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GENE THERAPY

What to Do When Clear Success Comes With an Unclear Risk?

An expert panel, meeting in an emergency session last week, urged the U.S. Food and Drug Administration (FDA) to lift a hold it had placed on three gene therapy trials after a patient treated with gene therapy in France developed cancer (*Science,* 4 October, p. 34). The panel made the recommendation after concluding that the cancer was almost certainly caused by the gene therapy. For safety reasons, the United States, France, and Germany have suspended clinical trials that use the same gene-transfer technology. But the United Kingdom has not, leaving it up to clinicians and patients to weigh the risks and benefits. FDA's advisers seem to favor the British approach.

Chaired by molecular biologist Daniel Salomon of the Scripps Institute in La Jolla, California, the FDA panel confirmed what many had feared: A 3-year-old boy in the French trial has developed cancer that probably was caused by a modified retrovirus that was used to shuttle healthy genes into his cells. Yet panel members also recognized that the trial resulted in the only unequivocal success for gene therapy so far. Alain Fischer and his colleagues at the Necker Hospital for Sick Children in Paris have treated 11 children with severe combined immunodeficiency (SCID), a disease that often causes children to die from infections before they are 1 year old. Nine now have sound immune systems. Because the benefits seem clear and the risks are poorly understood, the panel agreed that the research should go on but with strict monitoring of therapies that involve retroviruses.

The evidence linking the boy's cancer to the retrovirus used to treat him came from the French team itself, working with Christof von Kalle, a molecular biologist now at the University of Cincinnati Children's Hospital in Ohio. Von Kalle discovered the problem, he explained in an interview, because "we were trying to follow the healthy cells" of young patients. His analysis showed that eight of the patients were doing well. But an anomaly turned up earlier this year in patient number four, who had received therapy at the age of 1 month.

Thirty months after therapy, in spring 2002, this boy had a high concentration of a particular type of immune cell ($\gamma\delta$T cell) in his blood. Doctors initially thought this was a "sampling error," von Kalle explained. But by late August, the boy had anemia and an enlarged spleen. The cell count for the anomalous T cell shot up by 2 September to 300,000 cells per microliter of blood. Clinicians began giving him a type of chemotherapy used for T cell leukemia, while alerting health officials in France and other countries. Since September, the child's unhealthy T cell count has come down, but no one knows what course this unique disease will take.

Meet the press. FDA's Philip Noguchi (*above*) and biologist Christof von Kalle talk to reporters after panel meeting.

Stored blood samples revealed that the patient's explosive T cell growth likely began sometime between the 13th and 17th month after therapy. Von Kalle analyzed the errant T cells—a clonal outgrowth of a single treated cell—and found that they included the sequence of the retrovirus vector and the new curative gene it transported. But he also found something that left the FDA panel chair "scared": The foreign DNA had inserted itself, in reverse, in the initial coding region of a gene (*LMO2*) essential for the early development of blood cells. More than a decade ago, researchers tied aberrant expression of this gene to leukemia. Von Kalle described one additional anomaly that appeared in these T cells: Part of chromosome 6 was duplicated and attached to chromosome 13.

A few members of the FDA panel argued that gene therapy shouldn't get all the blame for triggering the unhealthy T cell growth. Some found it hard to believe that a short, reverse-oriented DNA insertion would have such a devastating effect. And, as von Kalle noted at the hearing, the boy got a chickenpox infection just before his T cell count soared, and a sibling and a distant relative had cancer in childhood. But oncologist Linda Wolff of the National Cancer Institute and retrovirus expert John Coffin of Tufts University in Medford, Massachusetts, both described how, in animals, retrovirus insertions can dramatically change the expression of genes—even distant ones.

Stuart Orkin of the Dana-Farber Cancer Institute at Harvard University in Boston then read a warning from a report he had coauthored in 1995, noting an inherent risk of leukemia in retrovirus-based gene therapy. He said that there are "potentially numerous sites within the genome that could contribute to leukemia," adding that the more he learns about the genome, the more possibilities he finds. In summing up, Salomon said there is no avoiding it—the most successful gene therapy trial also appears to have been the first to induce cancer.

Salomon and other panel members said FDA should ask clinics to step up their monitoring of patients who have been treated with retroviruses. FDA estimates that about 300 clinical trials have provided therapy using retroviruses and 150 are still active. The panel also recommended that SCID patients be excluded from this therapy if they can get a bone marrow transplant from a matching (HLA-identical) donor, and that clinicians warn volunteers that retrovirus therapy can cause cancer. "We should be absolutely clear," Salomon said: "This shouldn't be a line buried in acres of text."

