Joint Genome Institute in Walnut Creek, California, to take on the creature. Eighteen months later, about 50 biologists and bioinformaticists spent a week poring over the newly assembled draft genome. They identified as many genes as they could and compared the sea squirt sequence to existing genome information, focusing on how various types of genes had changed through time. The results of this effort are reported on page 2157.

The sea squirt's 117 million bases sequenced include 16,000 genes. Among the genes are single and double copies of genes that have multiplied several times in the mouse and human genomes. The sea squirt shares about 60% of its genes with the nematode and fruit fly, whereas about 5% have matches only in the human, mouse, and puffer fish genomes. And about 20% seem unique to *Ciona*, including several involved in the production of a stiff starch called cellulose, the main ingredient in its tunic.

"Every genome is like a history book," explains Peter Holland, an evo-devo biologist at the University of Oxford, U.K. "But the problem is [that] there don't seem to be any dates" for when different genes appeared over the course of evolution. The new sequence, however, should enable biologists to distinguish which genes arose in vertebrates and which predate the split between vertebrates and sea squirts. For example, *Ciona* lacks many vertebrate neural genes and certain immune system genes, suggesting that these came after the split between tunicates and early vertebrates. These additions, says Levine, made possible "probably the most spectacular [vertebrate] innovations": the complex nervous and immune systems.

To Holland, the fact that many genes have multiplied in vertebrates but not in *Ciona* "suggests that something dramatic happened to vertebrates" that caused this great expansion. Take *Smad* genes, which typically help regulate bone development. *Ciona* has five; mice have eight. This change in gene number is "a recurring theme in the analysis of the *Ciona* genome," Rokhsar points out.

Some genes' origins can be pinpointed to a time when the common ancestor to vertebrates and sea squirts thrived. For example, thyroid hormones and receptors are not found in other invertebrates but are present in *Ciona*. "We don't know what they are doing," says Rokhsar, but he suspects that they are involved in the transition from tunicate tadpole to sedentary adult, as they are in frogs' metamorphosis.

Meanwhile, *Ciona*'s unique genes for making cellulose "come out of nowhere," Carroll points out; they have not been found in other animals. Levine sees the genes as "very compelling evidence for remarkable horizontal gene transfer between bacteria and *Ciona*," as the sea squirt seems to have adopted bacterial enzymes needed to use cellulose.

Even more genomes must be sequenced before researchers can say whether Levine is right about the horizontal transfer. And the more genomes the better, evolutionary biologists argue. "As each complete genome unfolds," says Carroll, "we are getting a bigger and better picture of patterns of gene evolution and of gene families." –ELIZABETH PENNISI

RESEARCH INFRASTRUCTURE

NSF Urged to Boost Spending on Facilities

Nobody's talking about changing the National Science Foundation's (NSF's) name to Need to Support Facilities. But the foundation must spend a larger share of its $5 billion budget on research infrastructure to maintain U.S. leadership in science, declares a new report from its oversight body.

An internal survey of NSF's disciplinary offices yielded a wish list of almost $2 billion a year through 2012 for scientific tools ranging from computing networks and research vessels to telescopes and synchrotrons (see table). That's double NSF's current spending level. "The need is greater than we can address with our normal budget mechanisms, and it won't go away," says John White, chancellor of the University of Arkansas, Fayetteville, and chair of the National Science Board task force that produced the 41-page draft report posted this week (www.nsf.gov/nsb; 02-190).

A DECADE OF NEEDED FACILITIES

Price range (in millions)	Total
$1–$10	3950
$10–$50	5400
$50–$250	6800
$250–$500	1700
$500+	1000
TOTAL	**18,850**

Midsized crisis. There's a growing need for moderately priced facilities.

The top spending priority, according to the board, should be advanced cyberinfrastructure —not just more powerful computers but also better storage, analysis, visualization, and distribution tools—to benefit the entire scientific community. This is a broad program, "not just bigger machines at a few places," says board member Anita Jones of the University of Virginia, Charlottesville. But certain disciplines also have big needs, the board says. NSF would have to triple its annual spending on large research facilities—to $350 million—just to eliminate a backlog of detectors, telescopes, and other projects that the board has approved but Congress has yet to fund (*Science*, 14 September 2001, p. 1972). There's also a problem with "mid-sized" facilities—those costing tens of millions of dollars—that are too pricey for individual programs yet too small to rank as a major research installation.

