUST 19-24, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIRS: Victor Nizet & Nina van Sorge

VICE CHAIRS: Kelly S. Doran & Shiranee Sriskandan

- **The Leading Edge: Emerging Themes in Streptococcal Research** *Paul Sullam,* Jan-Willem Veening, Eric Pamer
- **Streptococcal Manipulation of Macrophage and Neutrophil Function** *Anna Norrby-Teglund,* Birgitta Henriques, Carlos Orihuela
- **Immune Responses to Streptococcal Infection: A Balancing Act** *Annelies Zinkernagel,* Douglas Golenbock, Pavel Kovarik, Mariela Segura
- **Finding a Niche: Streptococcal Colonization of Host Mucosal and Epithelial Barriers** *Lakshmi Rajagopal,* Anthony Flores, Katharina Ribbeck, Jeffrey Weiser, Elaine Tuomanen
- **Polymicrobial Interactions: Life Among the Microbiome** *Michael Gilmore,* Howard Hang, Kimberly Kline, Marvin Whiteley
- **New Paradigms in Streptococcal Virulence Factor Action** *Gunnar Lindahl,* Isaac Chiu, John McCormick, Mark Walker

> ***"Gordon Conferences are different from other scientific conferences because the format and setting stimulate genuine discussion and networking not only during formal sessions but also during the meals and social activities."***
>
> DR. ELIAS VLIEG
> Crystal Growth and Assembly GRC

- **Innovative Therapeutic and Vaccination Strategies Against Streptococcal Pathogens** *James Dale,* George Liu, Liangfang Zhang
- **"Streptococcomics": Big Data Approaches to the Pathogen** *Michael Wessels,* Johan Malmström, Andrew Waller
- **Young Investigator Presentations** *Kelly Doran,* Christopher LaRock

Structural Nanomaterials

Complexity and Heterogeneity in Microstructure and Their Relation with Properties

AUGUST 12-17, 2018 • THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY, HONG KONG, CHINA

CHAIRS: Z.P. Lu & Simon Ringer

VICE CHAIRS: Qing Ping Sun & Andrea Hodge

- **Keynote Session: Frontiers in the Approach to Materials Design** *Chain Tsuan Liu,* Herbert Gleiter, Dierk Raabe
- **Complexity and Nano-Heterogeneity in Microstructures** *Simon Ringer,* Irene Beyerlein, Wei Hua Wang, Xiaozhou Liao
- **Kinetics and Stability of Microstructure and Their Relation with Properties** *Andrea Hodge,* Sudarsanam Suresh Babu, Ian Baker, Easo George
- **Advanced Nanomechanics** *T.G. Nieh,* Huajian Gao, Paulo Branicio
- **Advanced Materials Characterization for Materials Design** *Ian Baker,* Mingwei Chen, Michael Mills, C. Cem Tasan
- **Atomistic and Nanoscale Simulations** *Easo George,* Long-Qing Chen, Zi-Kui Liu, Izabela Szlufarska
- **Engineering Nanoscale Heterogeneities for Advanced Properties** *Qing Ping Sun,* Jamie Kruzic, Lei Lu, Nobuhiro Tsuji, Stefanie Sandlobes, Jiehua Li
- **Advances in Nano-Compositing** *Gang Sha,* Juergen Eckert, Michael Ferry, Katharine Flores
- **Frontiers in Structural and Functional Nano-Biomaterials** *Hala Zreiqat,* Thomas Webster, Yufeng Zheng, Hung-Wei Yen

Synaptic Transmission

Integrating the Regulation of Synaptic Transmission Across Cellular and Circuit Levels

AUGUST 12-17, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIR: Kristen M. Harris

VICE CHAIR: Alison Barth

- **Late-Breaking Topics: Rapid Transmission of Synaptic Ideas** *Alison Barth*
- **Dynamic Regulation of Synaptic Transmission by Protein Turnover and Signaling to the Nucleus** *Graeme Davis,* Ege Kavalali, Silvio Rizzoli, Anne West, Daniel Choquet, Brenda Bloodgood
- **Resource Management and Synaptic Plasticity** *Christine Gall,* Thomas Schwarz, Nicola Allen, Cristina Alberini
- **Bidirectional Regulation of Presynaptic Release and Postsynaptic Response** *Mary Kennedy,* Graeme Davis, Lori McMahon, Jaideep Bains, Shernaz Bamji, Susumu Tomita
- **Synaptogenesis and Synaptic Plasticity** *Thomas Schwarz,* Takao Hensch, Kimberley McAllister, Christine Gall
- **Presynaptic Release, Postsynaptic Response, Calcium and Structural Plasticity** *Scott Soderling,* Samuel Young, Elise Stanley, Mary Kennedy, Kim Raab-Graham, Matthew Kennedy
- **Synaptic Circuit Structure and Function** *Mala Shah,* Scott Soderling, Dan Johnston, Albert Cardona
- **Specificity in Regulating Synaptic Transmission** *Shernaz Bamji,* Mala Shah, Terry Sejnowski, Tallie Z. Baram, Graham Knott, K. Ulrich (Ulli) Bayer
- **Keynote Session: Biochemical Computation in Single Dendritic Spines** *Kristen Harris,* Ryohei Yasuda

Synaptic Transmission
Synaptic Function in Neural Circuits
AUGUST 11-12, 2018
CHAIR: Christopher E. Vaaga

