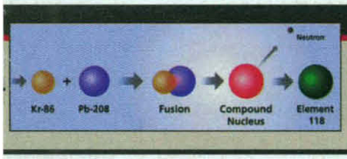
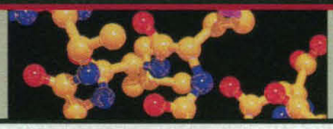
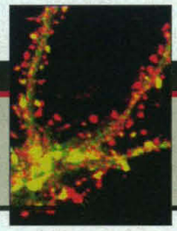


1751 Extending the periodic table

LEAD STORY 1752 Fallout from a $1 billion patent suit



1755 Memories are made of this



EDUCATION

Scientists Block NIH Plan to Grant Ph.D.s

National Institutes of Health (NIH) director Harold Varmus would seem to have everything he needs to create a world-class graduate school in biomedical science—about 1150 tenured and tenure-track researchers, the country's largest clinical research center, and scores of experts in the hot new discipline of bioinformatics. Only one element is missing: acceptance of the idea by outside scientists. But that may be a deal-breaker.

At odds. Can NIH's Gottesman (*left*) persuade Princeton's Tilghman to support grad school plan?

Last week, for the second time in 6 months, opposition from several scientists on Varmus's influential Advisory Committee to the Director forced him to withdraw a plan to establish a small graduate school on the NIH campus. He and Deputy Director for Intramural Research Michael Gottesman will advance the idea again only if they can find a way around "some central crevasses," Varmus told his advisory panel on 3 June. "Negative votes here count pretty heavily," he said.

Gottesman and Varmus were seeking the advisory panel's endorsement of a Ph.D.-granting program in disease-oriented, integrative biology that would enroll 15 students a year for a 5-year course of study. The curriculum is still "in a rather preliminary stage," Gottesman said, but instruction would be mostly tutorial or in small classes, and the program would emphasize areas of NIH strength in bioinformatics, clinical research, and genomics.

NIH already has about 700 graduate-level students on campus under a variety of training and outreach programs. But Gottesman said the course preparation and teaching involved in a degree-granting program would "add to the intellectual excitement in our laboratories," foster more interdisciplinary contact, and help NIH recruit top-level academic scientists who want to keep teaching. "We don't intend to use any extramural funds," Gottesman pledged. But that didn't mollify the critics. They called the grad school plan inadequately thought out and the wrong move at a moment when universities are already turning out too many life sciences Ph.D.s.

"We right now in this country have an excess of Ph.D.s trained in the biological sciences," said molecular biologist Shirley Tilghman of Princeton University. "For the NIH to turn around and start a graduate program sends the wrong symbolic message to the community." Tilghman has long been concerned about worsening job prospects for newly minted Ph.D.s. She chaired a National Research Council study last year that urged universities to freeze the size of graduate programs and forgo developing new programs "except under rare and special circumstances" (*Science*, 11 September 1998, p. 1584).

Philip Needleman, chief scientist of Monsanto Co. in St. Louis, said the NIH plan sounded neither focused nor unique. Cell biologist Marc Kirschner of Harvard Medical School in Boston not only echoed those concerns but also stated bluntly a consideration that usually goes unspoken at NIH advisory council meetings. "It's hard to see NIH proposing a program in these very important areas at the same time that NIH is not supporting, for example, a [training] program that we had at Harvard, which basically had this terrific cohort of graduate students," Kirschner said.

Neurobiologist Eric Kandel of Columbia University in New York City chided Kirschner a few minutes later. "I think our function on this committee is to make sure that NIH is as strong as possible, not that Harvard or Columbia is as strong as possible," said Kandel, who enthusiastically supports an NIH grad school. "I think we all sense that, from an academic point of view, this place could be stronger as a result of a Ph.D. program."

On a show-of-hands vote, Varmus won what he called "a partial vote of endorsement." A majority of the panel voted that he and Gottesman should keep trying to develop a grad school plan, particularly a more detailed curriculum. Tilghman, Needleman, and Kirschner voted "no."

