Breakthrough Online
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Breakthrough

#1 The Winner

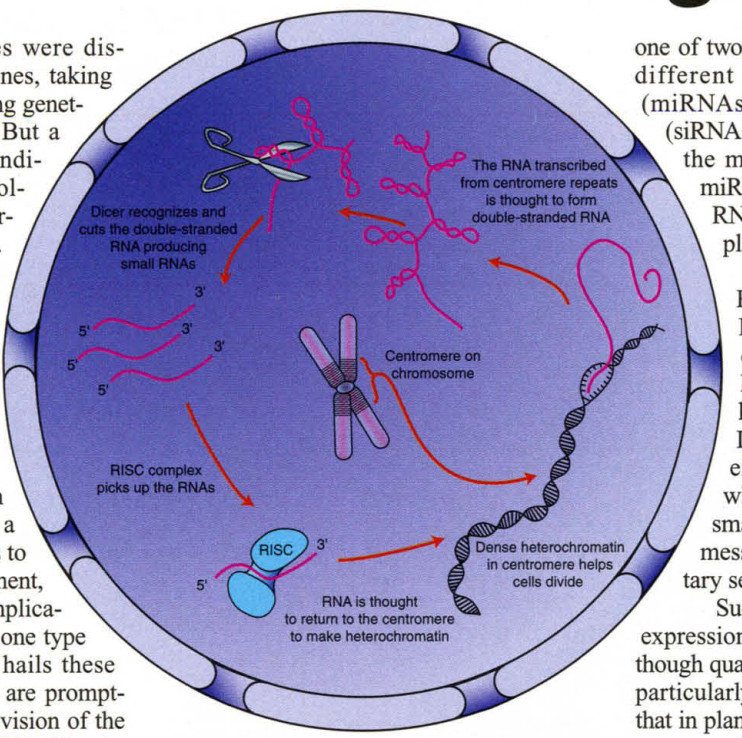
Just when scientists thought they had deciphered the roles played by the cell's leading actors, a familiar performer has turned up in a stunning variety of guises. RNA, long upstaged by its more glamorous sibling, DNA, is turning out to have star qualities of its own.

Small RNAs Make Big Splash

For decades, RNA molecules were dismissed as little more than drones, taking orders from DNA and converting genetic information into proteins. But a string of recent discoveries indicates that a class of RNA molecules called small RNAs operate many of the cell's controls. They can turn the tables on DNA, shutting down genes or altering their levels of expression. Remarkably, in some species, truncated RNA molecules literally shape genomes, carving out chunks to keep and discarding others. There are even hints that certain small RNAs might help chart a cell's destiny by directing genes to turn on or off during development, which could have profound implications for coaxing cells to form one type of tissue or another. *Science* hails these electrifying discoveries, which are prompting biologists to overhaul their vision of the cell and its evolution, as 2002's Breakthrough of the Year.

These astonishing feats are performed by short stretches of RNA ranging in length from 21 to 28 nucleotides. Their role had gone unnoticed until recently, in part because researchers, focused on the familiar larger RNA molecules, tossed out the crucial small ones during experiments. As a result, RNA has long been viewed primarily as an essential but rather dull molecule that ferries the genetic code from the nucleus to the ribosomes, the cell's protein factories, and helps assemble amino acids in the correct order during protein synthesis.

Signs that RNA might be more versatile came in the early 1990s, when biologists determined that some small RNAs could quash the expression of various genes in plant and, later, animal cells. But they didn't appreciate the molecules' true powers until 1998. That's when Andrew Fire of the Carnegie Institution of Washington in Baltimore, Maryland, Craig Mello of the University of Massachusetts Medical School in Worcester, and



Life cycle. With a helping hand from proteins RISC and Dicer, small RNAs are born. We now know that these molecules keep DNA in line and ensure a cell's good health.

their colleagues injected stretches of double-stranded RNA into worms. Double-stranded RNA forms when a familiar single strand kinks back in a hairpin bend, putting two complementary sequences alongside each other. To the researchers' surprise, double-stranded RNA dramatically inhibited genes that had helped generate the RNA in the first place. This inhibition, which was later seen in flies and other organisms, came to be known as RNA interference (RNAi). It helped prove that RNA molecules were behind some gene silencing.

Another crucial step came last year, when Gregory Hannon of Cold Spring Harbor Laboratory in New York and his colleagues identified an enzyme, appropriately dubbed Dicer, that generates the small RNA molecules by chopping double-stranded RNA into little pieces. These bits belong to one of two small RNA classes produced by different types of genes: microRNAs (miRNAs) and small interfering RNAs (siRNAs). SiRNAs are considered to be the main players in RNAi, although miRNAs, which inhibit translation of RNA into protein, were recently implicated in this machinery as well.

To bring about RNAi, small RNAs degrade the messenger RNA that transports a DNA sequence to the ribosome. Exactly how this degradation occurs isn't known, but scientists believe that Dicer delivers small RNAs to an enzyme complex called RISC, which uses the sequence in the small RNAs to identify and degrade messenger RNAs with a complementary sequence.

Such degradation ratchets down the expression of the gene into a protein. Although quashing expression might not sound particularly useful, biologists now believe that in plants, RNAi acts like a genome "immune system," protecting against harmful DNA or viruses that could disrupt the genome. Similar hints were unearthed in animals this year. In labs studying gene function, RNAi is now commonly used in place of gene "knockouts": Rather than delete a gene, a laborious process, double-stranded RNA is applied to ramp down its expression.

The year's most stunning revelations emerged in the fall, in four papers examining how RNA interference helps pilot a peculiar—and pervasive—genetic phenomenon known as epigenetics. Epigenetics refers to changes in gene expression that persist across at least one generation but are not caused by changes in the DNA code.

