GENE THERAPY

Patent Award Stirs a Controversy

When Gene Therapy Inc. (GTI) of Gaithersburg, Maryland, announced last week that it holds exclusive rights to a patent just awarded to the National Institutes of Health (NIH) for the most common type of gene therapy, the company's stock value wasn't the only thing to shoot up. So did the pulse rates of some gene-therapy experts who had helped develop the so-called ex vivo gene therapy but were not included on the patent. And if that wasn't enough to stir the blood, some experts in the field say the patent never should have been issued because the concept of ex vivo gene therapy was around long before NIH applied for its patent in 1989.

The patent is based on an experimental gene therapy to treat a rare severe immune disorder called adenosine deaminase (ADA) deficiency, developed by an NIH team led by molecular biologist French Anderson in collaboration with GTI. Although at one stage the team numbered more than 100 researchers, the patent lists only three inventors: Anderson and NIH's Michael Blaese and Steven Rosenberg. "I'm thrilled by the patent," says Anderson, who left NIH in 1992 for the University of Southern California in Los Angeles. Anderson, who heads GTI's board of scientific advisers, cautioned, however, that it's not yet clear how much of a money spinner the patent will be. Ex vivo gene therapy has yet to show its mettle against common diseases, and NIH has not filed for a patent in Europe.

Nonetheless, the patent is extremely broad, covering all ex vivo gene therapy, in which a therapeutic gene is inserted into cells that have been temporarily removed from the patient's body. According to some disgruntled researchers, however, the NIH team wasn't even the first to use the technique. Inder Verma of the Salk Institute in La Jolla, California, who heads a working group that is reviewing how NIH evaluates gene-therapy trials (*Science*, 17 March, p. 1588), points to a 1980 experiment in which Martin Cline of the University of California, Los Angeles (UCLA) tested ex vivo gene therapy for the red blood-cell disorder thalassemia. (Cline conducted the experiments in Israel and Italy, after having been refused permission by UCLA to do the trials in the United States.) The trials were intended only to test the concept of gene therapy, and Cline did not show a therapeutic benefit for the technique. Nonetheless, says Verma, Cline had clearly conceived of the idea of ex vivo gene therapy years before the NIH patent was filed with the Patent and Trademark Office (PTO). "I cannot imagine that [the Cline work] would not be considered prior art," he says.

The PTO was indeed concerned about the obviousness of ex vivo gene therapy, says Anderson. What tipped the balance in his team's favor, he says, is that "at the time of the ADA trial, a number of our competitors had expressed publicly—in magazines like *Science*—that the experiment would not work." By 1991, says Anderson, he had data that convinced the patent office otherwise.

Whether NIH can deal so effectively with complaints from at least two researchers that they were unfairly left off the patent remains to be seen. Dusty Miller, now at the Fred Hutchinson Cancer Research Center in Seattle, and Kenneth Culver, until recently executive director of the Human Gene Therapy Research Institute in Des Moines, Iowa, were members of the original NIH team who played key roles in developing the retroviral vector used to introduce genes into cells that had been removed from the body.

"If they are claiming transduction [the transfer of genes into cells] for gene therapy, then I had a fundamental role in making it work [and] I should have been [named] a co-inventor," says Miller, who now sits on the scientific advisory board of GTI competitor Targeted Genetics Corp. in Seattle. That's exactly what the NIH patent does claim, although it covers every gene-transfer method, not just retroviral vectors, which currently dominate the field.

Anderson refuses to be drawn in on the issue of inventorship. "It wasn't in my hands," he says. "It was a decision of the [NIH] patent attorney." According to the director of NIH's Office of Technology Transfer, Maria Freire, NIH "takes inventorship issues very seriously, as law requires that all inventors be named on a patent," but no concerns about inventorship were raised during the patent filing. As *Science* went to press, Miller and Culver were deciding what action to take. Says Culver, "It's not an issue of money; it's one of respect for our ideas in creating knowledge that will help people."