NEW! Systems Chemistry

Systems Chemistry from Concepts to Conception

JULY 29 – AUGUST 3, 2018 • JORDAN HOTEL AT SUNDAY RIVER, NEWRY, ME

CHAIRS: David Lynn & Gonen Ashkenasy
VICE CHAIRS: Sijbren Otto & Rein Ulijn

- **Keynote Session: Bottom-up Construction of Complex Chemical Systems** *David Lynn,* Jo Handelsman, Joanna Aizenberg
- **Compartmentalized Chemical Networks** *Kepa Ruiz-Mirazo,* Neal Devaraj, Christine Keating, Veronica Vaida
- **Alternative Genetic Systems** *Ignacio Alfonso,* John Chaput, Henderson Cleaves, Philipp Holliger
- **Dynamic Functional Materials** *Bing Xu,* Ivan Aprahamian, Dieter Braun
- **Energy Dissipation in Dynamic Systems** *Jay Goodwin,* Rafal Klajn, Rein Ulijn
- **Autocatalysis, Self-Replication and Replication Networks** *Martha Grover,* Niles Lehman, Sijbren Otto, Kenso Soai
- **Nucleic Acid Systems Chemistry** *Jennifer Heemstra,* Andrew Ellington, Rebecca Schulman, Christoph Flamm
- **Chemical Reactivity Far from Equilibrium** *Agota Toth,* Lee Cronin, Irving Epstein, Annette Taylor
- **Future of Systems Chemistry** *Gonen Ashkenasy,* Sarah Imari Walker, Jan van Esch
- **Power Hour** *Jennifer Heemstra, David Lynn*

Thin Film and Small Scale Mechanical Behavior

Micro- and Nano-Mechanics as a Tool for Materials Design

JULY 15-20, 2018 • BATES COLLEGE, LEWISTON, ME

CHAIR: Andrew J. Bushby
VICE CHAIRS: Gerhard Dehm & Ralph Spolenak

- **Small-Scale Testing in Challenging Environments** *David Armstrong,* Afrooz Barnoush, Olivier Pierron, Peter Hosemann
- **Microstructure-Property Relationship at Small Scales** *Javier Llorca,* Andrea Hodge, C. Cem Tasan, Sandrine Brochard
- **Mechanics of 3D Printed Micromaterials** *Ralph Spolenak,* Rostislav Daniel
- **Mechanics of Functional Materials and Systems** *Olivier Pierron,* Christoph Stampfer, Nikhilesh Chawla
- **Advances in Small-Scale (Mechanical) Analysis Methods** *Alfonso Ngan,* Jeffrey Wheeler, Marco Sebastiani
- **Microarchitectures and Their Mechanical Performance** *Erica Lilleodden,* Ruth Schwaiger, Ulrike Wegst
- **Materials Design** *John Balk,* Christopher Schuh, Matteo Seita
- **Nanoindentation Methods and Surface Tribology** *Andrew Bushby,* Cynthia Volkert, Christophe Tromas, Robert Carpick
- **Keynote Session: In Situ Microscopy and Diffraction** *Gerhard Dehm,* Mitra Taheri, Stefan Zaefferer, Katia Bertoldi

GRS Thin Film and Small Scale Mechanical Behavior
Exploiting Small-Scale Mechanics: From Theoretical to Functional
JULY 14-15, 2018
CHAIRS: Pralav P. Shetty & Alexandra A. Cackett

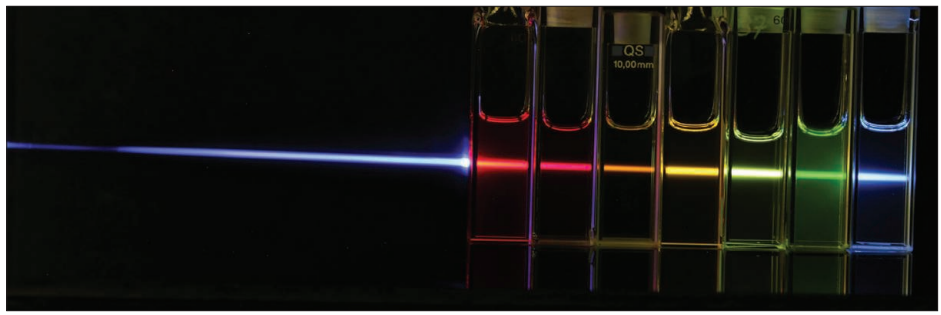
Thiol-Based Redox Regulation and Signaling

Mechanisms and Organizing Principles in Redox Signaling: Implications for Age-Related Disease

JULY 15-20, 2018 • REY DON JAIME GRAND HOTEL, CASTELLDEFELS, SPAIN

CHAIR: Tobias Dick
VICE CHAIR: Kate S. Carroll

- **Keynote Session: Concepts and Directions in Redox Signaling Research** *Tobias Dick, Kate Carroll,* Toren Finkel, Christine Winterbourn
- **New Tools for Redox Signaling Research** *Vsevolod Belousov, Andreas Meyer,* Huiwang Ai, Hadley Sikes, Jing Yang, Yi Yang
- **Mechanisms of Redox Signaling in Aging** *Michael Ristow, Rodney Levine,* Vadim Gladyshev, Ursula Jakob, Josh Rabinowitz
- **Dysregulation of Redox Signaling in Age-Related Disease** *Carola Neumann, Arne Holmgren,* Navdeep Chandel, Cristina Furdui, Kitai Kim
- **Pharmacological Manipulation of Redox Signaling** *Ana Denicola, Yvonne Janssen-Heininger,* Marcus Conrad, Michael Murphy, Amit Singh
- **Thiol Peroxidases in Redox Signaling** *Elisabeth Veal, Luis Netto,* Tobias Dansen, Elena Hidalgo, Leslie Poole, Sue Goo Rhee



Fluorescent probes used in ultrafast time-resolved infrared absorption spectroscopy illuminated by laser light. CREATED BY BOGDAN DEREKA. SUBMITTED BY THE 2018 VIBRATIONAL SPECTROSCOPY GRS CHAIRS.