In recent years, researchers have found that one type of epigenetic regulation is caused by adjustments in the shape of complexes known as chromatin, the bundles of DNA and certain fundamental proteins that make up the chromosomes. By changing shape—becoming either more or less compact—chromatin can alter which genes are expressed. But what prompts this shape-

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New roles for RNAs

Breakthrough of the Year

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of the Year

shifting remained mysterious.

This year, scientists peering closely at RNAi in two different organisms were startled to find that small RNAs responsible for RNAi wield tremendous control over chromatin's form. In so doing, they can permanently shut down or delete sections of DNA by mechanisms not well understood, rather than just silencing them temporarily.

That news came from several independent groups. In one case, Shiv Grewal, Robert Martienssen, and their colleagues at Cold Spring Harbor Laboratory compared fission yeast cells lacking RNAi machinery with normal cells. When yeast cells divide, their chromosomes untangle and migrate to opposite sides of the cell. The researchers already knew, broadly, that this chapter of cell division is governed by a tightly wrapped bundle of chromatin, called heterochromatin, around the centromere—the DNA region at the chromosome's "waist." The biologists found that their mutant cells, which were missing the usual small RNAs, couldn't properly form heterochromatin at their centromeres and at another DNA region in yeast that controls mating. This suggests that without small RNAs, cell division goes awry. The scientists theorized that in healthy yeast cells, small RNAs elbow their way into cell division, somehow nudging heterochromatin into position to do the job. That exposes DNA to different proteins and dampens gene expression.

Meanwhile, David Allis and his colleagues at the University of Virginia Health System in Charlottesville, along with Martin Gorovsky of the University of Rochester in New York and others, were focusing on a different organism, a single-celled ciliate called *Tetrahymena*. Biologists treasure *Tetrahymena* because it stores the DNA passed to offspring in a different nucleus from the one containing DNA expressed during its lifetime, making it easy to distinguish one gene set from the other. The researchers found that in *Tetrahymena*, small RNAs trigger deletion or reshuffling of some DNA sequences as a cell divides. RNAi appeared to be targeting structures analogous to heterochromatin, only this time strips of DNA were discarded or moved elsewhere. The mechanism remains unclear, however.

The two sets of experiments might help explain why small RNAs exist in the first place. In both the yeast and *Tetrahymena*, small RNAs' frenetic activity is focused on genome regions, such as centromeres, that contain repetitive DNA resulting from transposons. Transposons are bits of DNA that can jump around the genome and insert themselves at different locales; at times, they jam transcription machinery and cause disease. It appears possible—although still largely hypothetical—that small RNAs evolved very early in life's history to help protect the genome against instability.

This is just one of many areas that remain to be explored. Researchers are still trying to sort out how the well over 100 different miRNAs function and which species contain which ones. There are hints that they behave differently in plants and animals. And some recent work suggests that miRNAs exert more control over gene expression than previously believed. Also a focus of research are the proteins, such as Dicer, that are critical cogs in the RNAi machinery.

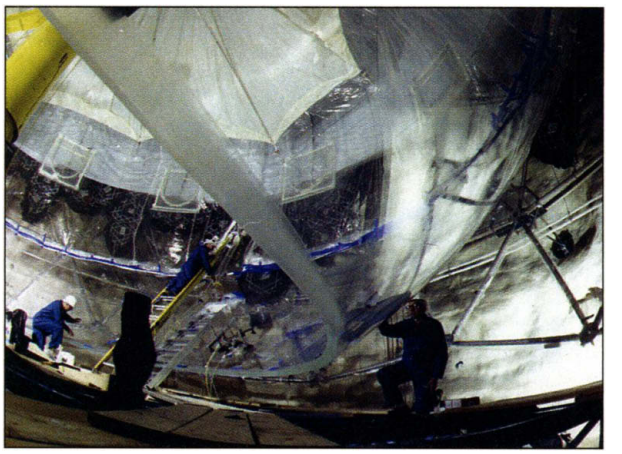
Researchers are also probing RNAi's possible role in development and disease. RNAi has been implicated in guiding meristems, the plant version of stem cells, so some biologists believe that it might help establish the path taken by human and other mammalian stem cells as they differentiate into certain tissues. If so, RNAi could prove an essential tool in manipulating stem cells. And if small RNAs influence cell division in humans as they do in yeast and *Tetrahymena*, minor disruptions in the machinery could lead to cancer.

The extraordinary, although still unfulfilled, promise of small RNAs and RNAi has split the field wide open and put RNA at center stage. Having exposed RNAs' hidden talents, scientists now hope to put them to work. **–JENNIFER COUZIN**

THE RUNNERS–UP

Science applauds discoveries ranging from the dawn of time to the dawn of our species.

#2 Neutrinos nailed. Neutrinos, mysterious and misunderstood, are finally getting the respect they deserve. For years, neutrinos were the terra incognita on the particle chart. Electrons, muons, taus, and quarks had all been analyzed for years, their properties measured and dissected. But neutrinos? Nobody knew even whether they had mass until a few years ago. They were essentially unknowns.



Positive ID. A huge sphere of heavy water caught fugitive neutrinos as they changed from one flavor to another.

CREDIT: SNO

No longer. In the last decade, physicists finally proved that neutrinos have mass, and since then, a flurry of experiments has begun to flesh out the elusive neutrinos' properties.

This year, the Sudbury Neutrino Observatory (SNO), a 1000-ton sphere of heavy water deep inside a nickel mine in Sudbury, Ontario, put the final nail in the coffin of the solar neutrino paradox. The nuclear reactions in the sun should produce a large number of electron neutrinos, but all observations had shown that only about one-third of the expected number were actually reaching Earth.

