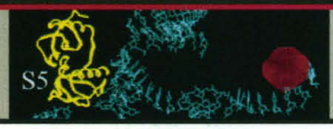
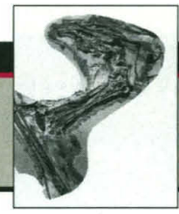
2044
Shaky precursor to Athens quake

LEAD STORY 2048
The race to the ribosome





2052
A plethora of feathered dinosaurs

The consortium's experience with chromosome 22 has helped the leaders of the Human Genome Project decide on a definition of "finished" that likely will be applied to sequencing of the remaining human chromosomes. Earlier this month, at a meeting in Cambridge of the international partners involved in this massive effort, the partners reached a consensus on what's needed. The three major criteria are: More than 95% of the chromosome must have been sequenced; the number, location, and size of remaining gaps must be pinned down; and individual gaps must be shorter than about 150,000 bases.

Dunham says the criteria may never be "written in stone," but the chromosome 22 consortium is already well within these criteria if the sequence data "in the pipeline" count, along with what has been posted in databases. What remains, he says, is to "check everything" and make sure that the entire sequence is correctly labeled and deposited in a public database. Completion of that task will be a signal to pop the champagne corks. But the celebration will be brief. "Mapping and sequencing has already taught us a lot about the nature of the genome," Shimizu says. The next step, he says, will be to clarify the biological significance of it all. And that work has barely begun.

–DENNIS NORMILE AND ELIZABETH PENNISI

SCIENCE PUBLISHING

Turnover at the Top at *Cell* and *NEJM*

Earlier this year, *Cell* and *The New England Journal of Medicine* went through abrupt transitions as *Cell* changed owners and the *NEJM*'s editor was forced out. Now, the management of both journals is changing again.

Cell Editor Steps Down

Benjamin Lewin, the editor of *Cell* and its sister journal *Molecular Cell*, announced to his staff and editorial board last week that he plans to retire on 1 October. His sudden departure represents "a big loss for *Cell*," says cell biologist Tony Hunter of the Salk Institute for Biological Studies in La Jolla, California.

After Lewin founded *Cell* in 1974, it quickly became a premier journal of molecular and cell biology. Scientists attribute the journal's success largely to Lewin's depth of scientific knowledge and his hands-on management style. "It will be very different without Benjamin there," says Hunter, who has been on the journal's editorial board since 1980. "He was always there to talk with you about your paper or someone else's. This was in contrast to most other journals."

Lewin sold the journal, along with its three sister journals—*Neuron*, *Immunity*, and *Molecular Cell*—to Dutch science-publishing giant Elsevier Science in April, for an amount rumored to be close to $100 million. Insiders wondered how long Lewin would stay on, although Elsevier had announced that he would remain editor for 5 years. When reached by *Science*, Lewin declined to comment.

Some close to the journal fear that Lewin's departure, combined with Elsevier's takeover, will trigger an exodus of staff. But Deputy Editor Vivian Siegel will stay on at the helm, and editorial board member Ira Herskowitz of the University of California, San Francisco, expresses "absolute faith" in her. Siegel, he says, shares Lewin's engaged management style, but he expects *Cell* to "evolve in some manner. She is not a clone of Ben."

–MARCIA BARINAGA

NEJM Publisher Resigns

The publisher of *The New England Journal of Medicine*, Joel Baron, quit his job less than 2 months after former Editor-in-Chief Jerome Kassirer was forced out. In a 13 September letter to colleagues, Baron said that after an expansionary push in which the journal's owner, the Massachusetts Medical Society, launched several new publications, he was ready to move on.

Under Baron's 2-year tenure, the society has started up new publications such as *Heartwatch*, a consumer newsletter, and acquired *Hippocrates*, a journal for physicians. It has also been looking into lucrative arrangements with commercial publishing enterprises. Now that things have quieted down, Baron, who calls himself a "strategist" rather than an "implementation" person, said in the letter, "I think I will be able to make a bigger contribution elsewhere." (Baron couldn't be reached for comment.)

Some observers suspect that in the turmoil following Kassirer's dismissal, Baron no longer had a free hand to do what he was hired to do. Kassirer was pushed out because of "differences of opinion" with the medical society over activities that he claimed would compromise the journal's good name (*Science*, 30 July, p. 648). "There's been enough concern expressed by editors of the journal and the academic community" over the new publications initiatives that management may have decided to shelve its plans for the present, says *NEJM* Associate Editor Morton Swartz, former chief of infectious disease at Massachusetts General Hospital in Boston.