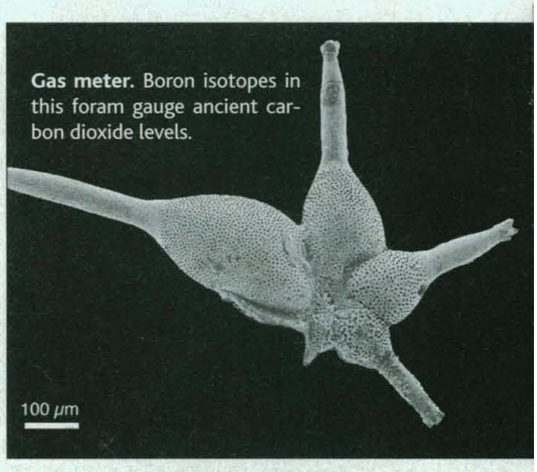
Varmus won't try to cram the idea down the throats of extramural scientists. He noted that if U.S. research universities object, Congress would likely raise questions, too. "This is not the issue over which we would want to put the entire NIH at risk," he said. But he indicated he may make one last try by naming a subgroup of the advisory committee to help refine the proposal. It might not be a bad idea for him to invite Tilghman to join in. At the end of the day, she left a possible opening. Although NIH's plans at this point don't look "terribly different" from other graduate programs, Tilghman said, "I would be extremely enthusiastic about a true Ph.D. in bioinformatics." **–BRUCE AGNEW**

Bruce Agnew is a writer in Bethesda, Maryland.

PALEOCLIMATOLOGY

Slide Into Ice Ages Not Carbon Dioxide's Fault?

As an agent of climate change, the carbon dioxide in the atmosphere gets a lot of respect. It's famous as the force behind the predicted greenhouse warming fueled by human activities. And in research circles, falling levels of carbon dioxide are the presumed culprit behind the recent 100 million years of climatic cooling—a long, bumpy slide that started in the balmy age of the dinosaurs and plunged the world into an ever-deepening chill, culminating in the ice ages of the past 2 million years. But two independent studies now raise questions about whether this big chill really can be blamed on carbon dioxide.



Gas meter. Boron isotopes in this foram gauge ancient carbon dioxide levels.

In this issue (p. 1824), paleoceanographers Paul Pearson of the University of Bristol in the United Kingdom and Martin

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Palmer of Imperial College, London, report that about 43 million years ago, when the world was perhaps 5°C warmer than today, carbon dioxide levels were not dramatically higher than they are now. An independent study by paleoceanographer Mark Pagani of the University of California, Santa Cruz, and his colleagues in this month's *Paleoceanography* comes to a similar conclusion for a warm spell about 15 million years ago. Even when climate did shift, Pagani's team says, carbon dioxide levels stayed fairly constant.

The new studies suggest that "we may have to think harder about what's driving the [climate] system on these long time scales," says paleoclimatologist Thomas Crowley of Texas A&M University in College Station. "It could be the whole carbon dioxide paradigm is crumbling," at least when it comes to explaining very long-term climate change. Carbon dioxide is still a powerful driver of climate, Crowley and others say—powerful enough, researchers think, to warm the world in the coming century—but over millions of years, other factors such as changing ocean circulation may have warmed or chilled the planet.

Lacking any way to sample air directly from tens of millions of years ago, researchers often seek clues to past carbon dioxide levels in ancient marine sediments. One technique uses the carbon isotope composition of the organic matter from tiny algae called phytoplankton, which like all plants tend to incorporate the lighter isotope of carbon, carbon-12, over carbon-13. The phytoplankton can afford to incorporate more light carbon when there is plenty of carbon dioxide in the water—and therefore in the air. Such analyses have tended to support the carbon dioxide–climate link, putting carbon dioxide levels 65 million years ago and for many millions of years thereafter as high as five to six times today's values.

