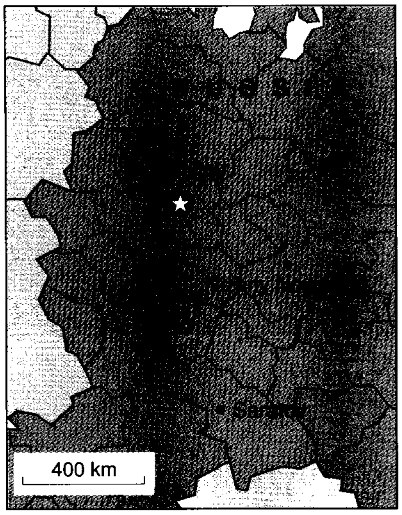
RUSSIAN SCIENCE

Program Luring Foreign Talent Gets a Boost

NIZHNY NOVGOROD, RUSSIA—For half a century this city was shrouded in mystery, closed to foreigners for much of the Cold War. But in a sign of how life has changed since the Soviet Union broke up, Nizhny Novgorod is now spearheading an effort to lure foreign scientists to Russia for short stints of teaching or research. The idea is that distinguished colleagues from abroad will fire up students—and, perhaps, preserve high-level science in the fraying former superpower. The program "helps students feel they aren't doing provincial science," says Alexander Litvak, dean of the University of Nizhny Novgorod's (UNN's) Advanced School for General and Applied Physics.



Centers of gravity. INCAS pulls in top guns.

In a tribute to how highly regarded the 4-year-old program—called the International Center for Advanced Studies (INCAS)—has become, it is now being replicated in two other regions. Earlier this month, the Open Society Institute (OSI), a foundation set up by financier George Soros to support reform in Eastern Europe, approved plans to fund INCAS centers in Saratov and Moscow, in partnership with local authorities. "INCAS is one of the little success stories that flies in the face of conventional wisdom that all is terrible in Russia now," says Neal Abraham, vice president for academic affairs at DePauw University in Greencastle, Indiana.

The idea for INCAS was born in late 1994, when Mikhail Rabinovich, a physicist at the Institute of Applied Physics (IAS) in Nizhny Novgorod and the University of California, San Diego, concluded that budding Russian researchers needed exposure to "aggressive, active scientists." Rabinovich first successfully pitched the idea to his former student, Boris Nemtsov, then the governor of Nizhny Novgorod region. Next he wooed Valery Soyfer, director of a Soros program that gives stipends to Russian educators and students. Soyfer praised INCAS to Soros, who told OSI to take a look. INCAS's merits and its shoestring budget—about $100,000 a year—convinced OSI to share costs with the regional government, now headed by Ivan Sklyarov, and Russia's science ministry.

Since then Rabinovich, IAS Director Andrei Gaponov-Grekhov, and dedicated volunteers have run annual grant competitions open to all institutes and universities in Nizhny Novgorod region. INCAS so far has awarded some 60 grants for local labs to host foreign scientists, who do everything from studying the optical properties of fullerenes to giving lectures on herbivorous insects. The typical research grant averages $4500, lasts less than 6 months, and pays expenses of visiting scientists, as well as stipends for a few young Russian students and researchers.

Foreign researchers say the visits produce results. Patrick Weidman, a physicist at the University of Colorado, Boulder, says his 3-month stint in 1996 for research on soap films yielded two peer-reviewed papers. But he also found that experimenting in Nizhny Novgorod can be a challenge: Supplies are scarce, and he had a hard time making devices. "The machine shop had no schedule," he says. "It just depended on whether the poorly paid machinists wanted to show up for work or not." Nevertheless, Weidman gives the program high marks and plans to return next summer.

Some visits have forged lasting ties. For instance, Princeton University and UNN have set up a joint graduate program in plasma physics. That way Princeton "won't just take away the best and brightest young people, but will use those young people as bridges" for future collaborations, says Princeton's Nathaniel Fisch. INCAS has also set up exchanges with the Catalan Society of Chemistry in Spain and the University of Bremen in Germany.

