million during his 8-year tenure, allowing the institute to hire 20 new faculty members and carry out needed renovations. "He rejuvenated that institute," says Salk molecular biologist Tony Hunter.

The need to raise money isn't a new task for the head of Salk, of course. Murphy's immediate predecessors, Salk structural biologist Thomas Pollard and current CEO Frederick Rentschler, managed to boost Salk's endowment from under $50 million in 1996 to $120 million today, although Pollard stepped down as CEO a year ago to focus on his research. Even with that success, Salk's endowment is only one-tenth the size of those of similar places like the Rockefeller University in New York City, notes Charles Stevens, a Salk neuroscientist and member of the search committee that tapped Murphy.

Large endowments allow top-tier research institutes to pay for expensive equipment such as gene chip arrays for genetics and nuclear magnetic resonance machines for structural biology, says Hunter. Not having that pot of money, he adds, "makes it harder for us to compete." It also prevents Salk from providing much salary support for its 54 faculty members and puts it at a disadvantage in recruiting, says Stevens.

Hunter, Pollard, and others are optimistic that Murphy can keep Salk in the race. "It's a terrific selection," says Pollard. And although Salk's scientific luster doesn't need much polishing, Hunter hopes that Murphy's arrival will also stop the revolving door: "We would love to have someone who sticks around for a while." **–ROBERT F. SERVICE**

With reporting by Wayne Kondro in Ottawa.

MOLECULAR BIOLOGY

## Cancer Fighter's Modus Operandi Revealed

Researchers have deciphered how a promising cancer drug acts like a smart bomb, homing in on only a very narrow range of its potential targets in the cell. The compound, known as STI-571, has shown remarkable success in early clinical trials on patients with chronic myelogenous leukemia (CML). Now, in work reported on page 1938, John Kuriyan and Thomas Schindler of the Rockefeller University in New York City and their colleagues reveal just how the compound works—information that could aid in the design of similar cancer therapies. "It's a very neat story," says cell biologist Tony Hunter of the Salk Institute for Biological Studies in La Jolla, California.

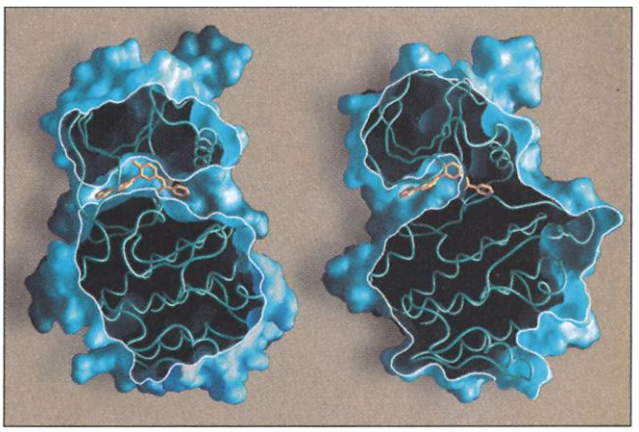
Scientists already knew that STI-571 blocks the enzyme produced by the *abl* oncogene, whose activation has been linked to the massive proliferation of leukemia cells in CML patients. They have been hard put to explain, however, why the compound doesn't also block closely related enzymes. The *abl* oncogene is one of hundreds of genes identified over the past 25 years that can, when abnormally active, lead to cancer. The hope is that the proteins made by these oncogenes will provide good drug targets. But many oncogenic proteins, including the Abl protein, belong to one of the largest enzyme families in the cell—the protein kinases, which transfer a phosphate group from ATP to proteins. Thus any effort to snuff out an aberrant kinase could easily produce a great deal of collateral damage and unacceptable side effects for cancer patients.

But STI-571 is a notable exception. It was identified in the early 1990s by scientists at the pharmaceutical company Novartis, who found that it inhibits the kinase that acts as the receptor for platelet-derived growth factor. Subsequent tests by Brian Druker's group at the Oregon Health Sciences University in Portland showed that the compound, a small 2-phenylaminopyridine, also inhibits the oncogenic form of Abl and the c-kit kinase, but none of the 50 or so other kinases screened.