However, other factors can also bias the carbon isotope ratio, including the species of plankton, their shape and growth rate, and contamination by organic matter from land. So Pagani and his colleagues Michael Arthur and Katherine Freeman at Pennsylvania State University, University Park, refined the technique. They focused on a single type of organic molecule—long-chain ketones called alkenones—that are made exclusively by a type of phytoplankton called coccolithophorids. These plankton lived in nutrient-poor waters and presumably grew at low and constant rates.

With this method, Pagani found that 17 million years ago, when much of the ocean was up to 6°C warmer than today, carbon dioxide was actually lower than 270 parts per million (ppm), its value just before the industrial buildup began. And when the ocean abruptly chilled and ice began piling up on Antarctica 14.5 million years ago, carbon dioxide rose slightly rather than falling. Between 25 million and 10 million years ago—when climate was generally warmer than today—atmospheric carbon dioxide varied between 260 and 190 ppm.

Pearson and Palmer found a similar decoupling of carbon dioxide and temperature when they monitored ancient carbon dioxide levels using a different set of isotopes: isotopes of boron in the skeletons of plankton called foraminifera. To build their skeletons, forams take up carbonate ions from seawater, but they sometimes incorporate boron instead by mistake. The isotope composition of that interloper boron depends on the relative proportions of borate and boric acid in seawater, which depends in turn on pH. And the ocean's pH depends, among other things, on the amount of carbon dioxide dissolved in the seawater as carbonic acid.

When Pearson and Palmer applied the boron technique to 43-million-year-old marine sediments from the tropical Pacific—a time of such warmth that the waters around Antarctica were perhaps 16°C warmer than now—they found that carbon dioxide levels were somewhere between 180 ppm and 550 ppm, with the most likely value being 385 ppm—well below the earlier reports of six times the present level. Either the climate system is extraordinarily sensitive to small changes in carbon dioxide, Pearson and Palmer conclude, or something other than carbon dioxide drove the 50-million-year cooling.

Taken together, the two studies suggest that "we need to reconsider the prevailing dogma," says paleoceanographer Edward Boyle of the Massachusetts Institute of Technology. No one is challenging carbon dioxide's status as a potent agent of climate change; there's little doubt, for example, that carbon dioxide rose and fell in step with climate over the 100,000-year cycle of recent ice ages. But researchers will be looking at other factors to help explain the long-term chill of the past 50 million years.

The leading alternative is a reorganization of the ocean currents that carry heat to high latitudes. When the ocean was cooling 15 million years ago, shifting continents were probably opening the way for the circumpolar Antarctic current to develop, isolating the Antarctic from tropical heat and tending to push the world into a colder climate, notes Pagani. Other climate-altering circulation shifts might have come when the eastern end of the now-vanished Tethys Sea between Asia and Africa closed around 15 million years ago and when the rise of the Isthmus of Panama separated the Pacific and Atlantic oceans 2 million to 4 million years ago—all times of cooling.

Of course, it's also possible that the methods behind these two studies are in error, as

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ScienceScope

Anti–Mouse Antibodies Groups that want biomedical researchers to stop harvesting antibodies from mice are organizing a scientific panel to press their case.

Every year, scientists kill about a million mice to get monoclonal antibodies, used for everything from analyzing tissue samples to attacking cancer. In April, a National Academy of Sciences (NAS) committee concluded that test tube alternatives were available for producing most antibodies (*Science*, 9 April, p. 230). But the panel, citing cost and other concerns, said it was too soon for the National Institutes of Health (NIH) to follow four European nations in restricting the mouse, or "ascites," method.

Proponents of such restrictions, notably the Alternatives Research and Development Foundation of Eden Prairie, Minnesota, hope to combat what ARDF head John McCardle calls a "heavily biased" NAS report by assembling their own expert panel. The panel—to meet in August in Bologna, Italy—will also draft a guide for labs interested in alternatives.