NSF now spends 22% of its budget on tools, a fraction that "is too low," according to the report. The task force would like to see it grow to about 27%, says board member Robert Richardson, vice provost for research at Cornell University. The report, 2 years in the making, expresses the hope that a growing NSF budget will provide "the majority of these additional resources." That's a reference to a projected doubling of NSF's budget over 5 years, a concept that Congress endorsed last month in passing a bill that reauthorizes NSF's programs.

Should the pie not expand rapidly enough, however, NSF officials might have to revisit the thorny issue of striking the right balance between "big" and "little" science. "I think that the PI [principal investigator] community could see it as a threat," says one science policy analyst who had not yet seen the report. At the same time, a university lobbyist speculates that the needs outlined in the report could be used by some federal legislators to help push for a broader economic stimulus package.

The board hopes for feedback from the community before issuing a final version of the report this winter. "The proposed changes are not radical, but they are significant," Richardson told board members before they signed off on the draft report. "And I think people should pay attention." –JEFFREY MERVIS

PATENTING LIFE

Canadian High Court Rejects OncoMouse

OTTAWA—Canadian researchers don't have to worry about paying licensing fees for the use of transgenic animals. The nation's top court ruled last week that higher life forms aren't patentable.

In a 5–4 decision, the Supreme Court of Canada ended Harvard University's 17-year quest to obtain Canadian patent protection for its OncoMouse, ruling that the cancer-prone rodent can't be owned. The court said that OncoMouse, developed by Philip Leder of Harvard Medical School in Boston, isn't an invention under a 1869 Canadian law that protects "any new and useful art, process, machine, manufacture or composition of matter."

Although the court prohibited the patenting of OncoMouse, it did allow Harvard to proceed with applications to protect the process by which the animal is engineered. "We're going to do our best to squeeze all the protection we can out of this judgment,"

says Ottawa lawyer David Morrow, who represents the university. Morrow believes that the decision leaves room for patents on cells, cell cultures, plasmas, and other aspects of OncoMouse, which is licensed to researchers through E. I. du Pont de Nemours and Co. of Wilmington, Delaware.

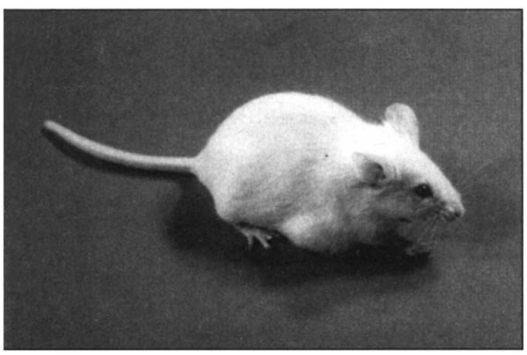
Writing for the narrow majority, Justice Michel Bastarache made a philosophical argument for the court's ruling, which stands in contrast to patents granted by 17 nations, including France, Germany, Japan, and the United Kingdom. "A complex life form such as a mouse or a chimpanzee cannot easily be characterized as 'something made by the hands of man,'" he wrote. Nor is OncoMouse a "composition of matter," he added. "Higher life forms are generally regarded as possessing qualities and characteristics that transcend the particular genetic matter of which they are composed," Bastarache noted. "A person whose genetic makeup is modified by radiation does not cease to be him or herself. Likewise, the same mouse would exist absent the injection of the oncogene into the fertilized egg cell; it simply would not be predisposed to cancer."

Although Canada has granted patent protection to lower life forms such as yeasts, Bastarache wrote, it's up to Parliament to sift through the thorny ethical issues and decide whether higher life forms should be patentable. Should Parliament decide that, it won't be easy to draw the line between what is patentable and what isn't, Bastarache warned: "There is no defensible basis within the definition of invention itself to conclude that a chimpanzee is a 'composition of matter' while a human being is not."

BIOTECanada president Janet Lambert says the decision has "sent a pall" through the burgeoning industry and could stifle new investment. But Matthew Spence, president of the Alberta Heritage Foundation for Medical Research in Edmonton, thinks that most Canadian researchers and companies will not be affected by the ruling. Although some small firms might move south out of fear that their intellectual property could be plundered, he says, others might favor the current environment, "because we're not getting delays due to patent considerations."

Some predict that the ruling might even stimulate research. "The patent only gives the patent holder the right to exclude others," says Arnold Naimark, director of the University of Manitoba's Centre for the Advancement of Medicine in Winnipeg and chair of the federal government's arm's-length Canadian Biotechnology Advisory Committee. "If there is no patent in Canada, there is no restriction on people being able to do research on the Harvard OncoMouse if they get a hold of it." **–WAYNE KONDRO**

Wayne Kondro writes from Ottawa.