- **Oxidative Stress Resistance and Damage Control** *Joris Messens,* Keith Blackwell, Gilles Charvin, Michael Davies, Marcel Deponte
- **Redox Control Across Membranes and Compartments** *Johannes Herrmann, Michel Toledano,* Neil Bulleid, Deborah Fass, Gyorgy Hajnoczky, Carolyn Sevier
- **Reactive Sulfur Species and Their Biomedical Relevance** *Beatriz Alvarez,* James Mitchell, Roberto Sitia, Peter Nagy
- **Power Hour** *Yvonne Janssen-Heininger*

GRS Thiol-Based Redox Regulation and Signaling
Redox Biology in Cell Signaling, Oxidative Stress and Disease
JULY 14-15, 2018
CHAIRS: Jesalyn Bolduc & Alyson E. Colin

Three Dimensional Electron Microscopy

Exploring the Capability of Cryo-EM to Provide Insight Beyond Static Structures of Macromolecules

JUNE 3-8, 2018 • SALVE REGINA UNIVERSITY, NEWPORT, RI

CHAIR: John Rubinstein
VICE CHAIR: Hongwei Wang

- **Keynote Session: Challenging Specimens** *John Rubinstein,* Eva Nogales, Erik Jorgensen
- **Cryo-EM in the Context of Developing Therapeutics** *Seungil Han,* Claudio Ciferri, Andrew Ward, Nieng Yan, Paula Da Fonseca
- **Advances in Specimen Preparation** *Bridget Carragher,* Christopher Russo, Eric Gouaux
- **Innovations in Hardware and Imaging** *Radostin Danev,* Wim Hagen, Grant Jensen, Holger Mueller
- **Selected Poster Presentations: Recent Breakthroughs in 3DEM** *Hongwei Wang*
- **Frontiers in Electron Tomography** *Jun Liu,* Daniela Nicastro, John Briggs, Benjamin Engel
- **Hybrid Methods** *Peter Rosenthal,* Gregory Alushin, Charles Sindelar, Adam Frost
- **New Developments in Algorithms** *Jose Maria Carazo Garcia,* Ali Punjani, Maya Topf, Xueming Li
- **Selected Poster Presentations: New Developments in 3DEM** *Sharon Wolf*

Tissue Niches and Resident Stem Cells in Adult Epithelia

Modeling Cell-Cell Interactions Governing Tissue Repair and Disease

AUGUST 19-24, 2018 • WATERVILLE VALLEY, WATERVILLE VALLEY, NH

CHAIRS: Carla Kim & Jane E. Visvader
VICE CHAIRS: Michael M. Shen & Valerie J. Horsley

- **Keynote Session: Modeling Cell-Cell Interactions Governing Tissue Repair and Disease** *Jane Visvader,* Elaine Fuchs, Fred De Sauvage
- **Imaging and Single Cell Approaches** *Jason Rock,* Fernando Camargo, Valentina Greco, Tannishtha Reya, Tushar Desai
- **Diverse Cell Types in Supporting Roles** *Carla Kim,* Emi Nishimura, Michael Rendl, Valerie Horsley
- **Developmental Pathways Regulating Adult Tissues** *Leanne Jones,* Wolfram Goessling, Melanie Koenigshoff, Norbert Perrimon, Li Xin
- **Modeling Epithelial Development in Disease** *Rongwen Xi,* Michele de Luca, Alexander Nikitin, Michael Shen
- **Immune Cell Interactions** *Alexander Nikitin,* Marcia Haigis, Ophir Klein, Jason Rock, Carla Rothlin
- **DNA Repair and Aging in Niches** *Marcia Haigis,* Heinrich Jasper, Leanne Jones, Carien Niessen
- **Epigenetic Regulation of Tissues and Their Niche** *Valerie Gouon-Evans,* Tudorita Doina Tumbar, Rongwen Xi, Omer Yilmaz
- **Engineering Niches** *Ophir Klein,* Hans-Willem Snoeck, David Tuveson, Valerie Gouon-Evans

GRS Tissue Niches and Resident Stem Cells in Adult Epithelia
Using Cutting-Edge Technology to Dissect the Cross-Talk Between Stem Cells and Niche Across Different Organs
AUGUST 18-19, 2018
CHAIR: Margherita Paschini

