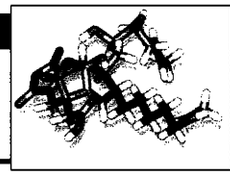
PAGE 1598
Synthesis of a "diabolical" molecule

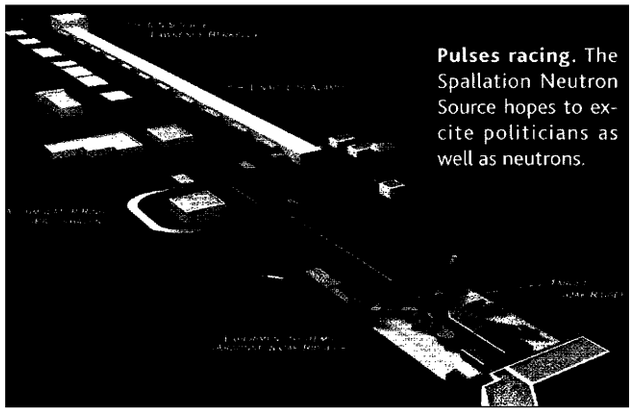


1601
Structure of an enzyme involved in metastasis

SPALLATION SOURCE

DOE Project Survives Close Call In Preliminary House Budget Vote

Neutron scientists are breathing a bit easier after their flagship U.S. construction project, the Spallation Neutron Source (SNS), walked a political tightrope last week in Congress—and survived. The key vote was cast by the House Science Committee, which reversed a thumbs-down verdict earlier in the day and agreed on a $100 million budget to begin construction. That authorization, combined with $169 million approved the previous week by a Senate spending panel, puts the $1.36 billion accelerator on firmer footing for budget battles later in the year.



Pulses racing. The Spallation Neutron Source hopes to excite politicians as well as neutrons.

The SNS, if built as planned at the Department of Energy's Oak Ridge (Tennessee) National Laboratory, will give scientists a uniquely powerful tool to probe the structure of matter, from proteins to metals, using a pulsed beam of neutrons (*Science*, 23 January 1998, p. 470). But as the largest new science project in the U.S. budget, it has drawn close attention from Congress. In particular, Representative James Sensenbrenner (R–WI), chair of the science committee, wants to make sure that the project's management structure, which teams five Department of Energy (DOE) national laboratories, won't produce a junior version of the failed $12 billion Superconducting Super Collider, an atom-smashing megaproject killed in midconstruction. As a result of that debacle, "the SNS is being held to a higher standard of review," says Martha Krebs, head of DOE's Office of Science.

Indeed, reports earlier this year that the project was becoming hobbled by management troubles and delays led DOE to reshuffle its supervisory lineup. It recruited neutron scientist David Moncton from the Argonne National Laboratory in Illinois—where he successfully delivered the $812 million Advanced Photon Source on time and under budget—to lead the project. "We have recruited a manager whose record cannot be questioned," crows DOE Under Secretary Ernest Moniz.

However, Moncton's arrival wasn't enough to satisfy Sensenbrenner. In late March, after a visit to Oak Ridge, he announced his opposition to DOE's 2000 budget request for $196 million in construction funds until the project passed a July review and implemented other planned reforms, including giving Moncton greater authority over the project. At a 25 May committee meeting, he unveiled a bill that prohibited any SNS construction spending and challenged DOE to deliver on its promises before he would consider authorizing any money. "If DOE can get its act together, we can authorize this project," he said.

But rather than wait to start the clock, Representative Jerry Costello (D–IL) proposed an amendment that would have restored $150 million in construction funds sooner. Sensenbrenner's bill "would effectively pull the plug on the nation's number one science project," Costello charged, adding that the fiscal uncertainty would scare away recruits. He also warned that House appropriators—who actually set DOE's budget—would use Sensenbrenner's stance as an excuse to starve the project. After a heated debate, the amendment failed on a 17–17 vote and the committee recessed for lunch.

During the break, Representative Bart Gordon (D–TN) drew up a compromise plan that included $100 million for construction once DOE met all of Sensenbrenner's conditions and offsetting cuts in other DOE programs. The amendment passed, 28–0. "At the end of the day, the committee had no reason to block construction," Gordon said. "This is good news for maintaining the project's momentum," Krebs declared.

Even so, the House vote virtually ensures that the SNS will receive less construction money next year than the $196 million requested. And that could pose a problem, say DOE officials, who argue that the project needs at least $150 million to stay on track. A final decision on the 2000 budget may not come until late this year. –DAVID MALAKOFF

ORGAN TRANSPLANTS

New Drug Blocks Rejection in Monkeys

People with failing kidneys face a difficult choice: chronic dialysis or a kidney transplant with a lifetime of immunosuppressive drugs, which boost the risk of cancer and are themselves toxic to kidneys. But that choice may someday be easier, if tests of a new drug in monkeys eventually pan out in people.

In monkeys, blocking a key immune system signal for only a few months after a transplant leads to long-term acceptance of the new organ—with no detectable side effects, according to a report in the June issue of *Nature Medicine* by transplant immunologist Allan Kirk and endocrinologist David Harlan of the Naval Medical Research Center in Bethesda, Maryland, and their colleagues. Human trials are just getting under way, but the primate results are "really, truly amazing," says transplant immunologist Norma Kenyon of the Diabetes Research Institute at the University of Miami in Florida.

The scientists caution that it's too soon to know if the monkeys have permanently accepted their new organs. The animals have developed antibodies to the transplanted kidneys, and although after more than a year those antibodies don't seem to be doing any harm, they may be the first signs of eventual rejection, says Kirk. But even with such caveats, "it is spectacular to have a monkey off of immunosuppression, with good graft function, for more than a year," says transplant immunologist Christian Larsen of Emory University in Atlanta, Georgia.