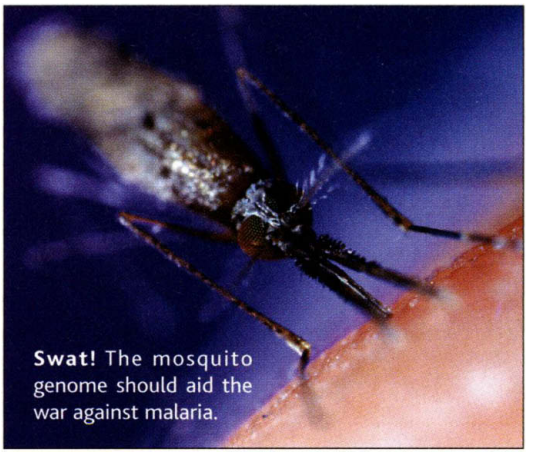
If neutrinos have mass, they can change flavors—from electron neutrinos into tau or mu neutrinos, for example—and that could explain the missing electron neutrinos. SNO showed, once and for all, that this is the case. In April, scientists at SNO announced that they had measured the abundances of all three types of neutrinos—electron, mu, and tau—by detecting when they split apart atoms of deuterium. When they added up the solar electron, mu, and tau neutrinos streaming through the detector, the total matched the number that should be created by nuclear reactions. Electron neutrinos change flavor during their journey to Earth.

As a bonus, the SNO measurements allowed scientists to drastically limit the "mixing angles" that define the neutrinos' flavor-changing abilities and, in December, the KamLAND experiment in Japan restricted the limits even further—with nuclear reactor–created antineutrinos instead of solar neutrinos. Although physicists still don't know how much neutrinos weigh, the evanescent

beasties are no longer blank spots on the particle chart.

#3 Genomes head south. This year's DNA sequencing efforts should prove to be a boon for the developing world. Two international consortia took a stab at malaria—which kills 3 million people a year, primarily in tropical Africa—by deciphering the genome sequences of both the parasite and the mosquito responsible for transmitting most of the deadliest cases. With a highly organized draft of 278 million bases of the mosquito *Anopheles gambiae* genome and the genome sequence of the parasite *Plasmodium falciparum* now in hand, biomedical researchers hope to find better ways to fight this devastating tropical disease.

Developing countries should also benefit from rapid progress toward sequencing the rice genome. In April, a private company and a Chinese group independently published



Swat! The mosquito genome should aid the war against malaria.

draft sequences of the *japonica* and *indica* rice strains consumed in Japan and China, respectively. Just this week, the International Rice Genome Sequencing Project released a more highly polished draft sequence of *japonica*, two chromosomes of which are now published. Originally, this publicly funded effort planned to finish the sequence by 2008, but two companies have made their sequences available to the international group, allowing it to move up the target date for completing the work to 2005.

This past year, sequencers got detailed looks at several other large genome sequences as well. A U.S.-British team has completed and analyzed a high-quality draft sequence of the mouse genome; a U.S. public-private partnership has assembled a draft for the rat. Nailing these two genome sequences will cover two of the most important research animals. Researchers now know the order of the DNA bases in the genome of the Japanese puffer fish, which has the smallest known genome of all vertebrates. The DNA of two tunicates—sessile invertebrates with vertebrate-like larvae—has

Areas to Watch in 2003

Science's editors use their powers of prognostication to come up with next year's hot research topics.

Whither the ice? Glaciologists are scrambling to sort out which of the world's ice houses may be about to empty themselves under the onslaught of greenhouse warming. Mountain glaciers are clearly receding, and high-mountain tropical glaciers could soon disappear. But the behavior of the great ice stores of Greenland, Antarctica, and West Antarctica is proving more subtle. Satellite-borne radar and other new geophysical tools will be monitoring the comings and goings of ice in these constantly shifting sheets, providing a better understanding of what our warmer future holds.

A sun-climate connection. As more and more wiggles matching the waxing and waning of the sun show up in records of past climate, researchers are grudgingly taking the sun seriously as a factor in climate change. They have included solar variability in their simulations of the past century's warming. And the sun seems to have played a pivotal role in triggering droughts and cold snaps. To gain complete respectability, sun-climate researchers are working to identify the physical link between relatively feeble solar fluctuations and climate. A leading candidate: solar-modulated cosmic rays and their effects on clouds.

Budget bust. Will 2002 be remembered as the year the good times ended? That's likely to be a little too dire, but it's a growing worry among scientists in developed nations, as a slumping world economy could dramatically slow the growth of government and private spending on basic science. Italy, Germany, and France are already facing cuts or freezes in government spending. In the United States, cratering stock prices have shrunk university and foundation endowments by one-third or more. The White House has already signaled that it won't support continued double-digit increases for biomedical research spending. And war with Iraq could quash growing hopes of doubling taxpayer outlays on the physical sciences. But there is a bright side: Low interest rates are allowing stretched institutions to keep many lab construction projects on track.

R-evolutionary genomics. With genome sequences for most of the major microbial groups in hand and ever more DNA of complex organisms being deciphered, researchers expect to be able to make better sense of life's many evolutionary relationships. Meanwhile, studies of human genetic variation will continue to shed light on our deep past, and the chimp genome project may begin to reveal what makes us human.

