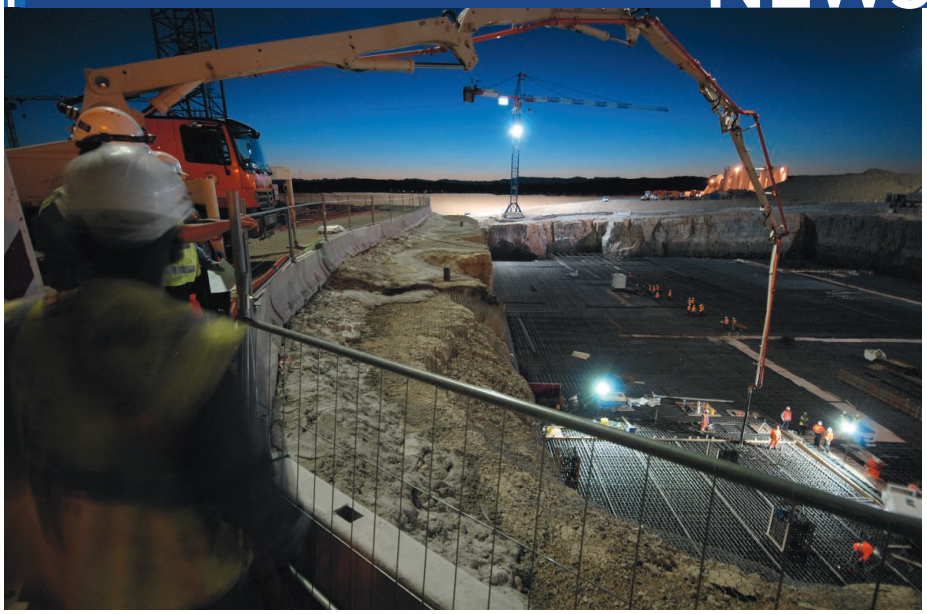


Under way. U.S. concerns about ITER costs come as construction moves ahead in Cadarache, France.

FUSION

U.S. Support for ITER Wavers as Costs Spiral

Soaring costs are jeopardizing the U.S. contribution to the international fusion energy project, ITER. Last week, a key member of Congress reacted with alarm to new projections showing that the U.S. share of the cost for the massive machine could reach $3.9 billion—roughly four times the original estimate made in 2006.

"I'm really beginning to believe that our involvement in ITER is not practical, that we will not gain what we hope to gain from it, and instead this money could be much better be spent elsewhere," said Senator Dianne Feinstein (D–CA), the chair of an appropriations subcommittee that controls ITER funding, at a hearing on 9 April. The Senate panel could move as early as next month to cut U.S. funding for ITER, which is already under construction in Cadarache, France, says a staffer who works for the Senate's Democratic majority.

Backing out of the commitment may be difficult. It would require the approval of Congress and the White House, and some U.S. officials worry that reneging on the deal could carry steep diplomatic costs with the other ITER partners, such as Europe and Japan. But the prospect of losing U.S. support has unsettled ITER leaders. "I'm very worried," says Robert Iotti, chair of the ITER Council of member nations and a nuclear engineer with CH2M HILL in Englewood, Colorado. "And frankly every day I'm more and more worried because things seem to be going in the wrong direction."

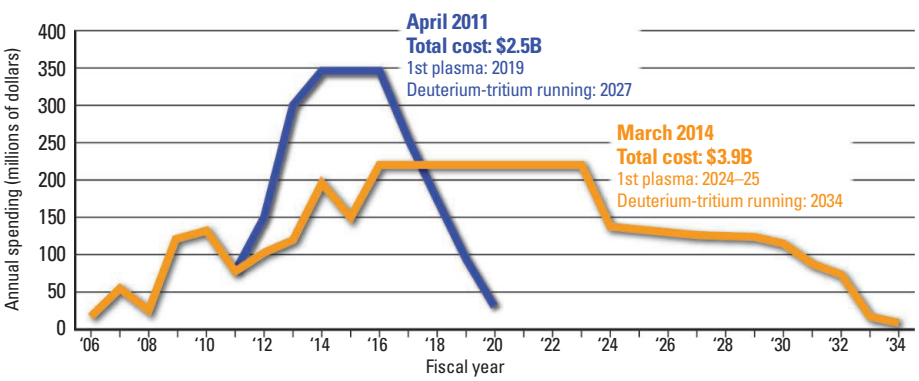
This isn't the first crisis to face U.S. supporters of ITER, which aims to use an enormous doughnut-shaped electromagnet to create a "burning plasma" that produces more energy than the machine consumes. Backers first proposed the project in 1985 as a joint venture with the Soviet Union and Japan. But the United States backed out in 1998, citing concerns over cost and feasibility—only to jump in again in 2003. At the time, planners estimated ITER would cost roughly $5 billion. That estimate had grown to $12 billion by 2006, when the European Union, China, India, Japan, South Korea, Russia, and the United States signed a formal agreement to construct the device, which was scheduled to start operations in 2016. As a result of delays and management problems, the ITER Organization now estimates the reactor will cost at least $21 billion and won't run until 2020 at the earliest—although some say even those figures are wildly optimistic.