CREDITS: (BOTTOM) HARVARD MEDICAL SCHOOL

Hands off. Canada says it won't grant patent for Harvard's OncoMouse.

GENE THERAPY

RAC's Advice: Proceed With Caution

BETHESDA, MARYLAND—The cancer that appeared earlier this year in a patient who took part in a French gene therapy trial appears to have been caused by a rare combination of factors, a panel of experts concluded at a meeting here last week. The risk of a second occurrence seems sufficiently remote, the panel agreed, that this trial and others like it should go forward.

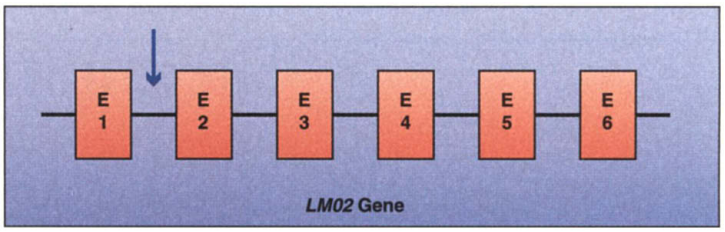
This review by the National Institutes of Health's (NIH's) Recombinant DNA Advisory Committee (RAC) was the second major U.S. inquiry into an adverse event in a trial of therapy for severe combined immunodeficiency (SCID) at the Necker Hospital for Sick Children in Paris. Nine of 11 children in the study have shown remarkable improvement. But after one boy developed a leukemia-like disorder in September, lead investigator Alain Fischer and co-workers halted the study out of concern that the therapy might have triggered cancer. Agencies in several countries, including the U.S. Food and Drug Administration (FDA), put other SCID trials on hold.

The French team, working with Christof von Kalle, a molecular biologist at Cincinnati Children's Hospital Medical Center in Ohio and the University of Freiburg, Germany, concluded that the retrovirus they used to shuttle working genes into the patient's cells had inserted into a gene called *LMO2* that has been linked to T cell leukemia (see diagram). A single γδT cell with this insertion then began proliferating, and the child's T cell count soared. In mid-October, an FDA advisory committee decided that three pending U.S. SCID trials should go forward, but it asked for changes to monitoring plans and informed-consent documents (*Science*, 18 October, p. 510). Investigators are still working on the revisions. SCID trials remain on hold in Italy and Japan but were not suspended in the United Kingdom. Germany last month decided to resume some halted retrovirus trials.

At last week's meeting, experts noted that they have suspected "for decades" that a retrovirus could insert in the wrong place, but the risks have been theoretical until now. Said Theodore Friedmann of the University of California, San Francisco (UCSF), RAC's chair: "This event represents kind of a watershed event in the field of gene therapy."

The case also might be unique. At the meeting, Alexander Rakowsky of NIH's Office of Biotechnology Activities reported that OBA has now looked for other unexpected cancerlike disorders in 181 trials, registered with the office since 1988, that used retroviruses. NIH found eight suggestive reports but no evidence that any cancers were caused by gene therapy.

Von Kalle reported that the leukemic cells from the affected child in the French trial contained another anomaly—a copy of part of chromosome 6 attached to chromosome 13—



Bad location. DNA from a retroviral vector inserted between the first and second exons of *LMO2*, a gene linked to T cell leukemia.

that does not appear to have been caused by the gene therapy. Fischer and Von Kalle's group postulates that this 6;13 translocation somehow contributed to the cells' cancerous morphology. The child, who is being treated with chemotherapy, no longer has detectable T cells with morphology typical of leukemia, von Kalle said, even though cells carrying the altered *LMO2* gene are still present.

The child's extended family had an unusual occurrence of two cases of a particular childhood cancer. This led many of the 17 RAC panelists to conclude that this predisposition and other factors, possibly involving the 6;13 translocation, worked in concert with the *LMO2* insertion to produce leukemia. "Given this family's history, we may never see another leukemia," said cancer researcher David Sidransky of Johns Hopkins University in Baltimore, Maryland. Not everyone agreed, however: Maxine Lineal of the Fred Hutchinson Cancer Research Center in Seattle warned, "It wouldn't surprise me if in 20 years, we were seeing tumors in more of these children."

Unlike the FDA panel that met in October,