The new drug is an antibody that binds to a protein called CD154, one of two signals that the immune system's T cells need to launch an attack against an invader. When

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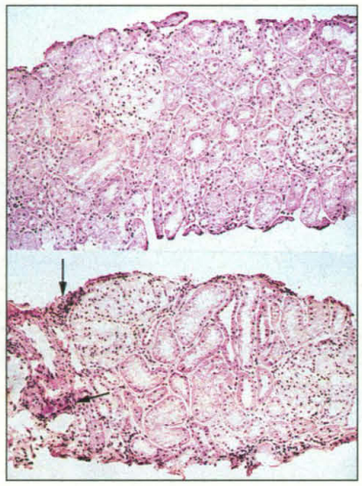
T cells encounter a foreign molecule such as those on transplanted tissue, they become activated and produce more CD154, which in turn binds to a receptor called CD40 on other immune cells. That sends a signal for an all-out, devastating assault on the transplanted organ. The antibody is designed to block the attack by binding to CD154 and preventing it from binding to its receptor.

The strategy has so far surpassed expectations. Building on initial animal trials, the team transplanted new kidneys into 25 juvenile monkeys. To increase the challenge, donors and recipients were mismatched for the major histocompatibility complex, the series of proteins on cells that help the immune system distinguish between native and foreign cells. The mismatch had lethal consequences: Control monkeys given either no treatment or standard immunosuppressive drugs rejected the organs and died in 9 days or less.

But animals given the drug fared much better. A group of nine monkeys received weekly doses of the antibody for 1 month and monthly doses for 5 months afterward. All treatment was then stopped. More than a year after treatment, eight of that group are still alive and well. The one death was due to complications during a routine blood draw, and an autopsy revealed that the monkey had normally functioning kidneys when it died. Another monkey from a different trial received a transplant in March 1997, was given a month of therapy, and has been living off a mismatched kidney ever since. "It just works every time," says Harlan of the drug. "I'm half expecting the balloon to pop at some point, but so far it hasn't."



No reject. Transplanted monkey kidney tissue *(bottom)* shows clusters of active immune cells (arrows), but looks like healthy tissue *(top)* and functions normally.

The technique, moreover, is not limited to kidney transplants. Kenyon's team has achieved similar success using the same antibody to block rejection of pancreas cell transplants in monkeys. In a paper in press at the *Proceedings of the National Academy of Sciences*, she reports that all six monkeys who received the CD154 antibody with their transplants have functioning islet cells as much as a year and a half later.

So far, Kirk and Harlan haven't been able to detect any side effects. Their monkeys have normal numbers of immune cells, did not develop wound infections, and responded normally to vaccines, indicating healthy immune function. Initial safety trials of the drug in humans, ongoing for more than a year, haven't produced any side effects, either. "I'm sure there are some downsides," says Kirk, "but we haven't found them yet."

One puzzling finding is that standard immunosuppressive drugs seem to interfere with the antibody's effect: Of the 11 animals that received a combination of standard immunosuppressors and the antibody, five died after acute rejection episodes. And no one is sure why the monkey's immune system accepts the foreign tissue long after the drug is stopped, although there are several theories.

Some scientists suspect that T cells activated by the foreign organ but lacking the CD154 signal simply die shortly after a transplant, although it's not clear why new generations of T cells wouldn't recognize and attack the tissue. Others suspect that the "stalled" T cells may somehow be protective. Biopsies of the transplanted kidneys reveal small clusters of activated T cells, which look like the ones seen in a few rare patients who, against doctors' orders, stop taking immunosuppressive drugs and surprisingly don't reject their transplants, says transplant immunologist Hans Sollinger of the University of Wisconsin, Madison. That may also help explain why the antibody performs poorly in combination with immunosuppressive drugs, which block T cells' initial activation.

That interference has made it difficult to design human trials for the new drug. Asking patients to forgo standard drugs to allow the experimental treatment to work is a "daunting" ethical challenge, says transplant immunologist Laurence Turka of the University of Pennsylvania. But the promising animal data prompted the National Institutes of Health last year to set aside a wing in its clinical center for trials of tolerance-inducing therapies, and researchers have enrolled a few patients for trials of a combination of the new drug and low doses of standard immunosuppression. If those prove as successful as the monkey trials, transplants may become an easier choice. **–GRETCHEN VOGEL**

CREDITS: (LEFT): KIRK *ET AL.*, *NATURE MEDICINE* 5, 6 (JUNE 1999); (TOP RIGHT) DFG; (BOTTOM RIGHT) RUPERT OBERHAUSER/BLACK STAR

GERMAN SCIENCE POLICY

Panel Calls for More Flexibility in Research

Germany's vaunted research system may be too rigid for its own good. Critics have accused it of being overly hierarchical and too slow to respond to hot research areas, and complained that it tends to hold back some young researchers by keeping them under the thumb of older professors. Last week, an international panel of prominent scientists echoed some of those gripes and went on to suggest a raft of reforms that aim to achieve more flexibility, greater cooperation between research institutes and universities, and give postdocs considerably more independence.

Reform school. Winnacker and Bulmahn back change.

The report was requested by the Federal-State Commission for Educational Planning and Research Promotion (BLK), which represents research and higher education ministries at the state and national level. In a summary issued last week, the 10-member panel—led by materials scientist Richard Brook, chief executive of Britain's Engineering and Physical Sciences Research Council—praised the overall quality of German research, which is based on three pillars: universities, the Max Planck Society, and the DFG basic research granting agency. "This is a strong, high-achieving research system," says Brook.

But the panel also highlights areas in