A different light. Several satellites tuned to wavelengths outside the glamorous optical band should shine in 2003. The European Space Agency's Integral mission, launched in October, will soon observe gamma rays from black holes, supernovas, and other scenes of violence, and NASA's Swift explorer will start tracking gamma ray bursts by December. The Space Infrared Telescope Facility, slated for launch in April, will examine the heat from distant galaxies and dusty clouds where stars and planets form. And astronomers will get their best map of microwave ripples in the sky—a chilly imprint of the big bang—when results from the Microwave Anisotropy Probe are released early in the year.

Important matter. In 2002, two rival teams at the CERN laboratory near Geneva produced cold, slow-moving antihydrogen atoms—antielectrons orbiting antiprotons—for the first time. Antihydrogen will be a powerful tool for studying the difference between matter and antimatter, but scientists have to trap significant amounts of it before they can zap it with a laser and measure its properties. It might not happen in the coming year or even in the next, but there's no question that the game is afoot. Antihydrogen futures are brighter than ever.

CREDITS: (TOP TO BOTTOM) JAMES GATHANY/CDC; ILLUSTRATION: TERRY E. SMITH

been deciphered as well. These sequences should provide clues about how vertebrates evolved.

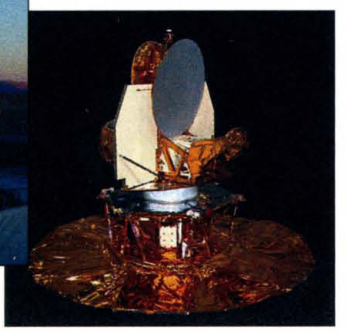
In addition, the sequences of microbial genomes keep pouring in: another strain of anthrax and a bacterium called *Shewanella*, useful for bioremediation, to name just two. And the flood of genome sequences shows no sign of abating: Work has begun on chimp, corn, and poplar. The honey bee, dog, cow, chicken, and sea urchin are supposed to be up next.

#4 Cosmic twist. Even though it's less than 3° above absolute zero, the cosmic microwave background (CMB) is very, very hot. In 2002, astronomers and physicists watched the end of the tale of the beginning of the universe.

Discovered in 1965 by Arno Penzias and Robert Wilson of Bell Laboratories in New Jersey, the CMB is the remnant of a time, 400,000 years after the big bang, when free-streaming nuclei and electrons finally cooled and formed atoms. As the electrons settled down into their orbitals, high-energy light, liberated from its cage of matter, streamed forth. Stretched and attenuated by 14 billion years of travel, the CMB appears as a faint but ubiquitous microwave static coming from all regions of the sky.

In 2000 and 2001, airborne and ground-based microwave telescopes generated exquisitely detailed pictures of fluctuations in the CMB, fluctuations that reveal not only the universe's past but its future. Not only did these fluctuations give rise to the agglomerations of galaxies that we see today, but they also revealed the "curvature" of the universe, which shows that the universe will expand forever, rather than recollapsing in a big crunch. In May, the Cosmic Background Imager (CBI), a microwave telescope high atop the Andes mountains in Chile, put an exclamation point on those observations by detecting "peaks"—characteristic patterns in the fluctuations—that revealed structures far smaller than other telescopes had yet seen. In January 2003, other physicists are expected to reveal the first results from the Microwave Anisotropy Probe (MAP), an orbiting satellite that will be the ne plus ultra of fluctuation detection until the end of the decade.

CBI



MAP

But the real CMB triumph this year was the first detection of polarization by the Degree Angular-Scale Interferometer team at the University of Chicago. The discovery of this faint signal heralds the beginning of a new chapter in CMB research—one that might reveal the state of the universe when it was a minuscule fraction of a second old by revealing the subtle scarring caused by gravitational waves during the birth of the cosmos.

#5 Fast moves. If action flicks seem to be getting faster these days, just wait. This year, laser physicists succeeded in making the first-ever movies in which individual frames were measured in attoseconds, or billionths of a billionth of a second. The new high-speed filmmaking techniques are expected to spawn a new genre of cinema devoted to tracking the motion of electrons around atoms.

Laser physicists have been refining their

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Scorecard 2002

In which we take our lumps for predictions made last year

Stem cells abroad. The raging political debates of previous years died down in 2002, as more countries settled on regulations governing work with human embryonic stem cells. The pace of headline-grabbing scientific breakthroughs has also slowed as the relatively young field works to decipher the complex mechanisms controlling cell fate—and some scientists complain that access to human embryonic stem cells is still frustratingly slow.

Proteomics. Fundamental advances in figuring out protein interactions have begun to migrate to medical and biotech applications as hoped. Proteomics companies announced this year that they had discovered novel proteins that appear to be linked to diseases such as cancer and asthma. These companies are now developing novel therapeutics to target the proteins and diagnostics capable of tracking them. Actual drug products based on proteomics have yet to emerge. But developing a new drug typically takes more than a decade. Meanwhile, basic research on mapping biologically important proteins continues. In May, the Human Proteome Organisation, a group seeking to keep proteomics from being locked up in proprietary interests, outlined five initial projects. The U.S. National Institutes of Health, meanwhile, announced an initiative in October to spend $157 million over 7 years to create 10 new proteomics centers.

Eyes on the sky. It's been a very good year for astronomical viewing. Optical systems that automatically adapt to visual conditions have come into their own (see Runner-Up item on p. 2301). Solid discoveries have been popping out of the Sloan Digital Sky Survey this year on quasars (*Science*, 28 June, p. 2317), globular clusters (*Science*, 14 June, p. 1951), and brown dwarfs (*Science*, 4 January, p. 64). And member nations of the International Virtual Observatory Alliance (www.ivoa.net) have ramped up demonstration projects linking the world's astronomical instruments.