Transglutaminases in Human Disease Processes

Towards Understanding and Modulating Transglutaminases in Human Diseases

JUNE 17-22, 2018 • LES DIABLERETS CONFERENCE CENTER, LES DIABLERETS, SWITZERLAND

CHAIR: Mari T. Kaartinen
VICE CHAIR: Jeffrey Keillor

- **Keynote Session: Towards Understanding and Modulating Transglutaminases in Human Diseases** *Kapil Mehta,* Laszlo Fesus, Martin Griffin
- **Modulators and Medicinal Chemistry of Transglutaminases** *Soo-Youl Kim,* Ralf Pasternack, Reik Loeser, Jeffrey Keillor, Jong Bae Park
- **Transglutaminases in Neurological Diseases** *Micha Wilhelmus,* Chris Proschel, Katsura Takano, Manuela Basso
- **Activation and Substrates of Transglutaminases** *Kiyotaka Hitomi,* Claus-Werner Franzke, Henning Wiegmann, Hideki Tatsukawa, Shun Kawabata
- **Transglutaminases in Inflammatory Diseases** *Zsuzsa Szondy,* Yang Xia, Anne-Marie Van Dam, Zoltan Balajthy
- **Transglutaminases in Hemostasis and Cardiovascular Diseases** *Verena Schroeder,* Alisa Wolberg, Cora Beckers, Robert Arĺns, Nikolaos Frangogiannis
- **Transglutaminases in Tissue Remodeling, Fibrosis and Scarring** *Timothy Johnson,* Patricia Sime, Elisabetta Verderio, Laszlo Muszbek
- **Transglutaminases in Cancer** *Richard Eckert,* Nami McCarty, Daniela Matei, Francoise Dantzer
- **Transglutaminases in Gluten-Related Disorders** *Ludvig Sollid,* Marios Hadjivassiliou, Fleur DuPre, Kapil Mehta

GRS Transglutaminases in Human Disease Processes
Understanding the Role of Transglutaminases in Health and Disease: Recent Discoveries and Technological Advances
JUNE 16-17, 2018
CHAIRS: Magdalena Adamczyk & Huifang Sun

Tribology

Progress in Tribology at the Interface Between Disciplines

JUNE 24-29, 2018 • BATES COLLEGE, LEWISTON, ME

CHAIR: Ashlie Martini
VICE CHAIR: Julien Fontaine

- **Tribochemistry: Understanding Shear-Driven Chemical Reactions** *Marina Ruths,* James Batteas, Seong Kim
- **Industrial Perspectives: Relevance of Tribology to Current and Future Industrial Trends** *Sophie Loehle,* Aaron Greco, Peter Jacobs, Naruhiko Inayoshi

- **Electronic Effects: Understanding and Using Electronic Effects to Control Friction** *Lars Pastewka,* Jacqueline Krim, Andrew Rappe
- **Lubricants and Lubrication** *Bart Raeymaekers,* Philippe Vergne, Gary Doll, Lelia Cosimbescu
- **Earthquake Tribology, Young Investigator Presentations** *Philip Egberts,* Chris Marone
- **In Situ Methods: Looking Inside Contact and Shear Processes** *Erin Flater,* Fabrice Dassenoy, Hiroyuki Fujita, Tevis Jacobs
- **Surface Reactions: Chemical Reactions Occurring on and Within Surfaces During Sliding** *Filippo Mangolini,* Gianpietro Moras, Kathryn Wahl
- **Materials Matter: Friction and Wear Across the Scales and Material Dimensionality** *Alison Dunn,* Brandon Krick, Qunyang Li, Elisa Riedo
- **Keynote Session: Tribology of Elastomers** *Julien Fontaine,* Chris Dimitriou

Tribology
Progress in Tribology at the Interface Between Disciplines
JUNE 23-24, 2018
CHAIRS: Harmandeep S. Khare & Meagan Elinski

Two Dimensional Electronics Beyond Graphene

Properties and Applications of 2D Materials and Heterostructures

JUNE 3-8, 2018 • STONEHILL COLLEGE, EASTON, MA
CHAIRS: James Hone & Ji-Woong Park
VICE CHAIRS: Xiaodong Xu & Deji Akinwande

- **Synthesis of 2D Materials** *Jing Kong,* Zheng Liu, Manish Chhowalla
- **2D Heterostructure Assembly** *Jeehwan Kim,* Kibum Kang, Rebeca Ribeiro-Palau
- **Optoelectronics and Valleytronics** *Xiangfeng Duan,* Jie Shan, Xiaoyang Zhu, Wang Yao
- **Quantum and Nonlinear Optics** *Ji-Woong Park,* Mete Atature, Dmitri Basov
- **Spintronics and Magnets** *Daniel Ralph,* Michael McGuire, Zhihong Chen
- **Modeling Grand Challenges** *David Tomanek,* Efthimios Kaxiras, Evan Reed
- **Complex Phenomena** *Marco Polini,* Philip Kim, Eugene Mele, Michael Crommie
- **Integrated Devices and Applications** *Seong-Jun Park,* Frank Koppens, Tomas Palacios, Nanshu Lu, Cinzia Casiraghi
- **2D to 3D** *SungWoo Nam,* Paul McEuen

Unifying Ecology Across Scales

Diverse Structures and Hidden Meanings: Synthesizing Information, Energy and Matter to Understand Ecology of a Changing World

JULY 22-27, 2018 • UNIVERSITY OF NEW ENGLAND, BIDDEFORD, ME
CHAIR: Mary I. O'Connor
VICE CHAIR: Angelica Gonzalez

- **Keynote Session: Ecology: Toward an Integrated Science of Information, Energy and Matter** *Melanie Moses,* James Gillooly, Jessica Flack
- **Influences of Behavior, Cognition and Signaling on Evolutionary Outcomes and Ecosystem Functions** *Alexei Sharov,* Renee Duckworth, Andy Sih
- **Metabolic Constraints on Flows of Energy, Information and Matter Across Scales** *Nick Dulvy,* James Brown, Geoffrey West
- **Species Interactions and Food Web Modules as Nodes of Information, Energy and Material Flows** *Joey Bernhardt,* John Delong, Ulrich Brose, José Montoya, Bailey McMeans
- **Stoichiometric Constraints on Evolutionary Outcomes and Ecosystem Function** *Seeta Sistla,* Angie Peace, Helmut Hillebrand

"I volunteered to Chair a GRC because from my first GRC I was hooked on the format and I wanted to contribute to keep this successful meeting going."

