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.

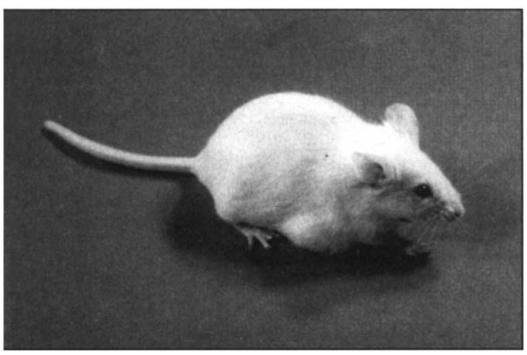
Writing for the narrow majority, Justice Michel Bastarache made a philosophical argument for the court's ruling, which stands in contrast to patents granted by 17 nations, including France, Germany, Japan, and the United Kingdom. "A complex life form such as a mouse or a chimpanzee cannot easily be characterized 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.

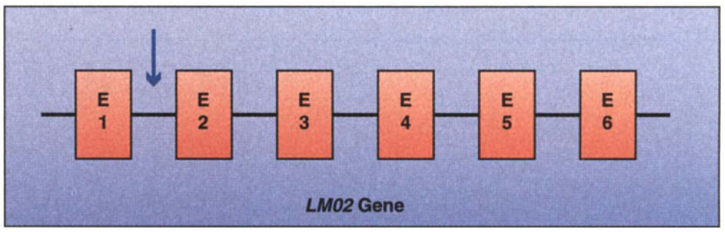
This review by the National Institutes of Health's (NIH's) Recombinant DNA Advisory Committee (RAC) was the second major U.S. inquiry into an adverse event in a trial of therapy for severe combined immunodeficiency (SCID) at the Necker Hospital for Sick Children in Paris. Nine of 11 children in the study 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,

RAC concluded that the gene therapy was "a cause" of rather than "likely caused" the child's leukemia, and that "other predisposing factors may have contributed." Although other SCID trials should proceed, RAC concluded, federal guidelines should be revised to include a suggestion that gene-therapy researchers do more intensive monitoring for signs of cancer and archive tissue so that molecular events can be traced. "We would know nothing about the French patient if they had not archived samples," says UCSF's Diane Wara.

RAC is scheduled to vote on further recommendations at its next meeting in March, when it will expand the discussion to other gene-therapy studies that use retroviruses. "This is just the beginning," Friedmann says.

–JOCELYN KAISER

PLANETARY SCIENCE

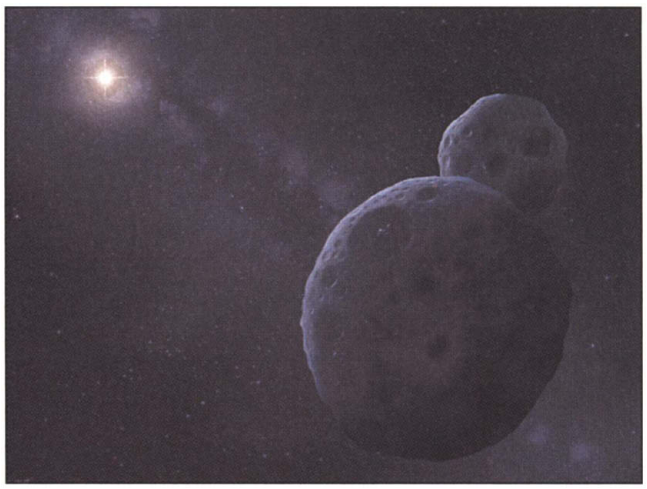
How a Pair Marries For the Eons

Planets have satellites. Asteroids have satellites. So astronomers weren't too shocked to discover in 1998 that Kuiper belt objects —icy remnants from the solar system's formation—have them, too. But they were mystified nonetheless: The pairs of Kuiper belt objects (KBOs) spotted out beyond Pluto seemed impossibly large and widely separated; companions are of comparable size and hundreds if not thousands of times their own diameters distant from each other. Collisions between asteroids suffice to loft bits of rock into close orbit, but how could so much mass get so far from its companion? In this week's issue of *Nature*, three astrophysicists more likely to be working on stars and galaxies than nearby ice balls suggest a way that such binary KBOs might have come into existence in the earliest days of the solar system without the help of collisions.