The discovery that STI-571 blocks Abl activity raised the possibility that it might be used to treat CML. Bone marrow transplants offer a potential cure, but suitable donors can be found for only one-third of patients. And current drug therapies, usually with interferon α, only control the disease for a few years before it eventually progresses to the acute—and fatal—stage. One of the diagnostic hallmarks of this cancer is an abnormal chromosome—the so-called Philadelphia chromosome—formed when a portion of chromosome 22 fuses with the chromosome 9 segment bearing the *abl* gene. As a result, a portion of the *bcr* gene becomes attached to *abl*, and for reasons that are poorly understood, the hybrid protein produced by this fusion gene shows increased kinase activity. What's more, work in animals has shown that the Bcr-Abl protein is all that it takes to cause leukemia.

In the past 2 years, Druker has coordinated a series of trials to determine whether STI-571 does in fact help CML patients, and so far the work looks very promising. For example, at last year's meeting of the American Society of Hematology, he presented the results of a phase I clinical trial—which is primarily aimed at determining tolerable doses—involving 54 patients who no longer responded to interferon α. The cancer cells seemed to disappear from the blood of all 31 of the patients who got doses of 300 milligrams and above, Druker says. What's more, 30 of those patients have remained in remission for about a year of follow-up, and they have reported only mild side effects including some nausea, diarrhea, and muscle cramping.

Druker and his colleagues have since concluded enrollment in a phase II trial to test STI-571's efficacy and have embarked on a phase III trial pitting the drug against standard CML treatments. Researchers familiar with the trials are already enthusiastic. "I can certainly say the results are terrific. It's a home run," says Owen Witte of the University of California, Los Angeles, School of Medicine, whose own work was instrumental in showing Abl's importance in CML. James Griffin, a leukemia expert at Harvard Medical School in Boston, agrees, predicting that "this is going to change the way we treat CML."



**Locked up tight.** The drug STI-571 (in yellow) binds to the inactive form of the Abl protein, shown at left. But as depicted at right, the drug doesn't fit the active form of Src, another oncogenic kinase.

CREDIT: L. LEIGHTON/ROCKEFELLER UNIVERSITY

The Rockefeller team's work now explains how STI-571 homes in on the Abl kinase. The researchers crystallized the catalytic region of the human Abl protein together with an STI-571 variant. They then used x-ray crystallography to determine the three-dimensional structure of the drug-protein complex. Abl, like many other kinases, has an "activation loop" that has to have a phosphate group added before the enzyme can add phosphate groups to other proteins. This alters the shape, or conformation, of the enzyme, opening it up so that the kinase can bind ATP and its target proteins. What the crystal structure reveals, Kuriyan says, is that STI-571 binds to the inactive conformation of Abl.

This presumably prevents it from acquiring the activating phosphate, thus locking Abl in its inactive conformation, a mode of action that Witte says "makes good sense with how [STI-571] works in the leukemia." Targeting the inactive conformation also explains why

so few other kinases are inhibited by the drug. "When the kinases are active, they look very similar," Kuriyan says. "But when they are turned off, they can look very different from one another." He also notes that drug developers tend to think in terms of designing enzyme inhibitors that bind to the active enzyme, but for the kinases the inactive forms may make better targets.

A good many questions remain to be answered about STI-571. Clinicians will want to know, for example, how long its effects can be maintained in patients and whether it will work against solid tumors as well as CML. There are hints that it might. For example, Griffin's team has shown that it inhibits the growth in culture of small lung cancer cells, a cancer in which the kit oncogene kinase is often activated. But researchers are already pleased that what they have learned about the gene changes leading to cancer is beginning to pay off. "It's total vindication of the need to do basic science on the mechanisms of cancer," Witte says.

–JEAN MARX

EUROPEAN SCIENCE

## Call to Arms for Life Scientists

**GENEVA**—Seeking to create "a force for change in European research," nearly 2000 European life scientists gathered here last week at their first congress to promote solidarity, forge collaborations, and air complaints about how European managers dole out science funding.

"There is an enormous amount for [us] to do, when we compare the European situation to that in the United States," says cell biologist Kai Simons, president of the new European Life Scientist Organization (www.elso.org). Modeled in part on the American Society for Cell Biology, ELSO sprang from the brows of Simons and several other alumni of the European Molecular Biology Laboratory (EMBL), who saw the need for an organization to help unite Europe's molecular life scientists and to lobby Brussels to improve European Union (E.U.) research policies.