DR. JUERGEN HENNIG
In Vivo Magnetic Resonance GRC

- **Biodiversity Across Scales of Biological Organization** *Volker Rudolf,* Colleen Webb, Dustin Marshall, Leticia Aviles
- **Animal Movement as a Driver of Flows of Information, Energy and Material Across Scales** *Anthony Dell,* Andrew Hein, Samraat Pawar, Erin Mordecai
- **Genes to Ecosystems: Information Across Scales of Life** *Art Woods,* Sarah Imari Walker, Matthew Pennell, Robert Ulanowicz, John Harte
- **Keynote Session: Meeting Grand Challenges with a Unified Ecological Science** *Van Savage,* Andrew Gonzalez, Sally Goerner, Angelica Gonzalez
- **Power Hour** *Joey Bernhardt*

Unifying Ecology Across Scales
Unifying Ecology Across Scales Based on Individuals, Currencies or Data
JULY 21-22, 2018
CHAIRS: Julie Messier & Diego Barneche

NEW! Venom Evolution, Function and Biomedical Applications

Evolution and Function of Venom Arsenals

AUGUST 5-10, 2018 • MOUNT SNOW, WEST DOVER, VT
CHAIRS: Mandë Holford & Raymond Norton
VICE CHAIRS: Marymegan Daly & Glenn King

- **Keynote Session: Venom to Drugs** *Yvonne Angell,* Richard Lewis, Baldomero Olivera
- **Venom Evolution** *Ron Jenner,* Greta Binford, Nicholas Casewell, Ashlee Rowe
- **Next-Generation Methods for Investigating Venom Components** *Juan Calvete,* Adam Claridge-Chang, Beatrix Uerberheide
- **Venom and Channels** *Michel Lazdunski,* David Julius, Jan Tytgat, Simone Weyand
- **Late-Breaking Topics** *Lauren Esposito*
- **Characterizing Venom Compounds** *Les Miranda,* Ren Lai, Yehu Moran, Irina Vetter
- **Modeling and Docking Venom Peptides** *Helena Safavi-Hemami,* Gauray Bhardwaj, Changlin Tian
- **Venom Diversity and Ecology** *Maria Modica,* Philippe Bouchet, Adam Reitzel, Ricardo Rodriguez de la Vega
- **Keynote Session: New Ground in Venom Research** *R. Manjunatha Kini,* Denise Tambourgi, Glenn King

Vibrational Spectroscopy

Molecular Probes of Structure, Dynamics and Function

JULY 29 – AUGUST 3, 2018 • UNIVERSITY OF NEW ENGLAND, BIDDEFORD, ME
CHAIRS: Andrew Orr-Ewing & Nien-Hui Ge
VICE CHAIRS: Lauren Webb & Aaron M. Massari

- **Applications of Vibrational Spectroscopy in Materials and Energy Conversion** *Jessica Anna,* Tanja Cuk, Zefeng Ren, Poul Petersen
- **Probing Biological Systems with Vibrational Spectroscopy** *Judy Kim, Matthew Tucker,* Jens Bredenbeck, Karin Hauser, Feng Gai, Megan Thielges
- **Theory and Simulation of Vibrational Spectra and Dynamics** *Victor Batista,* Akihiro Morita, Ryan Steele, Anne McCoy
- **Spatially Resolved Vibrational Spectroscopy** *Carlos Baiz, Renee Frontiera,* Ara Apkarian, Gilbert Walker, Bin Ren, Andrew Crowther
- **Atmospheric and Analytical Applications of Vibrational Spectroscopy** *Mitchio Okumura,* Gerard Wysocki, Christa Fittschen, Nathalie Picque
- **Vibrational Spectroscopy and Dynamics of Gas-Phase Molecules** *Etienne Garand, Yunjie Xu,* Thomas Rizzo, Anouk Rijs, Richard Saykally, David Plusquellic
- **Probing Structure and Dynamics at Interfaces with Vibrational Spectroscopy** *Luis Velarde,* Tahei Tahara, Wei Xiong, Mary Jane Shultz
- **Vibrational Probes of Structure and Dynamics in Solution** *Amanda Case, Christopher Cheatum,* Amber Krummel, Peter Hamm, Minhaeng Cho, Sean Garrett-Roe
- **Vibrational Spectroscopy of Molecular Clusters** *Mark Johnson,* Knut Asmis, Jana Roithova, Mischa Bonn
- **Power Hour** *Judy Kim*

Vibrational Spectroscopy
Chemical Structure, Dynamics and Reactivity Resolved with Molecular Vibrations
JULY 28-29, 2018
CHAIRS: Layla N. Qasim & James D. Gaynor

Visual System Development

Genetics, Genomics and Evolution of the Eye

MAY 20-25, 2018 • RENAISSANCE TUSCANY IL CIOCCO, LUCCA (BARGA), ITALY
CHAIR: Graeme Mardon
VICE CHAIR: Seth Blackshaw