According to the new calculations, the relationships developed slowly. Newborn KBOs would have interacted through their gravitational pulls, first forming loosely bound, unstable pairs during close encounters and then being stabilized by gravitational interactions with other KBOs. The proposed mechanism predicts that, as astronomers sharpen their view of the Kuiper belt, they'll find that most KBOs are tightly bound binaries, or even triplets, and that the standoffish partners seen so far are outliers. "It's an exciting paper," says planetary dynamicist William Bottke of the Southwest Research Institute (SwRI) in Boulder, Colorado. "It's a really creative mechanism." But it's not the only proposed solution. A closer look at the Kuiper belt should determine the winner, or winners.

In the past, theorists have come up with viable explanations for binaries of all kinds. In the 1980s and early '90s, studies of terrestrial craters began suggesting that about 15% of impactors were actually doubles. So in 1996, Bottke and planetary dynamicist Jay Melosh of the University of Arizona, Tucson, argued that if collisions have battered all but the largest and the very smallest asteroids into flying piles of rubble, Earth's tidal forces could pull apart any rubble-pile asteroid that flew within 10,000 kilometers or so—much as Jupiter ripped apart comet Shoemaker-Levy 9. Sometimes, the ruptured rubble pile would form a binary that would later hit Earth. Discoveries in the last few years confirm that about 15% of near-Earth asteroids are indeed closely bound binaries.

Out in the main asteroid belt, there's no planet handy, so after the 1994 discovery of tiny Dactyl orbiting Ida, the first asteroid seen to have a satellite, theoreticians quickly came to rely on collisions to explain binaries there. Two chunks of debris from the catastrophic disruption of an asteroid could go into orbit around each other, a glancing blow might set an asteroid spinning so fast that it split into a binary, or ejecta from an impact might go into orbit and agglomerate to form a satellite. But "in the case of KBOs, both tidal fragmentation and collisional formation seem very unlikely," says Bottke. "We probably need a completely different formation scenario."



Partners. If Kuiper belt objects bond without a collision being involved, astronomers should find particularly close pairs such as this one.

That's where astrophysicists Peter Goldreich, Yoram Lithwick, and Re'em Sari of the California Institute of Technology (Caltech) in Pasadena came in. Lacking a convenient planet or the necessary huge collisions, they looked at close, purely gravitational KBO encounters, which would have been far more frequent than collisions were. The Caltech group first calculated how often two large KBOs passing near each other would temporarily fall into orbit around each other before again going their separate ways. They then calculated how often such a transient binary could lose enough energy to become a stable binary, the way retrorockets rob energy from a spacecraft to bring it into orbit. A third large KBO passing nearby in the century or two before breakup could do the trick. More subtly, the cumulative gravitational influence of the sea of small KBOs that the pair is passing through could gently rob energy from it. Together, the two mechanisms would have produced the small percentage of widely separated binaries observable today, according to the Caltech calculations.

Collisionless formation of KBO binaries "is definitely promising," says planetary dynamicist Daniel Durda of SwRI, Boulder, because it overcomes the "need for incredibly huge projectiles" in collisional mechanisms. But there might be another way too, Durda notes. Planetary dynamicist Stuart Weidenschilling of the Planetary Science Institute in Tucson has just published a hybrid mechanism in the November issue of *Icarus*. He uses a collision, but the two colliding KBOs merge. When their merging takes place within the gravitational influence of a third KBO, the combined body can form a binary pair with that third body. Both the Caltech group and he "did primitive, back-of-the-envelope calculations," says Weidenschilling. "There's a lot more work needed to compare calculations against observations. It may be both mechanisms are viable."

Goldreich and colleagues disagree. Whatever conditions are assumed for the nascent solar system, they write, the close encounters their mechanism requires will always be far more abundant than are the collisions that Weidenschilling needs. "You never need these collisions," says Sari. "You just need the third body to be there."

Resolution could come with more detailed observations. The collisionless mechanism predicts that, like most stars, most KBOs are binaries (although today's instruments can't yet distinguish small, closely spaced pairs). KBO pairs would have formed with wider separations but spiraled inward until they were too close for current telescopic observations to separate them. The hybrid mechanism, on the other hand, predicts a decreasing abundance of binaries at smaller separations. At stake are insights into what the early, still-forming solar system was really like, including how Pluto and its huge moon Charon came to be paired. "It's going to be very interesting," says Durda.

–RICHARD A. KERR