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.

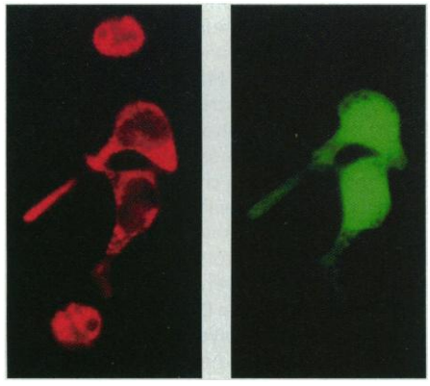
The same study section considered a revised proposal 8 months later, and although it still noted "several weaknesses," it deemed the trial design "significantly improved." This time around, it earned a priority score of 178, placing it in the 18.1 percentile, an excellent ranking. On 16 September, NIAID 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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