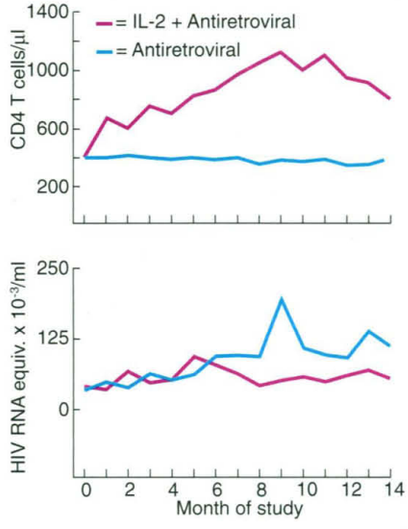
Taking it one departure at a time, the society last week announced the appointment of a search committee, headed by Harvard Medical School professor Ronald A. Arky, chair of the medical society's publications committee, to look for Kassirer's replacement.

–CONSTANCE HOLDEN

AIDS THERAPY

Ambitious Clinical Trial Stirs Debate

The National Institute of Allergy and Infectious Diseases (NIAID) last week decided to fund what will likely be the largest and most expensive trial of an AIDS treatment the institute has ever backed. During the next 5 years, the $43 million study will follow 4000 HIV-infected people who are already taking anti-HIV drugs to see whether adding an immune-



Mixed results. IL-2 treatment raised CD4 levels but had little effect on viral load.

system messenger called interleukin-2 (IL-2) can help prevent disease and death. The study, which went through a stringent but unusual review process because NIAID director Anthony Fauci holds a patent on the treatment, will involve 210 sites in 18 countries, creating an enormous new clinical trials network that will include some of the world's leading AIDS clinicians. "It's tremendously ambitious," acknowledges Jack Killen, head of NIAID's Division of AIDS. "But this is about as good a shot as we're going to get at answering a very important question."

Whether the so-called Esprit trial is likely to yield meaningful results is, however, being fiercely debated within the AIDS research community. Some researchers believe its flexible design and relatively healthy subjects may blur any results. And numerous other logistical, procedural, and ethical questions have also dogged this trial since it was first conceived 3 years ago, including whether the costly study is needed when smaller IL-2 trials are already planned in sicker subjects.

Small-scale studies have shown that genetically engineered IL-2 significantly boosts levels of CD4 cells in HIV-infected people. (CD4s are the main white blood cells that HIV selectively destroys.) "We have seen changes in CD4 counts, but we don't know what they mean clinically," explains NIAID's clinical director Clifford Lane, who pioneered this treatment strategy and shares the patent with Fauci and NIAID's Joseph Kovacs. (The patent is assigned to the government, and Chiron, the maker of engineered IL-2, has a license; the researchers are entitled to a maximum of $150,000 of any payments each year, which Fauci donates to charity.) Specifically, none of the trials have yet shown that the CD4 increases result in longer, healthier lives, and the treatment does not seem to decrease the amount of HIV in a person's bloodstream.

The trial aims to mimic the diverse ways IL-2 would be used in the real world. In the first 6 months, 2000 people already taking any combination of anti-HIV drugs will give themselves injections of IL-2 for 5 days every 8 weeks. After those three cycles, physicians will use their discretion to determine the frequency of subsequent cycles of IL-2 treatment, which can cause flulike symptoms. Another 2000 people who are taking only anti-HIV drugs will serve as the control group. "This will give some pretty clear information," asserts Lane.

Others aren't so sure—including the peer-review group that ultimately gave the trial a thumbs-up. "A lot of people are skeptical about whether it will be possible at the end of a large trial like this to sort out the cause and effect when people cycle through different treatments," acknowledges Killen. And the link may be further blurred because Esprit will recruit people who have suffered relatively modest immune damage from HIV and thus are more likely to respond to the immune booster; to be eligible, HIV-infected people must have at least 300 CD4 cells per millimeter of blood at the trial's start. (The normal range is 600 to 1200.) As a result, it may take longer than 5 years to see enough AIDS-related disease and death to determine conclusively whether IL-2 helps. "You could be holding your breath a long time," says Robert Schooley of the University of Colorado Health Sciences Center in Denver, who heads the AIDS Clinical Trials Group (ACTG), an NIAID-supported network that conducts most trials of AIDS drugs.

The fact that ACTG will not be running this trial is another point of contention. James Neaton of the University of Minnesota, Minneapolis, a biostatistician who is Esprit's principal investigator, says he couldn't interest ACTG. "People I worked with [in the ACTG] wanted to participate, but they couldn't get approval from the executive committee," says Neaton. Schooley explains that not only would the expense overwhelm the ACTG's budget, but ACTG is already conducting a smaller scale trial of IL-2 in sicker patients. "Our feeling is it really offers more to people with advanced disease," he says. (Indeed, Chiron last month launched a large efficacy trial of the treatment in people with 50 to 300 CD4s.) Schooley also questions whether patients with relatively high CD4 counts will choose this toxic and expensive drug. "If you have 700 CD4s, you're going to do well for a long time," says Schooley.