The United States committed to building 9% of the ITER machinery, which in 2006 the Department of Energy (DOE) estimated would cost $1.1 billion. By 2011, the estimate had risen to $2.5 billion. U.S. officials had not released an updated cost profile in recent years. But now the U.S. contribution is expected to total $3.9 billion by the time ITER is fully operating in 2034, Ned Sauthoff, project manager for U.S. ITER at Oak Ridge National Laboratory in Tennessee, told a meeting of DOE's Fusion Energy Sciences Advisory Committee in Rockville, Maryland, on 9 April. The estimate assumes ITER will start running with ordinary hydrogen fuel in 2024 or 2025 and will shift to deuterium and tritium fuel—the mixture needed for a burning plasma—10 years later.

In spite of the delays, the U.S. effort is making "strong progress," Sauthoff says. "U.S. components needed for the construction sequence are being completed for delivery in 2014 and 2015," he says.

Much of the increase is the result of a DOE decision to stretch out ITER spending over a longer time period, which amplifies the effects of inflation and requires larger amounts of "contingency" funding to cover budget uncertainties. Early plans called for DOE to spend $350 million a year on ITER from 2014 through 2016. But that would have eaten up most of DOE's fusion budget, leaving little for domestic programs. So in

U.S. ITER Budgets—Old and New



Longer, costlier. U.S. ITER costs are rising as spending gets spread out.

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Published by AAAS

formulating this year's budget, department officials proposed capping ITER spending at $225 million; in the end, Congress gave ITER just $200 million of DOE's $505 million fusion budget. The White House proposes spending even less on ITER, $150 million, in the 2015 fiscal year which begins 1 October.

That low request may reflect a division within the Obama administration, says the Democratic Senate staffer. Diplomats at the U.S. State Department argue that the U.S. commitment is akin to a treaty and can't be broken, he says. (State Department officials declined comment.) But some DOE officials may be happy to walk away from the troubled project, he adds. Congress could break the deadlock when lawmakers revise, or mark up, the administration's proposed budget for 2015. In the Senate, "our intention is to make a decision for ourselves in our markup," the staffer says. "They won't have a choice."

The Senate's final stance could depend on how well the ITER Organization responds to a scathing management review it received this past February (*Science*, 28 February, p. 957), a Republican staffer in the Senate says. Among its 11 recommendations: replacing ITER Director-General Osamu Motojima, reducing the number of senior managers by half, developing a realistic schedule, and creating a culture of urgency in the project. "If they make those changes, then there is viability in the [U.S.] program," predicts the staffer. But if "they don't, there isn't."

The ITER Organization is striving to implement those recommendations, Iotti says. "We are taking immediate action on all of them." But some changes—such as finding a new director-general—will take time, he notes. And some problems may never be completely fixed. Iotti notes that, according to the ITER agreement, the director-general cannot give orders to member nations; he can only try to persuade them to make changes.

Even if the Senate follows through on its threat, U.S. work on ITER won't stop immediately. The House of Representatives, which has been more supportive of fusion research, must pass its version of the budget, and any final spending must win approval of both houses of Congress and the White House. That process will take months, one Republican House staffer predicts. The Senate may use its markup to send a message, he says: ITER must shape up.

Still, Iotti worries that the U.S. flare-up puts the fate of ITER as a whole at risk. "In my opinion, it might be fatal [to the project] if the U.S. were to drop out," he says. Suddenly, that seems like a possibility.