Next in genetics. The multiple genes involved in diabetes, cancer, and other complex diseases continue to elude researchers. Some progress was made—a diabetes gene here, a Hirschsprung's disease gene there—but now geneticists are pinning their hopes for progress on the HapMap, a major multiyear undertaking to map variation in stretches of human DNA called haplotypes.

Optical clocks and constants. Last year, the future for clocks and reference standards based on high-frequency optical emissions from atoms looked bright. But the hands on the clock of progress have slowed: Translating the basic breakthroughs in optical physics to practical applications has proven harder than expected. Given the lead times in the field of metrology, the future of optical clocks may still light up in the long term.

Visualization. Powerful computing and clever imaging are combining to create better snapshots of cells and molecules. One technique, cryoelectron tomography, has yielded unprecedented views of cellular machinery (see Runner-Up item on p. 2301). New methods of fluorescent imaging produced dramatic scenes of protein translocation in single cells (*Science*, 8 March, p. 1910), and a new variant of green fluorescent protein offered a novel tool for tracking intracellular protein dynamics. And new initiatives, such as the MIT School of Engineering and Whitehead Institute's proposed center for bioimaging, are seeking to join supercomputing with state-of-the-art imaging methods.

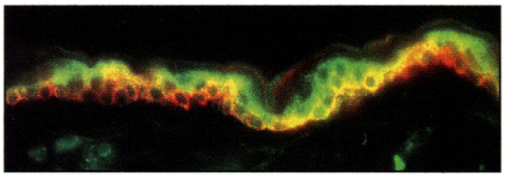
high-speed moviemaking approaches for years. But most rely on the same basic principle, using ultrashort pulses of laser light like bursts from a strobe light to freeze motion in flight. Researchers now routinely use the technique to capture the blur of molecules as they break and weld bonds in a chemical reaction, events that take place on the order of 1 to 100 femtoseconds, or 10^{-15} seconds.

Dutch and French researchers broke the attosecond barrier last year, when they trained ultrashort laser pulses on a gas of argon atoms, which in turn emitted a train of pulses, each lasting just 220 attoseconds. A team of Austrian, Canadian, and German researchers followed hard on their heels with a related technique that turned out individual 650-attosecond pulses, which are more easily used as moviemaking strobes.

This year, researchers turned their new attosecond strobes onto the action within atoms. In October, the Austrian and German members of the original team used their attosecond pulses to excite electrons in krypton atoms, each of which left behind an electron vacancy. With another laser pulse, they were then able to track the timing with which excited electrons gave up some of their energy and fell back into the more stable energy levels. It's not Hitchcock, but attosecond movies will give physicists a whole new view of life inside the atom.

#6

A taste for temperature. The heat of four-alarm chili and the coolness of spearmint chewing gum aren't just metaphorical: To some cells, taste and temperature are the same. This year, researchers tunneled into ion channels that respond to such sensations. They're tuned to warmth, minty coolness, or, in mice at least, another steamy stimulus: pheromones.



Feel the heat. Skin cells host TRP ion channels that respond to warm temperatures.

So-called transient receptor potential (TRP) ion channels are proteins that snake in and out of the cell membrane. When they're tickled appropriately, they allow calcium or other ions to surge into a cell. In neurons, this can make the cell fire off a signal to its neighbors. Mammals harbor at least 21 flavors of TRP channels, but most of their functions are unknown.

The first report that certain TRP channels promiscuously respond to either a chemical or a thermal stimulus came in 1997, with the identification of a TRP channel that gets steamed up by either hot temperatures (above 43°C) or capsaicin, the active ingredient in chili peppers. This year, a similar multitasking channel was found in nerves of the mouth and skin. It reacts when exposed to either cool temperatures (15° to 25°C) or menthol, the chemical that makes mint minty.

A warmth-sensitive (~34°C) TRP channel debuted this year as well. It is concentrated in skin cells, suggesting that the skin itself senses heat and passes the message to neurons.

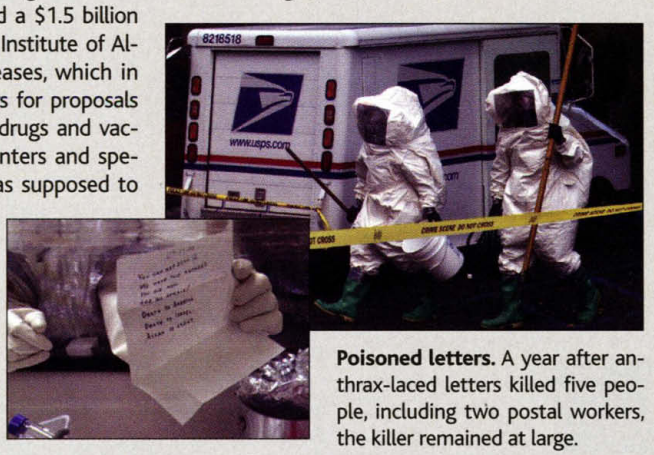
Bioterrorism: The Calm After the Storm

The 11 September terrorist attacks and the mysterious anthrax letters, mailed a few weeks later, are beginning to put their stamp on the research enterprise, especially in the United States. But although 2002 has been marked by much talk about bioterror, it has also become a year of waiting for action, with major decisions on research funding, regulation, and smallpox vaccination stalled by politics and technical debate.

Meanwhile, despite one of the most expansive investigations in FBI history and a $2 million reward, the anthrax killer is still on the loose.

Infectious-disease researchers are confident that the attacks will eventually produce a funding windfall. In his 2003 budget, President George W. Bush requested a $1.5 billion increase for the National Institute of Allergy and Infectious Diseases, which in turn has asked researchers for proposals on everything from new drugs and vaccines to new research centers and specialized labs. Congress was supposed to approve the spending by 1 October, but election-year politics has stalled any decision until at least January.