- **Keynote Session: Corneal Stem Cells and Neuronal Circuits** *Graeme Mardon, Seth Blackshaw,* Rachel Wong, Julie Daniels
- **From Retinal Patterning to Cell Fate Specification** *Muriel Perron,* Nadean Brown, Kristen Kwan, James Fadool, Ruth Johnson
- **Axonal Guidance and Synaptogenesis** *Iris Salecker,* Peter Robin Hiesinger, Alex Kolodkin, Carol Mason, Andrew Huberman
- **Central Visual System Development** *Marek Mlodzik,* Herwig Baier, Michael Crair, Elly Nedivi, Alain Prochiantz
- **Retinal Regeneration** *Katia Del Rio-Tsonis,* Zhigang He, Valerie Wallace, David Hyde, Muriel Perron
- **Non-Neuronal Development** *Ruth Ashery-Padan,* Adi Inbal, Hisato Kondoh, Peter Lwigale
- **Genomics of Visual System Development** *Rui Chen,* Stein Aerts, Ruth Ashery-Padan, Shiming Chen, Michael Dyer
- **Unconventional Photoreceptors** *Andrew Huberman,* Ethan Buhr, Anna Matynia, Harold Burgess
- **Emerging Model Systems** *Markus Friedrich,* Robert Johnston, Kristin Tessmar-Raible, Bret Pearson
- **Power Hour** *Ruth Johnson*

Visual System Development
Development of the Visual System: Cells, Circuits and Disease
MAY 19-20, 2018
CHAIRS: Revathi Balasubramanian & Philip A. Ruzycki

Water and Aqueous Solutions

Water: Driving Life, Medicine, Energy and Environment

JULY 22-27, 2018 • HOLDERNESS SCHOOL, HOLDERNESS, NH
CHAIR: Alenka Luzar
VICE CHAIR: Mary Jane Shultz

- **Water Hydrogen Bond Dynamics** *James Skinner, Martina Havenith,* Richard Saykally, David Manolopoulos
- **Water at Electrified Interfaces and Electrochemical Energy Storage** *Adam Willard, Maria Fernandez-Serra,* Michiel Sprik, Frieder Mugele, Veronica Augustyn
- **Hydrophobic Gating and Interaction** *Lawrence Pratt, William Ducker,* Zuzanna Siwy, Uri Sivan
- **Water in the Environment** *Pablo Debenedetti, Francesco Paesani,* Thomas Koop, Werner Kuhs, Douwe Bonthuis
- **Water with Ionic Liquids and Electrolytes** *John Weeks, Gregory Schenter,* Markus Valtiner, Peter Hamm
- **Water in Materials and Biomimetic Design** *Susan Rempe, Amish Patel,* David Quere, Lyderic Bocquet, Baoxia Mi,
- **Water and Origin of Life, Late-Breaking Topics** *Pavel Jungwirth, Daniela Russo,* Ali Hassanali
- **Water in Biological Systems and Medicine** *Peter Rossky, Toshiko Ichiye,* Songi Han, Pratyush Tiwary, Sean Sun
- **Keynote Session: Fifty Years of Water Research: Future Challenges / Young Investigator Presentations** *Shekhar Garde, Nancy Levinger,* John Finney
- **Power Hour** *Valeria Molinero, Sapna Sarupria*

Water and Aqueous Solutions
Towards a Unified View of Water: Marrying Theoretical and Experimental Results for the Structure and Dynamics of Complex Aqueous Systems
JULY 21-22, 2018
CHAIRS: Eva Pluharova & Grayson L. Jackson

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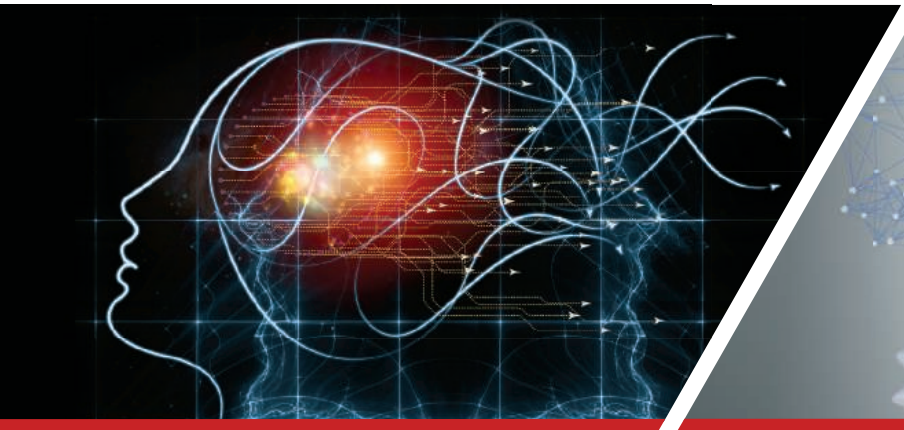

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Dean of the Faculty of Science

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The University now invites applications and nominations of qualified candidates for the Deanship of the Faculty. The Dean will be a member of the University senior management team, reporting to the University Council via the Vice-Chancellor/President or the Provost. As the academic and executive head of the Faculty, the Dean will provide academic leadership and discharge administrative responsibilities in respect of academic, staff, resource (budget and space) as well as student matters. He/she will also actively engage in alumni and community relations and in extending networks.