Building on its success, the program last year began seeking partners in other regions. It selected Saratov and Moscow, which along with Nizhny Novgorod will receive INCAS support for 2 years. INCAS-S, as it's called, will be run out of Saratov State University and be slanted toward the region's world-class research on nonlinear dynamics. INCAS-M will be headquartered at the Kurchatov Institute, the well-known nuclear physics center. These two regions beat out others interested in hosting INCAS centers because they anted up matching funds. Establishing a center in Moscow seemed to run counter to INCAS's philosophy of supporting science in the struggling provinces, but Kurchatov director Evgeny Velikhov persuaded his friend Rabinovich that Moscow was having as hard a time as anywhere else. "Usually we are trying to find partners in the provinces," admits Vyacheslav Bakhmin, director of OSI-Russia's culture division. "But sometimes exceptions take place."

INCAS officials say it's too soon to tell whether the program is convincing young scientists to make a go of it in Russia. But their effort is being applauded. "Without input and close interactions involving scientists from other countries, the once-powerful scientific activities within Russia may come to ruin," says John Eaton of Baylor College of Medicine in Houston. "It is precisely programs such as those at INCAS which hold promise for reversing the downward spiral in the quality and quantity of Russian science."

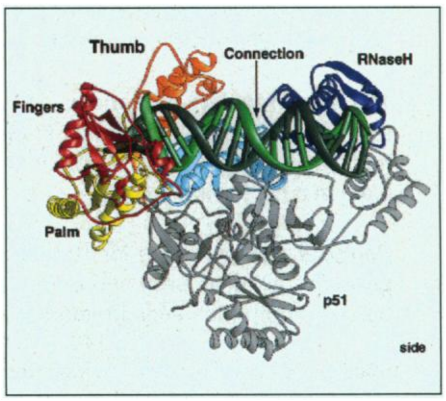
–RICHARD STONE

AIDS RESEARCH

Outsmarting HIV Drug Resistance

For many HIV-infected people, a cocktail of antiviral drugs is all that stands between them and the immune system collapse that characterizes full-blown AIDS. And sooner or later, this defense falters. Many of the drugs act by interfering with a key HIV enzyme called reverse transcriptase (RT), and eventually the replicating virus mutates into strains whose RT is resistant to the drugs, forcing patients to move on to new drugs or drug combinations. Now a team from Harvard University has obtained an atomic portrait of the enzyme that should give new clues to how the virus foils existing drugs, along with targets for new drugs that might be harder to thwart.

On page 1669, chemical biologists Gregory Verdine and Huifang Huang and structural biologists Stephen Harrison and Rajiv Chopra present the x-ray crystal structure of RT in a complex with the molecules with which it normally interacts in the HIV life cycle. They include one that binds to the same site as many of the existing anti-HIV drugs that work by inhibiting RT, including AZT and 3TC. As a result, says virologist Douglas Richman of the University of California, San



Pièce de résistance. Crystal structure of key HIV enzyme with its substrates.

CREDIT: (BOTTOM) HUANG ET AL.

Diego, "we can now visualize how the enzyme interacts with [RT inhibitors], which provides new insights into the mechanisms of resistance." Adds virologist Jaap Goudsmit of the University of Amsterdam, "This is a good paper, and it's very helpful."

Successfully blocking RT is critical to antiviral strategies because the enzyme catalyzes a vital early step in HIV infection: the copying of the virus's RNA genome into DNA, which is then integrated into the host cell's chromosomes. To do this, RT first copies its RNA strand into a DNA strand and then, using the DNA strand as a template, recopies it to make a DNA-DNA double helix. Although other groups have made x-ray structures of RT, no one had ever captured it as it acts on its natural substrates.

The Harvard team began by trying to crystallize a three-part complex made up of the RT protein; a DNA template, to which a short additional piece of DNA "primer" was bound; and a deoxynucleoside triphosphate (dNTP), a precursor building-block molecule that is repeatedly added onto the end of the primer to make the second DNA strand. Many RT inhibitors work by taking the place of dNTP and acting as DNA "chain terminators," gumming up RT function by bonding to the end of the growing DNA chain and barring the addition of new dNTPs.

Several groups, including Harrison's, had tried to crystallize this ungainly molecular complex for many years without success, apparently because the DNA primer–template combination associates only loosely with the RT protein. Harrison then asked Verdine's lab to help out, and Huang, after engaging in what Verdine calls "chemical biology heroics," succeeded in tethering the primer-template to RT with a disulfide chemical bond. The resulting complex was stable and uniform enough to form crystals, which the team took to two U.S.–based synchrotron sources to determine the structure of the enzyme, with all its substrates in place, to the detailed resolution of 3.2 angstroms. "This puts them all together and adds a critical piece to the puzzle [of resistance to RT inhibitors]," says biochemist Bradley Preston of the University of Utah, Salt Lake City.