CREDIT: R. KOENIG

**Leading the chorus.** Kai Simons is spearheading an effort to get European life scientists speaking with one voice.

Simons—who recently became head of the Max Planck Society's new Institute for Molecular Cell Biology and Genetics in Dresden—and many others are dissatisfied with the E.U.'s flagship research effort, Framework 5. The 5-year, $17 billion program restricts much of its spending to priority areas. Innovative research tends to slip through the cracks, Simons contends. Another common complaint, he says, is that Framework mostly ignores young researchers, leaving it to the national programs to shoulder much of the support for grad students and postdocs.

Simons and other ELSO council members are bringing their guns to bear on the architects of Framework 6, a 5-year portfolio to start in early 2003. The organization's key aims are for the new Framework to offer more grants for postdocs and far more "generic" funds for research that does not fit into Framework spending categories. ELSO's leaders have already presented Brussels with a list of priorities for Framework 6, and the organization will now push to add a new grant category to allow more independence for young European researchers. "A lot of European scientists complain about the Framework Program, but we don't do anything about it. This is going to change," says the Finnish-born Simons. The group also intends to fight for better job opportunities for female scientists and to stimulate mobility and collaborative research among European life scientists.

The meeting featured presentations by four Nobel laureates and symposia on topics ranging from cell death to trends in mammalian genetics. Although most conferees hailed from Germany, France, and Switzerland, more than two dozen came from Eastern Europe, where Framework is just taking root. ELSO "can help draw good scientists in Eastern Europe into the mainstream, and to lobby Brussels on the importance of expanding research programs there," says ELSO council member Maya Simionescu, who directs Romania's Institute of Cell Biology and Pathology.

Although there are several Europe-wide life sciences organizations, ELSO organizers say their group is different because it does not restrict who can join, and it is not a federation of national societies. "It's important to have a bottom-up organization that allows life scientists from different fields to develop some priorities and to lobby," explains ELSO council member Denis Duboule, a University of Geneva biologist. All meeting attendees became enrolled in ELSO; European newcomers are also welcome. Now funded mainly by corporate grants, ELSO won't charge dues until it has "proven its worth" through lobbying, communications, and conferences, Simons says. To keep up team spirit between annual gatherings, ELSO has launched a free bimonthly magazine, *The ELSO Gazette* (www.the-elso-gazette.org). It will feature research reviews by "up and coming young European scientists," along with news articles about European research, job listings, and editorials, says editor Carol Featherstone, a former EMBL cell biologist.

Although attendance in Geneva reached only half the original goal, Simons says he is pleased. "Up until this conference, ELSO was a virtual organization," he says. "Now it is real."

–ROBERT KOENIG

X-RAY SCIENCE

## French 'Sun' to Rise at Site Near Paris

**PARIS**—The sun is shining on French science this week with the selection of a site outside Paris as the home of the country's first "third-generation" x-ray source.

On Monday research minister Roger-Gérard Schwartzenberg announced that the machine, called SOLEIL, or "sun," would be built near Saclay, about 20 kilometers southwest of Paris. The project had been cancelled by his predecessor, Claude Allègre, who feared that its $200 million price tag for construction and 8 years of operation would pinch other research budgets. But Schwartzenberg said that the national government's share should not exceed 20%, with regional and local authorities paying 75% and the rest coming from the United Kingdom, Spain, Belgium, and Portugal. Paris regional authorities have said they hope the new machine will attract companies to the area, which already boasts several universities and research institutions. SOLEIL's construction will begin in fall 2001, and it should go online in 2005, Schwartzenberg said.

"France needs to have a third-generation synchrotron on its own soil," Schwartzenberg said, adding that several other European countries have their own state-of-the-art machines. High-powered x-rays will allow researchers to probe the atomic structures of biological molecules and industrial materials at resolutions of just a few angstroms. The accelerator will have an energy of 2.5 to 2.75 giga electron volts and 24 beamlines for experiments.

Schwartzenberg said that Saclay beat out a site near Lille as the home for SOLEIL. France has already agreed to support the planned Diamond synchrotron in Britain (*Science*, 6 August 1999, p. 819).

–MICHAEL BALTER