Candidates should have an excellent academic standing appropriate for appointment at the level of a full Professor in the Faculty. They should have an appreciation of the breadth of research/educational developments in the relevant fields and the range of intellectual interests represented in the Faculty, demonstrated capability of academic leadership and strategic management in higher education institutions, a long-term vision for the development of the Faculty, and excellent interpersonal and communication skills.

Salary and fringe benefits for the post will be highly competitive, commensurate with qualifications and experience.

Please send applications/nominations under confidential cover to the Search Committee for the Dean of the Faculty of Science, c/o Secretary, Search Committee for the Appointment of the Dean of the Faculty of Science, Personnel Office, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong [fax: (852) 3942 0947; e-mail: SCDeanship-Sc@cuhk.edu.hk]. All applications/nominations will be treated in strict confidence. The University's Personal Information Collection Statement will be provided upon request. Those who have responded to the previous advertisement for the same post need not re-apply in this instance.

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Faculty Position in Immunology
Department of Microbiology-Immunology

The Department of Microbiology-Immunology, Northwestern University Feinberg School of Medicine, invites applications for a tenure-track position at the Assistant, Associate or Full Professor level within the broad field of immunology. ALL areas of immunology are of interest. Applicants in the fields of mucosal immunity, autoimmunity, cancer immunology, transplantation, and infectious disease are encouraged to apply.

Applicants are expected to have a Ph.D., M.D., or equivalent degree as well as postdoctoral training. The successful candidate will be expected to establish and maintain a vigorous, extramurally funded research program and to participate in our strong graduate and medical student training programs. All applicants should have substantial peer-reviewed publications that demonstrate productivity and the ability to perform cutting edge research. Candidates for an Assistant Professor position should have current or pending external funding, which could include an NIH K level award. Candidates at the Associate Professor or Full Professor level should have substantial research productivity, current grant support and academic service. The primary criteria for selection will be excellence and creativity in research and scholarship. We offer a highly interactive collegial research environment with state-of-the-art research facilities. Starting date is negotiable.

Application materials will be reviewed as received, but to receive full consideration, should be received by **Apri 15, 2018**. Please send a complete CV, a one page research plan along with the name and contact information of at least three references by email to:

immunologysearch@northwestern.edu.

Northwestern University is an Equal Opportunity, Affirmative Action Employer of all protected classes, including veterans and individuals with disabilities. Women, racial and ethnic minorities, individuals with disabilities, and veterans are encouraged to apply. Hiring is contingent upon eligibility to work in the United States.

RUTGERS
New Jersey Medical School

Chief, Division of Allergy, Immunology and Infectious Disease

The Department of Medicine at Rutgers Robert Wood Johnson School of Medicine in New Brunswick, New Jersey, seeks an academic-physician for the position of Chief. The desirable candidate should have a history of extramural funding in basic or translational research and demonstrable leadership qualities. She or he must also have been successful in promoting teaching, scholarship, and research, as well as developing, managing, and implementing clinical programs. Extensive collaboration opportunities are available within Rutgers University's broad range of research programs including microbiology, immunology, oncology, pharmacology and global health. A competitive salary with a generous startup package is available to support the recruitment of the Chief and additional research and clinical faculty members. Candidates must have an MD or MD/PhD degree, have achieved the position of Associate Professor or Professor, be board certified in infectious disease, and eligible for licensure in New Jersey. Applicants should submit a letter of interest and current curriculum vitae to: **Steven R. Brant, MD, Professor of Medicine, Chair of ID Chief Search Committee, via email at steven.brant@rwjms.rutgers.edu**

Rutgers, the State University of New Jersey, is an Equal Opportunity/ Affirmative Action employer, and is compliant with the Americans with Disabilities Act (ADA). For more information, please visit http://recruitment.rutgers.edu/TheRUCommitment.htm. Women and minorities are encouraged to apply.

PRIZES

The 2018 (34th) International Prize for Biology

Calling for Nominations

This year's research field:

Paleontology

Please access at: **http://www.jsps.go.jp/english/e-biol**

Deadline: April 20, 2018

- The International Prize for Biology was established in 1985 to commemorate the 60-year reign of Emperor Showa and his longtime devotion to biological research.
- The Prize is awarded each year to an individual who has made an outstanding contribution to the advancement of basic research in a field of biology.
- The Prize shall consist of a medal and a prize of 10 million yen.

Recent Years Prize Winners

2017
Dr. Rita R. Colwell
(Marine Biology)

2016
Dr. Stephen P. Hubbell
(Biology of Biodiversity)

2015
Dr. Yoshinori Ohsumi
(Cell Biology)

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مـؤسسة الـكويت للـتقدم الـعلمي
Kuwait Foundation for the Advancement of Sciences

KUWAIT PRIZE 2018
Invitation for Nominations

The Kuwait Foundation for the Advancement of Sciences invites Universities, Scientific and Research Institutions and individuals (see items 3 and 4 below) to submit nominations of Kuwaiti and Arab scientists for the 2018 cycle of the Kuwait Prize.

The four fields for 2018 cycle of the Prize are*:

Fundamental Sciences:	Biological Sciences (including but not limited to; Cellular & Molecular Biology, Developmental Biology, Heredity and Epigenetics, Microbiology & Immunology, Comparative Proteomics).
Applied Sciences:	Clean and Sustainable Energy Technologies (including but not limited to; Renewable Sources, Hydrogen, Fuel Cells, Energy Storage Devices, Biomass and Lower Carbon-footprints Fossil Fuel).
Economics and Social Sciences:	Economics (including but not limited to; Energy Economics, Developmental Economics, Microeconomics, Macroeconomics, Econometrics .... etc.)
Arts and Literature:	Studies of Arabic Language and Literature (including but not limited to; Arabic Grammar and Linguistics, Classic and Modern Literary Studies).