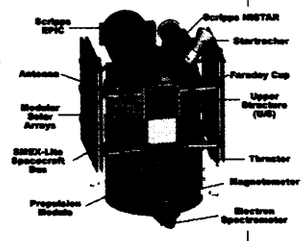
Neaton also considered another NIAID-sponsored clinical trials network, the Community Programs for Clinical Research on AIDS (CPCRA), but it did not have enough sites to recruit the needed number of patients. So, on advice from NIAID, he turned to a mechanism that is rarely used to fund large clinical trials: He submitted an investigator-initiated, "R01" grant.

To help avoid the perceived conflict-of-interest issues raised by Fauci's patent, the ad hoc "study section" of peers set up to evaluate the proposal was convened by the National Cancer Institute, not NIAID. "I can tell you for a fact that Tony had no influence whatsoever on the process of review or the decision about the funding of this," says Killen. Lane, who did help design the trial, says National Institutes of Health lawyers gave him a waiver for that purpose.

Unlike ACTG and CPCRA, study sections evaluate proposals behind closed doors. But interviews with members of the study section and documents provided by Neaton suggest that it received a rigorous review. When the study section first evaluated the proposal in June 1998, it gave it a score of 322, which put it in the unfundable 59.3 percentile. Among

ScienceScope

Triana Troubles A blistering internal critique of NASA's Triana satellite project, which would beam back video and data on the whole Earth, has infuriated NASA officials. NASA Inspector-General (IG) Roberta Gross last week concluded that Triana's changing mission, from inspirational to scientific, and increasing costs—from $50 million to more than $75 million—demand a reassessment.



NASA officials fear that the report's timing—it was released just days before this week's expected Senate vote on Triana funding—sounds the project's death knell. "I question the urgency to issue the report in such a hurry," says Ghassem Asrar, NASA's earth science chief. Other officials complain that Gross overstepped the IG office's traditional focus on fraud.

But Triana's Republican opponents on Capitol Hill (who view the mission, inspired by Vice President Al Gore, as a waste) embraced the findings. They have already convinced the House to kill the spacecraft's funding; NASA officials fear the Senate will follow suit.

Czechmate? Many Czech scientists will face a day of reckoning next year, after their government launches an evaluation of its universities and ministry-run institutes (*Science*, 27 March 1998, p. 2033). But the Ministry of Health is shaking up scientists already: It intends to fold its research institutes into university-based hospitals, to the chagrin of affected scientists. The move "will ultimately harm biomedical research," says Jiri Zavadil of the Institute of Hematology and Blood Transfusion (UHKT) in Prague.

Health Minister Ivan David recently announced plans to dissolve up to 12 institutes and shift staff to hospitals by the end of this year, arguing the move would improve clinical research. But scientists at UHKT and three other institutes fear the debt-laden hospitals will deprive them of scarce research money. "We are concerned about what will happen once we become part of the huge money-losing hospitals," says UHKT director Petr Jarolim.

Eyeing the drama is the Czech government's R&D council, which will begin its review early next year with help from foreign scientists. But the council can't make the ministry hold off, says Vice Chair Josef Syka: "We can only pressure them to do the reform in a proper way."

CREDIT: NASA

the many concerns listed by the study section was "whether the study as currently designed will result in interpretable data." Another sensitive topic was that some testing would be done in poor countries that may not be able to afford IL-2 if it is found to work: Three treatment cycles cost at least $5000.

The same study section considered a revised proposal 8 months later, and although it still noted "several weaknesses," it deemed the trial design "significantly improved." This time around, it earned a priority score of 178, placing it in the 18.1 percentile, an excellent ranking. On 16 September, NIAID formally announced that it would fund the trial. Leading clinicians in the United States (including those with the CPCRA), Canada, Europe, Australia, Greece, Israel, Thailand, and Argentina will participate.

Even if the treatment itself doesn't pan out, Neaton thinks the trial could have an important benefit: to show how "large, simple trials" that mirror real-world situations can answer tough questions. "I'm hoping to make this a model for how other research is done," he says. **–JON COHEN**

IMMUNOLOGY

On the Way to a Better Immunosuppressant?

