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-

CREDIT: ARAMBURU ET AL.

ing science budgets. "We're making a paradigm shift in leadership; it's clear the regents place a high value on corporate management skills," says Chris Wemmer, who directs the Smithsonian's Conservation and Research Center in Front Royal, Virginia.

The Smithsonian is best known as one of the United States' foremost tourist attractions, having lured 30 million visitors last year to its zoo and 16 museums, many of which line Washington, D.C.'s grassy mall. Less visible are the institution's more than 600 scientists, who toil amid world-class collections of everything from spiders to gems and conduct studies at seven far-flung research institutes, including the Harvard-Smithsonian Center for Astrophysics in Cambridge, Massachusetts, and a tropical research institute in Panama.

THE SECRETARIES OF THE SMITHSONIAN INSTITUTION

Name	Background	Tenure
Joseph Henry	Applied physics	1846–1878
Spencer Fullerton Baird	Natural sciences	1878–1887
Samuel Pierpont Langley	Aeronautics/astronomy	1887–1906
Charles Doolittle Walcott	Geology	1907–1927
Charles Greeley Abbot	Earth science/ astronomy	1928–1944
Alexander Wetmore	Ornithology	1945–1952
Leonard Carmichael	Psychology/ college president	1953–1964
S. Dillon Ripley	Ornithology	1964–1984
Robert McCormick Adams	Anthropology	1984–1994
I. Michael Heyman	Law/academic administration	1994–1999
Lawrence Small	Banking	2000– ?

Break with tradition. Small will be the first nonacademic, and only the second nonscientist, to lead the Smithsonian.

Over the last decade, some Smithsonian scientists say their influence—and funding—has waned as the institution expanded and spent aggressively on new art galleries and flashier exhibits. "There has been a slow but inexorable shift away from scholarship and toward public entertainment," believes spider expert Jonathan Coddington of the National Museum of Natural History. He and others worry that the perceived trend—which some have termed "Disneyfication" and others say is "dumbing down"—could undermine the institution's scientific prowess. Small says he has no desire to see research or educational outreach suffer under his tenure, which could last a decade or more. "I am more than aware that [Smithsonian founder] James Smithson's estate was bequeathed for the 'increase and diffusion' of knowledge—and that there was a point to putting 'increase' first," he told *Science*. There is "no great educational institution where research is not also considered enormously important," he says, adding that although "being a scientist is a wonderful way to spend your life, it doesn't necessarily prepare you for leading a large organization."

His own résumé includes 27 years at Citicorp, eight at Fannie Mae, and dozens of appointments to nonprofit boards. That background, observers say, should equip him well for the job of streamlining the Smithsonian's bureaucracy, a task Heyman began that earned him high marks from some researchers. Small will also have useful connections when it comes time to raise money, whether lobbying Congress for the 70% of the Smithsonian's budget that comes from taxpayers or seeking corporate gifts for a major upcoming capital campaign. Indeed, one of the new secretary's most valuable assets "may be his Rolodex," jokes one researcher. But Small says he also has a lighter side, pointing to his year in Spain studying flamenco guitar and a number of other "scholarly passions."

Small will get plenty of suggestions on how to spend any new funds. Many researchers, for instance, would like to see more money for graduate stipends and postdoctoral fellowships, noting that those budgets have eroded dramatically since the 1980s. The number of fellowships available at the Natural History Museum has slumped from more than 20 a decade ago to about five, researchers note, while the astrophysics center now has just two junior slots available annually on a staff of 300 Ph.D.s. "We are also falling behind in our computing capability," notes Irwin Shapiro, director of the astrophysics center.

For the moment, however, Small is keeping quiet about any plans he has for the organization. Indeed, he notes that he will have his hands full in the short run just finishing off two new projects—an annex at Virginia's Dulles Airport for aerospace exhibits too large for the existing facility on the mall, and a new Native American museum—that were begun by his predecessor.

–DAVID MALAKOFF

CREDIT: (LEFT TO RIGHT) FANNIE MAE; NATIONAL SCIENCE FOUNDATION

ScienceScope

Distance Learning Agency directors are supposed to go to any length for their boss. But most aren't called on to travel as far as National Science Foundation (NSF) chief Rita Colwell (right), who last week flew to Christchurch, New Zealand, to accompany President Clinton as he visited the agency's staging facilities for Antarctic trips. Clinton attended the Asian Pacific Economic Cooperation summit in Auckland and got a 2-hour tour from Colwell of the International Antarctic Research Center before giving a speech on Antarctica's environmental value. "I was pleased with his keen interest in the science there," says Colwell.

After a state dinner, Colwell climbed aboard Air Force One for the long flight home. Did she use the time to push NSF's 2001 budget request now being prepared? Well, White House Chief of Staff John Podesta had already signaled the president's strong support for research, she diplomatically said (*Science*, 17 September, p. 1827). And the end of a 5-day tour may not be the best time to lobby, she added: "To be honest, most people slept on the plane."

Thumbs Down In an embarrassing retreat, the Department of Energy (DOE) has withdrawn a controversial $100,000 grant that critics charged would support discredited "cold fusion" studies.

In June, after physicist Edwin Lyman of the nonprofit Nuclear Control Institute in Washington, D.C., and some DOE researchers challenged the science behind a concept for transforming radioactive waste into harmless byproducts, DOE officials said they were reconsidering the peer-reviewed award to nuclear engineer George Miley of the University of Illinois, Urbana-Champaign (*Science*, 23 July, p. 505). Miley said his experiment was not cold fusion—which seeks to spark nuclear fusion at room temperatures—but this month six new reviewers recommended that DOE spend its money elsewhere.

Miley couldn't be reached for comment. But DOE officials say the episode will prompt changes in its Nuclear Energy Research Initiative (NERI), touted for using top-notch reviews. Promises NERI manager John Herczeg: "We'll be taking a closer look from now on."

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