KFAS awards an annual Prize cash sum of K.D. 40,000 (Approx. $135,000) for each field.

Conditions and requirements:

1 - The nominee must be from an Arab nationality and have a proof of Arabic origin; either an Arabic birth certificate or a valid Arabic passport. A copy of the birth certificate or passport should be attached along with the submitted application.
2 - The work submitted should be innovative, significant in the announced field, and published during the past twenty years. Submitted work includes papers published or accepted for publication in refereed Journals and books with ISSN number (authored, translated, edited, and chapters in books). MA or PhD theses and any publications extracted from them shall not be evaluated as part of the nominee's scientific work.
3 - KFAS will consider nominations from universities, academic and research institutions, scientific centers, former laureates of the prizes and peers of the nominees.
4 - KFAS will accept self-nominations. To support self-nominations, nominees should provide a list of five references: four academics/ researchers and one scientific institution. KFAS will seek out support letters from three of these references. (two academics and the scientific institution) .
5 - KFAS decisions concerning the prizes are final and objections are not accepted.
6 - Nominees must fill in the prize nomination form and send it along with the submitted work electronically. The nomination form is obtained from KFAS website www.kfas.org. The nomination form for **Fundamental Sciences and Applied Sciences Fields** should be submitted in English version.
7 - The nomination form along with the comprehensive scientific achievements completed in the past twenty years should be sent in PDF format, through the cloud storage services sites such as **(Google Drive–Dropbox–OneDrive)** or via Prizes email: prize@kfas.org.kw
8 - Required documents must be sent no later than **end of June 2018**

For more information and inquiries please, contact the Prizes Office on the following: Tel: +965-22270465 Fax: +965-22270462 or E-Mail: prize@kfas.org.kw

*Topics of the fields are subject to change annually.

By **Rebecca M. Calisi**

Got milk, must conference

I sat huddled over my laptop in a cramped stall of a smelly public restroom, making last-minute changes to my upcoming talk. The whoosh-whoosh of the battery-powered breast pump attached to my hands-free nursing bra accompanied my typing. A toilet flushed in the next stall. It had been 15 minutes and I had barely pumped 2 ounces of milk, less than a third of what I had hoped. I had 10 more minutes before I would have to run to make the start of the conference session in which I was due to speak. To get my milk flowing, I thought of my 5-week-old baby at home and tried to relax, willing the milk to come out now instead of in the middle of my talk.

I had wanted so badly to bring my chubby, cooing baby with me, even though I knew that managing breastfeeding and a baby at a conference would not be easy. But I worried about the cost, the lack of social support, and the prospect that senior colleagues wouldn't take me seriously if they saw me with a baby. So I set out on my own. I needed a job. I needed to be seen. I needed to maintain relationships with collaborators and make new contacts. And I needed to feel like motherhood wasn't derailing my career.

I tried to ignore the painful pinch coming from my emergency C-section incision which, now red and warm to the touch, was no doubt infected. Fearful of how a hole in my CV would look come tenure time, I had pushed myself to return to work as quickly as I could, probably compromising my immune system in the process. I opened the growing to-do list on my laptop and typed, "schedule appt with MD." Another toilet flushed. Stressed, sick, and exhausted, I wiped away a tear and gritted my teeth in defiance.

Finally out of the bathroom stall, I set frantically to work rinsing off my many breast pump accoutrements in one of the scummy restroom sinks, waving my hand under the motion sensor to keep the water flowing. I threw my bulky pump carrying case over one shoulder, the clunky cooler of breast milk over the other shoulder, and my laptop case diagonally over my body, then grabbed my conference tote bag. I shuffled out of the bathroom sideways to fit through the door and booked it to the presentation room.

"Couldn't attending a conference be easier for a working mother?" I thought. Providing refrigeration space to store expressed milk as well as lockers or cubbies for pumps would literally have been a weight off my back—and I wouldn't have felt so much like the Junk Lady from the movie *Labyrinth*. But, like so many new moms trying to make it in science, I was scared to voice my needs for fear of retribution.

"We need more allies ... to advocate for resources to help level the playing field."

That was years ago. I've attended many conferences since then as I've progressed in my academic career. In some cases, I see the situation slowly changing for the better, but there's still lots of room to improve. This past November, I attended a meeting of more than 30,000 people where only three pop-up curtain areas were made available for lactation and child care. In each one sat a small, uncomfortable chair; a changing table; and some electrical outlets. To argue that this is better than nothing is akin to arguing that, despite a hostile work environment, women should be grateful that they are allowed to work in the first place. Nursing and child care, most often provided by women, are not a luxury; they are a biological necessity.

Now that I am more secure in my faculty position and supported by a university that truly values diversity, I feel empowered to speak out for those who hesitate to do so. The face of academia is changing, and we need more allies—not just mothers—to advocate for resources to help level the playing field. By engaging in efforts to help normalize pregnancy, lactation, and child care, we can come closer to creating a culture of equity and inclusion that benefits everyone. ■

Rebecca M. Calisi is an assistant professor at the University of California, Davis. Do you have an interesting career story? Send it to SciCareerEditor@aaas.org.

ILLUSTRATION: ROBERT NEUBECKER