"Kiwi" Clint Hallam, the world's first hand transplant recipient, celebrated the first anniversary of his new hand yesterday. He is

Roadblock. The two middle T cells contain the inhibitory peptide (also shown in green at right), which prevents NFAT (red) from entering the nucleus.

living proof that organ transplantation has come a long way since the first patient received a donated kidney back in 1954. But in spite of milestones like Hallam's, swapping body parts between different individuals has a major downside. It challenges our immune system's very raison d'être—fighting off anything recognized as foreign, whether invading pathogens or potentially life-saving organ grafts—and requires that the patients be given powerful immunosuppressive drugs. Now, a molecular smart bomb that targets a key molecular event in graft rejection could lead to improved immunosuppressants with fewer side effects.

In the early 1990s, immunologists discovered that when a foreign antigen—on a graft, for example—triggers the immune system's T cells, an intracellular enzyme called calcineurin is activated. Calcineurin clips chemical tags called phosphate groups from other proteins, including the so-called NFATs. When that happens, these proteins switch on a variety of genes encoding proteins that rev up immune cell activities.

Current immunosuppressive drugs such as cyclosporin A (CsA) or FK506 work by blocking calcineurin, but they often have nasty side effects such as kidney failure, diabetes, and an increased risk of cancer, presumably because they inhibit calcineurin's ability to remove phosphates from other proteins besides the NFATs. The new compound, which molecular immunologist Anjana Rao and protein chemist Patrick Hogan of Harvard's Center for Blood Research in Boston and their colleagues describe on page 2129, inhibits calcineurin more selectively and may cause far less of this "collateral damage."

The compound has only been tested in cultured cells and may not be suitable for clinical use, but if something like it eventually hits the pharmacy, it could be a boon to transplant recipients and other patients. "The pharmaceutical industry spent hundreds of millions of dollars to come up with a 'better cyclosporin,' but so far it all amounted to zero," says Ernest Villafranca, a protein crystallographer at Agouron Pharmaceuticals in La Jolla, California. A more selective immunosuppressant, he adds, might be used to treat conditions caused by an overactive immune system, such as asthma or autoimmune disorders like multiple sclerosis, for which physicians hesitate to prescribe current drugs because of their dire side effects.

Rao, Hogan, and their colleague José Aramburu took a first step toward the design of a more selective calcineurin inhibitor last year. They identified the site on NFAT that docks with calcineurin and showed that a short protein snippet, or peptide, from within that region can block the docking and activation. The peptide presumably acts by binding to calcineurin and, in effect, clogging its NFAT binding site. In the current work, the researchers have come up with a more powerful inhibitor.

In collaboration with Lewis Cantley of the Harvard Institutes of Medicine they synthesized a "library" of around 1 billion peptides in which they varied several amino acids of the natural NFAT sequence and then selected the peptide that bound most tightly to calcineurin. This synthetic peptide, the researchers found, is 20 to 100 times more potent than its natural counterpart at blocking NFAT activation by calcineurin—and most important, because the peptide doesn't block the catalytic center, it does this without affecting calcineurin's action on other proteins. "This means that if you've got the right wedge you can pry the two proteins apart," says Hogan.

Next, the team probed the effects of the peptide on gene activation in T cells. They found it was much more specific than CsA, turning off only genes thought to be NFAT-dependent, such as several genes for the immune system messengers called interleukins. Everyone agrees that much more work will be required to turn this promise into a drug, however. "There are still quite a few hurdles to overcome," admits Hogan. For one, although the tests with cultured cells are encouraging, the researchers haven't yet demonstrated that the peptide is in fact immunosuppressive. They plan to address that question in animal studies.

But even if the new inhibitor passes that test, it still may not be suitable for use in therapy. "Peptides are really not practical to use clinically," says Villafranca, because they are chopped up very fast in the body and often have problems getting inside the cell. But researchers might be able to find nonpeptide drugs with similar effects. "Pharmaceutical companies could simply take the assay with which we found the peptide and screen hundreds of thousands of compounds, for instance in bacterial broth," says Hogan.

Stanford molecular biologist Gerald Crabtree considers that a reasonable approach. "The only good immunosuppressants so far, CsA and FK506, have both targeted calcineurin. ... Maybe nature has already told us where the [immune system's] Achilles' heel is." **–MICHAEL HAGMANN**

MUSEUM MANAGEMENT

Smithsonian Taps Banker as New Leader

A banking executive with a flair for flamenco guitar and a passion for the arts will lead the world's largest museum and research complex. The Smithsonian Institution's Board of Regents announced last week that Lawrence M. Small, 58, second in command at the Fannie Mae mortgage corporation, will succeed retiring Secretary I. Michael Heyman in January.

Small's appointment breaks a 150-year tradition of naming a scientist or academic to lead the sprawling $570 million institution (see box). Some Smithsonian scholars are disappointed that they won't be working for one of their own, but many hope their new boss's management skills and boardroom connections will help inject cash into stagnat-

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