Meanwhile, the groups have petitioned NIH to cut back on ascites production. They say a suit is possible if they are unhappy with NIH's response, expected later this year.

Off the Table Georgetown University has officially abandoned a cost-saving plan that would have cut medical faculty salaries after 19 professors went to court to kill it.

As part of a pretrial settlement, the university on 27 May agreed to send a letter to all medical faculty pronouncing the policy "null and void." The plan, which would have required researchers to raise 70% of their salaries through grants, was shot down by a campus grievance committee last fall (*Science*, 11 December 1998, p. 1967). The administration nonetheless implemented it, then rescinded it in February after faculty members filed suit claiming the university was violating its own procedures as well as academic freedom.

The settlement allows the faculty "to bypass the grievance process and go straight to court" if there is any sort of "reincarnation" of the plan, says pharmacology professor Robert Glazer. The university notes that it is still "free to adopt a[nother] compensation policy in the future."

both techniques still require some assumptions. The boron technique assumes that seawater composition remained roughly constant over millions of years, and the alkenone method assumes that coccolithophorids grew at a steady rate. To check the validity of the methods, says Crowley, the techniques must be applied to a time of known carbon dioxide concentrations, such as the past few hundred thousand years. Pagani is even now marching his carbon analyses up a sediment core toward the present. If the technique proves reliable, carbon dioxide may have to share its role as prime mover of long-term climate change.

–RICHARD A. KERR

IMMUNOLOGY

Elusive Interferon α Producers Nailed Down

Almost everyone agrees that recycling is a good idea. Indeed, even our immune system seems to have picked up the idea for one of its most valued assets—cells. A paper in this issue of *Science* suggests that the body uses the same set of cells to perform two immune functions, one when the cells are young, and a second after they mature.

On page 1835, a team of immunologists led by Yong-Jun Liu at the DNAX Research Institute in Palo Alto, California, reports pinning down the origins of a key component of our immune defenses. They've isolated the hitherto elusive cells, known as natural interferon-producing cells (IPCs), that churn out huge amounts of interferon α (IFN-α). This so-called cytokine has a variety of immune stimulatory effects that help protect cells against viral and bacterial infections, and it also curbs tumor growth. The IPCs turn out to be the immature forms of a special type of dendritic cell (DC), an immune system sentinel that engulfs foreign proteins, or antigens, chops them up, and displays the pieces to other immune cells, the T cells. This kicks off a fierce, specific immune response directed at the triggering antigen.

The finding links the two branches of our immune system, the innate, more primitive immunity triggered by a wide variety of pathogens and the more sophisticated, adaptive immunity based on antigen-specific cells, which can be tailored against almost any intruder. "The study suggests that this cell type—which had previously been implicated in adaptive immunity—has the potential to also be an early player in the innate part of the immune response. This enriches the capacity of DCs to control immunity," says dendritic cell expert Ralph Steinman of The Rockefeller University in New York City. And because the IPCs seem to be involved in a variety of illnesses, from AIDS to cancer to autoimmune diseases, "having identified this cell type opens an immense amount of possibilities" to try to treat or control these conditions by manipulating the cells, says immunologist Jacques Banchereau of the Baylor Institute for Immunology Research in Dallas.

IPCs first appeared on immunologists' radar screens in the early 1980s, when it became clear that only a special, very rare type of white blood cell is capable of producing huge amounts of IFN-α. But immunologists did not identify a good candidate for the job until about 3 years ago, when Gunnar Alm and his colleagues at the Swedish University of Agricultural Sciences in Uppsala showed that IPCs "have all the characteristics of an immature DC," as Alm puts it. They found, for example, that cells that stain positive for IFN-α also bear characteristic DC surface markers.

At the same time, Liu and his colleagues isolated an odd cell type from human tonsils and blood, which they couldn't classify. Yet when Liu cultured the cells, they developed into a new type of DC with unique T cell–stimulating properties. He also realized that the cells, which he designated pDC2, bore a striking resemblance to Alm's. So he wondered whether the tonsil DC2 precursors and the natural IPCs were one and the same.