This three-dimensional view of RT in action, combined with earlier studies of the location of drug-resistant mutations along its polypeptide chain, is already yielding new information about how RT foils the inhibitors. For example, those mutations already known to confer resistance directly to the drugs are all clustered around the dNTP site, which the inhibitor occupies when it terminates DNA chain growth. The authors propose that these mutations interfere with the drug's ability to attach to the DNA, either by making it harder for the inhibitor to get into the right position or by reducing its stability or reactivity once it is bound.

According to the Harvard team, the new structure also points to at least one possible target for new RT inhibitors: a small "pocket" in the enzyme near one portion of the dNTP site. Researchers say that drug companies are unlikely to wait long before following up these and other hints provided by the RT structure. "This opens a path to structure-based drug design," says Preston. "It really wasn't feasible before." –MICHAEL BALTER

NUCLEAR PHYSICS

Experiment Stopped After Safety Concerns

Nuclear physicists will have to wait a bit longer for long-sought data on the structure of the neutron. In a decision that has stunned members of an international research team, the United States' flagship nuclear science center, the Thomas Jefferson National Accelerator Facility in Newport News, Virginia, has pulled the plug on a major experiment to chart the distribution of the charged particles—quarks—that make up the neutron. The cancellation, announced 12 November, came after an accident last month that heightened tensions between visiting researchers and managers of the 2-year-old facility. The decision, which reflects a growing attention to safety, "has left grown men crying," says team spokesperson Donal Day, a physicist at the University of Virginia, Charlottesville.

Fatal attraction. Magnet pulled a tripod through the aluminum window of this target device.

CREDIT: DONAL DAY

Day is one of several dozen researchers working on the \$2 million G_{EN} experiment, seen as a key to proving decades-old theories about how the neutron—the neutrally charged particle in an atom's nucleus—is put together. It involves smashing a beam of electrons accelerated through a kilometer-long circular tunnel against a barrel-shaped target containing supercooled ammonium atoms. By monitoring the collisions, researchers hoped to tease apart the configuration of the neutron's quarks. Indeed, conducting the experiment was one of the main reasons the Department of Energy (DOE) built the \$600 million, state-of-the-art lab. "It wasn't the only experiment scheduled to address the question, but it was extremely important," says Don Geesaman, a physicist at DOE's Argonne National Lab in Illinois and head of the Jefferson lab's user committee.

However, that experiment had been plagued by delays since it began earlier this year. And its undoing came on the morning of 7 October, after a surveying team entered the experimental hall to make sure that the electron beam was correctly aligned before the next run. A powerful magnet that is part of the particle-scattering target had been accidentally left on, and its force pulled a surveyor's metal tripod through a thin aluminum window into the target. The collision caused an explosive release of the supercooled helium and damaged the sensitive machine. Although nobody was hurt, and the target was repaired, the mishap prompted an investigation into safety practices.

That investigation—and the researchers' reaction to the findings—prompted Jefferson Lab Associate Director Lawrence Cardman to call off the experiment. In a 12 November memo widely distributed to lab users, Cardman wrote that he had uncovered a potentially dangerous design flaw in the target's helium release valve, as well as numerous violations of safety procedures. But he was most troubled by signs that the visiting scientists and Jefferson staff "had not developed a good working relationship." In particular, he cited reports that a senior scientist had "ridiculed" a recent safety memo and that the researchers had been slow to submit a safety plan.

By the time the plan was done in early November, he says, it was "too late. Experiments like this require cooperation, and they weren't taking their share of the responsibility," although he also faulted his own staff. Another factor in his decision, he says, is that DOE has taken "a lot harder line" on safety in recent years.

Cardman and Day say that such friction between visiting researchers and lab management is not uncommon at a large user facility and can usually be worked out given enough time. In this case, however, the researchers were up against a tight deadline: The target is scheduled to be shipped to the Stanford Linear Accelerator Center in Palo Alto, California, at the end of the year for experiments there aimed at understanding how quarks behave. "We were running out of time," says Day, who notes that his team had safely operated the target in the past.

It is not clear when Day's team will get a chance to complete its work. The target is scheduled to return to Virginia late next year, but the lab's experimental schedule is full. On the bright side, Cardman believes Day's group should be able to demonstrate that it can operate safely and says he doesn't hold a grudge: "We haven't banned them for life."

–DAVID MALAKOFF