Still, the vulnerability of the United States to the ultimate bioterror nightmare—a smallpox attack—has diminished considerably. Old smallpox vaccine supplies were dusted off and proven to still work. Together with new vaccine produced by Acambis, a government contractor, there's now enough to cover the entire U.S. population. But government officials were locked in debate for months about how many people should get preemptive shots, primarily because the vaccine is known to cause severe infections and death in a small number of recipients.



Poisoned letters. A year after anthrax-laced letters killed five people, including two postal workers, the killer remained at large.

Last week, the Administration finally announced plans to start vaccinating half a million health care workers and first responders, and another half million in the military. But eventually, the vaccine will be made available to anyone who wants it—a decision that's drawing outspoken criticism from public health experts (see News Focus story).

Another topic of intense but unfinished debate is how best to balance security needs against scientific freedom. Researchers are anxious, for example, about upcoming regulations on work with potential bioweapons. Poorly written rules could lead to misguided law enforcement, they say, pointing to the case of Tomas Foral, a 26-year-old graduate student at the University of Connecticut, Storrs, who became the first researcher to be criminally charged with mishandling dangerous agents after he allegedly stored anthrax samples in a lab freezer.

Foral avoided indictment by agreeing to perform community service, but research leaders worry that the incident heralds a new, chilly era in their labs. And the National Academy of Sciences' decision to censor a "sensitive" chapter from a recent report about agricultural bioterrorism has helped spark debate about what kinds of unclassified information scientists should withhold from the public in the name of security.

The trail of the real anthrax killer, meanwhile, appears to have grown cold, despite extensive help from anthrax scientists. In August, a break in the case appeared imminent after FBI sleuths twice searched the home of Steven Hatfill, a former Army microbiologist with an interest in bioterrorism. Hatfill lost his job as a bioterrorism preparedness instructor at Louisiana State University, Baton Rouge, after Attorney General John Ashcroft called him a "person of interest," but he was never charged with any offense.

–MARTIN ENSERINK

CREDITS: (TOP TO BOTTOM) A. M. PEIER *ET AL.*, *SCIENCE* **296**, 2046 (2002); MIKE STOCKER/*SOUTH FLORIDA SUN-SENTINEL*/CORBIS SYGMA; AP PHOTO/FBI

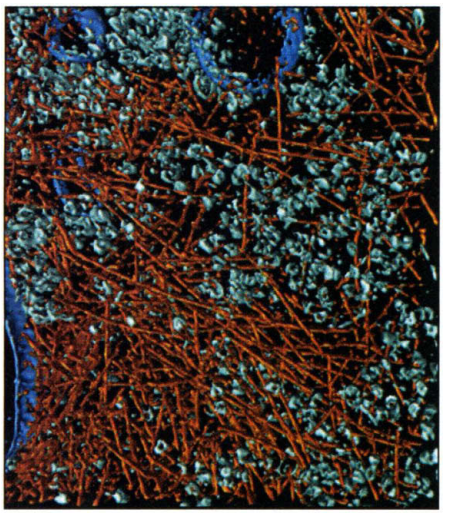
TRP channels are also necessary for another type of body heat. Male mice lacking a certain TRP channel are particularly thick-headed when it comes to mating, seemingly unable to distinguish between females and fellow males. These TRP channels inhabit a part of the nose that sniffs out pheromones.

Mutations in other TRP channels are responsible for certain cancers and other diseases, including, as discovered this year, an inability to regulate magnesium levels. These and most other TRP functions are still poorly understood, but researchers are picking up more coherent signals from TRP channels that buzz to sensations of taste, heat, and pheromones.

#7 Frozen images. Thirty years ago, researchers pitched the idea of reconstructing a 3D picture from electron micrographs. Today, cryoelectron tomography (cryo-ET) has overcome a series of technical obstacles to emerge as a breakthrough technique for viewing structures inside intact cells.

Biologists have long been able to capture the molecular structure of single proteins in cells, using techniques such as x-ray crystallography. But they haven't had a good way to get a 3D look at midsize organelles (~5 nm), such as the protein-packaging Golgi apparatus or energy-producing mitochondria—especially without removing them from their native environment. Cryo-ET fills this resolution gap and gives scientists a way to link atomic-level detail to whole-cell organization.

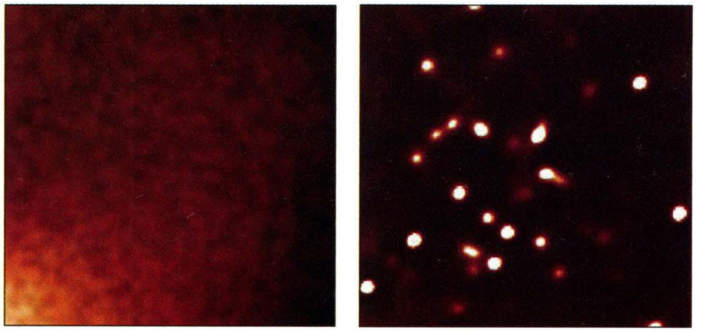
Cryo-ET works something like a doctor's computerized tomography scan. Penetrating beams of electrons create two-dimensional image slices that a computer assembles into a 3D image. Cells are flash-frozen and do not need to be fixed or have their membranes disrupted. (For years, the problem with cryo-ET has been that too much radiation causes structures to degrade.)



Actin in the act. Cryoelectron tomography captures new views of cellular components, such as these actin filaments.