To test this idea, the researchers purified more pDC2s from human blood, not a trivial endeavor given that there's only one pDC2 in every 1000 white blood cells. Under the electron microscope, Liu saw that the pDC2s have a prominent protein secretion apparatus, suggesting that the cells can produce huge amounts of protein. When the team stimulated the cells in culture with inactivated herpes simplex virus, they found that their purest pDC2 preparation did in fact make up to 1000 times more IFN-α than the same number of unpurified white blood cells. That response shows, says Liu, that the pDC2s are the natural IPCs.

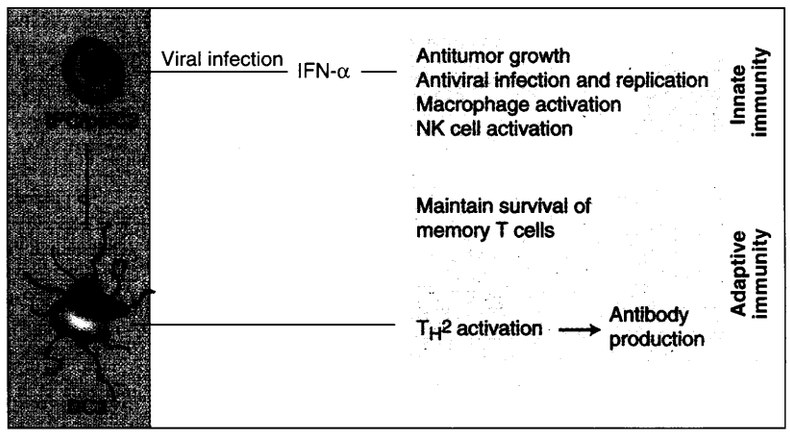
Many in the field are especially taken by the proposed versatility of the pDC2s and their mature version, the DC2s. "The cell seems to serve two masters at different stages of its [lifetime], which is quite unusual for immune cells. It's almost as if nature doesn't want to have cells just sitting around," Banchereau says. Liu adds that the shift in responsibilities as the cell ages makes sense. "If a virus invades, you need a quick response; otherwise you may die. And that's what [the pDC2s] do [by producing IFN-α] within only a few hours. After that you'd want to call in the adaptive immune system for help—and that's the job of the DC2s."

Still, Paola Ricciardi-Castagnoli, an immunologist at the University of Milano in Italy, points out that no one has shown yet that pDC2s produce the same skyrocketing amounts of IFN-α in the body as they do in cell culture. Also unknown, says Ken Shortman, a developmental immunologist at the Walter and Eliza Hall Institute in Melbourne, Australia, is whether "pDC2s ever turn into mature DCs in the body."

If the pDC2s are indeed the long-sought IPCs, their isolation may yield significant medical benefits, as researchers look for ways to stimulate them or rein them in. Boosting IPC activity could be beneficial in AIDS, which seems to correlate with a drastic drop in IPC count, as indicated by, among other things, a drop in the patients' production of IFN-α, and perhaps also in cancer. Conversely, Alm has recently found evidence that IPC activity could contribute to the abnormal immune attacks of autoimmune disorders, such as systemic lupus erythematosus, suggesting that curbing the cells might be valuable there.

The next challenge, everybody agrees, is to learn more about them. "Now we need to know how to produce these cells in large amounts and then how to modulate their function," says Banchereau. "This is going to be one of the hot spots of the future," he predicts.

–MICHAEL HAGMANN



Two-pronged attack. In response to microbial infections, type 2 dendritic cell precursors (pDC2s) produce IFN-α, which activates other immune cells such as macrophage scavengers and natural killer (NK) cells. Then, the mature cells (DC2) stimulate type 2 T helper (T_H2) cells to induce antibody production.

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