–ADRIAN CHO

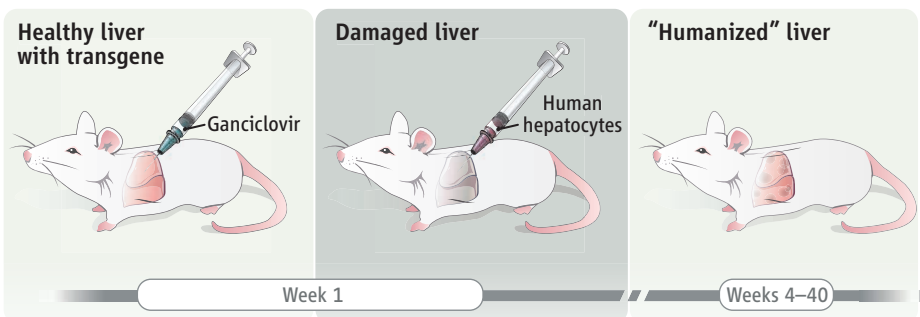
TOXICOLOGY

'Humanized' Mouse Detects Deadly Drug Side Effects

After five patients died in a small clinical trial of an experimental hepatitis B drug in 1993, high-level committees scrambled to work out what went wrong. In the end, they blamed not the researchers but the lab animals. Earlier studies, including several in animals, simply failed to show that the drug was toxic.

Now, researchers say they have developed an animal model that would have detected the drug's toxicity: an engineered mouse with a humanlike liver. They say it could serve as a versatile testbed for liver toxicity, a worrisome side effect of many drugs.

Gary Peltz, a rheumatologist at Stanford University School of Medicine in California, heads one of several groups that have engineered mice to have "humanized" livers. Other groups have primarily used their models to investigate fundamental questions about metabolism, and some have reported drug effects. But none has taken the toxicology model as far as the FIAU study that Peltz and co-authors published in the 15 April edition of *PLOS Medicine*. This is "the first definitive example of a human-specific, drug-induced toxicity that could



Recipe for a chimeric mouse. Researchers first kill mouse liver cells, and then transplant human hepatocytes.

"The study is a tour de force," says Jay Hoofnagle, director of the Liver Disease Research Branch at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland. Hoofnagle was not involved in the work, although his division partly funded it. He led the infamous 1993 trial, which tested a hepatitis B drug known as fialuridine (FIAU).

That phase II study was designed to evaluate different doses of FIAU in 15 people who had chronic hepatitis B infections. The drug caused severe lactic acidosis in seven patients; two died quickly, and five received liver transplants, but only two survived. Earlier experiments in mice, rats, dogs, and monkeys had tested FIAU at various doses and found no detectable harm. Similarly, small human studies conducted by other researchers had not tied any serious adverse events to the drug. Expert committees convened separately by the U.S. National Institutes of Health (*Science,* 10 June 1994, p. 1530) and the Institute of Medicine (*Science*, 24 March 1995, p. 1759) each determined that Hoofnagle and collaborators had acted appropriately in conducting their trial.

be detected in chimeric mice, but not in conventional rodent, dog, or monkey toxicity studies," the researchers assert. (One of the co-authors, Stanford's Jeffrey Glenn, has collaborated with Hoofnagle on hepatitis studies.)

Peltz's team destroys the liver cells in an immunodeficient mouse strain called NOG by stitching in a transgene of an enzyme, thymidine kinase, from herpes simplex virus-1. Then they give the mice the drug ganciclovir, which becomes active only in the presence of this enzyme, selectively killing mouse liver cells but not otherwise harming the animals. Finally, they transplant human liver cells into the mice, which they dubbed TK-NOG. The resulting mice live for up to 8 months, and their livers metabolize drugs in much the same way as a human liver.

For their new study, Peltz and co-workers wanted to demonstrate the mouse's value for drug testing. "I called a number of people and asked what was the best example of a drug where preclinical toxicology failed to predict what would happen in humans," says Peltz, who formerly ran genetics and genomics research at Roche's now-closed

CREDIT: V. ALTOUNIAN/*SCIENCE*, ADAPTED FROM G. PELTZ, *TRENDS IN PHARMACOLOGICAL SCIENCES*, **34** (MAY 2013)