Long, steady progress has solved many of the early snags. Autorotation of the specimen through a range of imaging angles and better calibration of the microscope stage have dramatically reduced exposure time. Improved clarity by reduced scattering of the electrons allows thicker specimens to be viewed. Advances in cryosectioning, slicing up the specimen in layers, have also enabled this technique to be used with thicker samples.

This year, cell imagers used cryo-ET to catch the first glimpse of actin filaments in the act, braced against the edge of the cell membrane. They also captured the first view of spatial arrangement of tubules and receptors in the sarcoplasmic reticulum, the components responsible for the chemical cascade that sets off a muscle contraction. And efforts are currently under way to create the first detailed 3D map of the spatial relationship of all the organelles in a eukaryotic cell.



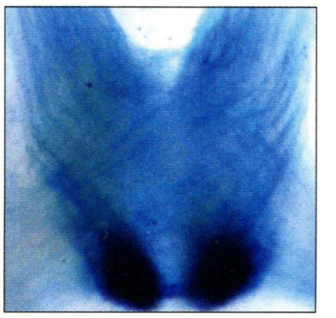
Popping into view. Flexible mirrors transform the Milky Way's innermost core from a diffuse glow (*left*) to sharp stars (*right*).

#8 Clear skies ahead. This year, astronomers converted the promise of adaptive optics (AO) into crisp new views of the heavens. AO systems erase the blurring of Earth's atmosphere by flexing the surfaces of thin mirrors hundreds of times each second, precisely canceling the turbulence overhead. This optical wizardry is easier said than done—it took years of painstaking engineering to make AO work routinely at the world's biggest telescopes.

The wait was worth it. Both the W. M. Keck Observatory in Hawaii, with its twin 10-meter telescopes, and the European Southern Observatory's Very Large Telescope array of four 8.2-meter telescopes in Chile used AO this year to peer at the heart of our Milky Way. Sharp images of the central stars dashing around a hidden body gave the best evidence yet of a supermassive black hole. Other striking AO images included a huge volcanic blast on Jupiter's moon Io and new details about the shapes of distant galaxies. Even a daytime observatory joined the club. A Swedish solar telescope on the Canary Islands snapped the clearest pictures of the sun's surface with a new AO system, revealing dark ribbons of seething magnetic fields around sunspots.

These studies require a bright star or planet, providing enough light for the AO sensors to gauge the air's ripplings. However, lasers mounted on the sides of telescopes can create "artificial" stars high in the atmosphere, making it possible to clarify vision anywhere in the sky. Astronomers showed this year that laser AO works well on smaller telescopes; the big eyes on the sky should have laser systems within a year.

#9 Retina receptors. Researchers hit the jackpot this year in understanding how light resets the circadian clock, our internal timepiece that regulates daily patterns of behavior and physiology. After years of searching hard for the so-called photoreceptor cells that relay that light signal to the clock in mammals, circadian biologists had tantalizing clues but no answer. They knew the photoreceptors must be in the eye. But the eyes' only known photosensitive cells, the rods and cones, weren't doing the job. Then last winter, five independent research teams discovered a brand-new class of light-responsive cells in the mammalian retina that connect directly to the brain's clock.



Good timing. Blue-stained melanopsin-containing retinal neurons connect with the brain's clock (dark blue).

First, researchers found a pigment called melanopsin in a small subset of retinal ganglion cells (RGCs) in the eyes of rats. Most RGCs don't respond to light, but it turned out that the melanopsin-containing ones do, making them a brand-new class of previously unknown light-responsive retinal cells. What's more, researchers traced their connections and found that they hook up directly to the suprachiasmatic nucleus, the brain area that houses the clock.

That's not all. More recent neuroanatomy studies have shown that the melanopsin-containing RGCs also link up to brain areas that control a variety of responses to light that

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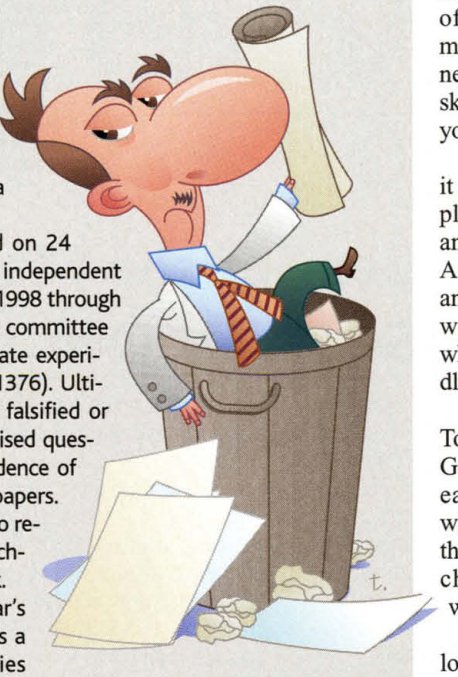
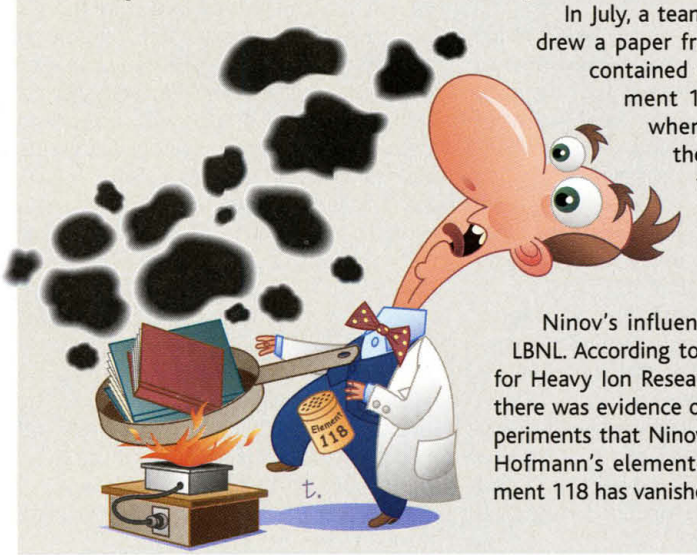
Breakdown of the Year: Physics Fraud



The past year witnessed more than just high points. The physics community suffered two stunning setbacks when separate investigations concluded that a physicist at Bell Laboratories in Murray Hill, New Jersey, and another at Lawrence Berkeley National Laboratory (LBNL) in California committed fraud.