FDA usually follows advice from such panels. Philip Noguchi, the agency's gene-therapy specialist, said he thought the panel had reached a "remarkable consensus" on several points. He said that FDA plans to re-

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quest "some modifications" and ask clinicians using retroviral vectors to notify participants in their study of the leukemia found in this case and revise their consent forms to include this information. But he couldn't say when the trials might resume.

One panel member—Abbey Meyers, president of the National Organization for Rare Disorders—made a pitch for placing all retrovirus-based trials on hold because no one can judge the risks. But her message didn't carry as much emotional weight as another advocate's. A woman who identified herself only as a grandmother of a SCID child rose from the audience to ask that the trials continue. Her grandson, she said, has failed bone marrow transplantation four times and has been waiting 3 years to be enrolled in a trial, now on hold, at the National Institutes of Health. The FDA panel paid heed.

–ELIOT MARSHALL

NSF BUDGET

Panel Prescribes Study To Treat Growing Pains

Call it tough love. Last week a U.S. House spending panel approved a 13% increase for the National Science Foundation (NSF), putting it on course for a doubling of its budget in 5 years. But the committee, concerned that the agency might not be ready to handle such an infusion, asked an outside group of management experts to delve into how NSF does its business. The review is expected to question some well-worn practices at the 52-year-old agency, including borrowing many of its managers from academia.

The House Appropriations Committee approved a 2003 budget for NSF of $5.42 billion. That's $70 million more than its Senate counterpart approved in July (*Science*, 2 August, p. 755) and $394 million more than the Bush Administration requested for the new fiscal year, which began 1 October. Although Congress is currently mired in a budgetary morass, the similarity of the House and Senate numbers augurs well for NSF. "It's a historic time," says Director Rita Colwell about the congressional vote of confidence.

Within that overall boost, both NSF's research and its major facilities accounts would get 15% hikes, with the House adding $26 million to finish a high-altitude environmental research plane and $25 million for a neutrino experiment beneath the South Pole. Education programs would get only the requested 4% rise, although the panel took $40 million from the $200 million sought for math and science partnerships and distributed it among several smaller programs. The overall NSF number is very close to the 15% annual rate needed to double the agency's budget over 5 years, a cherished goal of community lobbyists.

With the agency about to march off in double time, legislators are asking the National Academy of Public Administration (NAPA) to see if NSF is ready for the journey. "We're not criticizing them, but we want to be sure they can handle the growth," says one congressional aide. Looking at recent budgets, legislators wonder if NSF has gorged itself on top-down cross-disciplinary initiatives in information technology, nanotechnology, and biocomplexity while starving individual fields, in particular physics, chemistry, and astronomy. Those disparities, says a report accompanying the spending bill, could undermine a time-tested precept that "the choice of research priorities and individual projects should flow principally from practicing scientists ... through external peer review." Notes another aide, "A lot of NSF's budget is broken down into tiny pieces, with the chunks carved up at the top. Is that the best way to stay at the cutting edge of science?"

The report language also expresses concern about NSF's extensive use of scientists borrowed for a few years from somewhere else, usually a university, to fill positions at all levels. NSF officials believe strongly that such rotators, who make up almost 40% of NSF's 600-person scientific work force, represent new blood and also spread the word about NSF after returning to their home institutions. But the result might also be staff members "who have less experience and could have split loyalties between their federal roles and past or future employers," says the report. Legislators are especially concerned about the prevalence of rotators at the top: The heads of five of NSF's seven research directorates are currently on temporary assignments. (There's a search on for a sixth chief.)

Colwell says NSF "welcomes the attention" from NAPA or any other group asked to look at its management acumen, although she insists that the agency "is already seen as a model organization" within the federal government. And she strongly defends NSF's personnel practices. "It's a constant renewal of ideas and views," she says about the use of rotators, who typically stay for 2 to 4 years. The NAPA study, which can't start until after NSF's 2003 budget is approved, is expected to take a year or so.

–JEFFREY MERVIS

CREDIT: (LEFT) SAM KITTNER

Management model. NSF's Rita Colwell "welcomes" review of agency practices.

NASA BUDGET

Plans for Pluto and Hubble Gain in Congress

Pluto was the Roman god of the dead, but a $488 million mission to his planetary namesake is very much alive. Last week, a U.S. House spending panel brushed aside objections by the Bush Administration and agreed to a Senate plan to continue funding the effort. The decision, coupled with a National Research Council report this summer that backs exploration of Pluto and the nearby Kuiper belt, virtually ensures that the controversial mission will move forward.

Pluto's kiss of life came from the House Appropriations Committee, which voted to boost NASA's 2003 budget by $400 million over this year's $14.9 billion. That's $300 million more than the Administration requested, although most of that will go to projects requested by individual legislators. Within science programs, the bill increases funding to explore Mars, asks NASA to consider extending the life of the Hubble