At Bell Labs, device physicist Jan Hendrik Schön was fired on 24 September, shortly after officials there received word from an independent committee that Schön fabricated data and falsified reports from 1998 through 2001 (*Science*, 4 October, p. 30). Bell Labs officials organized the committee in May to look into allegations that portions of figures in separate experiments appeared to have been duplicated (*Science*, 24 May, p. 1376). Ultimately, the committee members concluded that Schön either falsified or fabricated data in 16 of the 24 cases they reviewed, and they raised questions about the other eight cases. The committee found no evidence of misconduct by any of Schön's 20 co-authors on the suspect papers. Schön, who has denied the charges, and co-authors have moved to retract the 16 suspect papers, and Bell's parent company, Lucent Technologies, has pulled six patent applications based on Schön's work.

Schön, unfortunately, doesn't have a monopoly on this year's alleged misconduct in physics. One of LBNL's claims to fame is a rich history of creating new elements, unstable heavy species that decay in a fraction of a second. But that history has been tarnished.



In July, a team of physicists from the lab withdrew a paper from *Physical Review Letters* that contained evidence for the creation of element 118—evidence that disappeared when investigators looked closely at the original tapes. After the laboratory concluded that the data had been fabricated, Victor Ninov, who was in charge of the analysis, was fired. Ninov has filed a grievance contesting the charges.

Ninov's influence might have extended beyond LBNL. According to Sigurd Hofmann of the Institute for Heavy Ion Research (GSI) in Darmstadt, Germany, there was evidence of fabricated data in two other experiments that Ninov worked on when he was part of Hofmann's element-hunting team. Luckily, only element 118 has vanished in a puff of smoke.

–ROBERT F. SERVICE

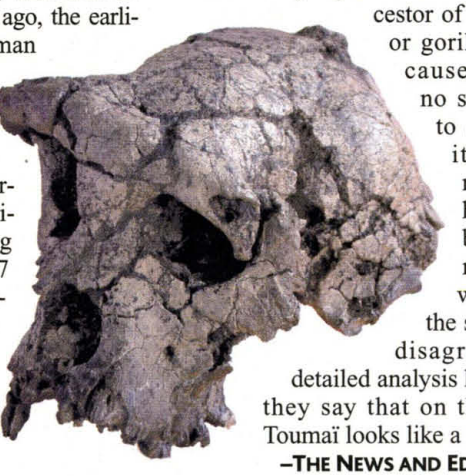
don't require the image-forming visual system, such as constriction of the pupils and the direct effect of light on sleep-wake state—what makes us drowsy in dark seminar rooms or wakeful if the lights are kept on all night.

Most of the pieces have fallen neatly into place, but technical difficulties prevented researchers from proving that melanopsin responds chemically to light. Without that evidence, some were reluctant to accept it as the RGCs' light-capturing pigment. Now that issue has been put to rest: In last week's issue of *Science* (13 December, pp. 2211 and 2213), researchers showed that mice that lack melanopsin do not normally reset their circadian clocks in response to light, suggesting that melanopsin is capturing and relaying the light signal.

CREDITS: (TOP TO BOTTOM) ILLUSTRATIONS: TERRY E. SMITH; MPFT

#10 Evolutionary headlines.

Only a decade ago, the earliest known human ancestor was a species whose most famous member, Lucy, lived in east Africa about 3.2 million years ago. But in July, the nearly complete cranium of a primate that lived twice as long ago—between 6 million and 7 million years ago—was introduced as the oldest known hominid, the lineage that includes humans but not other apes. This fossil, found by a team of French and Chadian researchers, fills a crucial gap at the dawn of human evolution when almost nothing is known; the next oldest published hominid skull is almost 3 million years younger.



It also is important because it was found in an unexpected place: along the shores of the ancient Lake Chad in western Africa. Until now, the earliest ancestors of the human family were found in east Africa, which has been called the cradle of humanity.

The fossil, nicknamed Toumaï for "hope of life" in the Goran language, shows that the earliest hominids were more widely distributed across Africa than previously thought, and it challenges old views about where the first hominid arose.

At this early age, Toumaï looks most like an ancient ape, with a brain the size of a chimpanzee's, large incisors, and widely spaced eyes like those of a gorilla. But the shape and size of its canines and lower face resemble those of human ancestors that came later; it has small, unsharpened canines and a flat lower face, unlike the protruding snout of living apes. The mix of features convinced the fossils' discoverers that they had found a new genus and species of hominid, which they named *Sahelanthropus tchadensis*.

Controversy is another prominent feature of these fossils. A competing team of researchers (who have discovered another, slightly younger fossil that they say is the earliest hominid) argues that Toumaï is the ancestor of an extinct ape or gorilla, partly because there are no skeletal bones to show whether it walked upright—the hallmark of being a hominid. Others who have seen the skull, however, disagree. Although detailed analysis has just begun, they say that on the face of it, Toumaï looks like a hominid.

–THE NEWS AND EDITORIAL STAFFS