–Rachel Nowak

GENOME SEQUENCING

Commotion Over *E. coli* Project

A minirevolt has broken out in the genome community over a decision to overhaul one of the Human Genome Project's biggest sequencing efforts. The furor was touched off when the National Center for Human Genome Research (NCHGR) recently decided not to renew a 4-year, $7.8 million grant held by Frederick Blattner's team at the University of Wisconsin to sequence the genome of *Escherichia coli*, one of the genome project's key "model" organisms. Over the past 2 months, several prominent scientists have been circulating petitions and letters protesting the move, and some top labs have served notice that they will not apply for a grant to continue Blattner's work.

Blattner's team has been slogging its way through the 4.7 million base pairs of the *E. coli* genome since 1991. Although the group's work is widely recognized as being extremely thorough and of high quality, there has also been grumbling in the genome community that it was far too slow (*Science*, 13 January, p. 172). So far, only 60% of the *E. coli* genome has been sequenced. NCHGR Director Francis Collins says Blattner's bid for renewal was rejected last December after a peer-review panel convened to study the proposal gave it low marks; Blattner's grant runs out on 30 June.

Last month, NCHGR issued a request for applications for a $2 million grant to finish the sequence in 2 years. The new grant would begin on 30 September. Collins, who says he is well aware of the importance of the *E. coli* project to microbiologists and as a testing ground for the upcoming assault on the human genome, insists the move will speed, not delay, completion of the project.

But some researchers aren't convinced. "We are astonished and chagrined [at the decision]," reads a petition circulated by microbiologist Monica Riley of the Woods Hole Marine Biological Laboratory. The petition noted that a Japanese effort led by Katsumi Isono of Kobe University had also lost its funding and expressed concern that *E. coli* sequencing could grind to a halt when Blattner's grant runs out. Another letter, written by Nobel laureate Richard Roberts of New England Biolabs in Beverly, Massachusetts, and signed by fellow Nobelists Sidney Altman of Yale University, Hamilton Smith of Johns Hopkins Medical School, and James Watson of the Cold Spring Harbor Laboratory, asked Collins to give Blattner an administrative extension of his grant. Such a move, the authors argue, would avoid serious delays in sequencing the bacterial genome.

The petitioners also expressed concern that the new grant will not include funds for annotation of the sequence—the time-consuming process of correcting and publishing gaps and errors in previous data and identifying genes. A particularly careful annotation was partly responsible for Blattner's slow pace, and many in the *E. coli* community believe it is valuable work. "We prefer the more meticulous approach," states Riley's petition, "albeit more expensive and time consuming."

Feelings of solidarity with Blattner are running so high in the genome-sequencing

community that some researchers have said they will not compete for the new grant. And any abstentions of this type could severely restrict the field of contenders: By most estimates only five or six labs in the United States are capable of finishing the *E. coli* project. "There are not very many of us," says Craig Venter, scientific director of The Institute for Genomic Research in Gaithersburg, Maryland, "and to cut one of the pioneer labs off at the roots when he was doing a very high-quality job, on a very important project, is not something that we like to see." Venter, who also signed Roberts' letter, says his group is not going to apply for the grant "out of respect for Blattner's work."

One lab that will apply is Blattner's. Blattner, who says he is "heartwarmed" by the letters and petitions, says he will also seek outside funding to support an annotation effort as well as needed technological improvements. At least one company, Genome Therapeutics Corp. (GTC) of Waltham, Massachusetts, also intends to apply. Gerald Vovis, GTC vice president for research, claims that in terms of being able to keep up with technology, stick to goals, and produce sequence fast, "industry has an advantage over academia."

The dispute over the *E. coli* project may foreshadow other tough funding decisions and how big-science sequencing will get done as NCHGR shifts funds into the effort to sequence the massive 3-billion-base-pair human genome. "Funding is going to get very tough," predicts Stanford University geneticist Ronald Davis, who says he has sent in a letter of intent to apply for the *E. coli* grant but may bow out because of the uproar in the community. "You will not only have to do something well; you will also have to do it very cost-effectively," says Davis.

–Antonio Regalado

SCIENCE AND THE NEW CONGRESS

Agency Merger Plan Faces High Hurdles

Representative Robert Walker (R–PA), the new chair of the House Science Committee, intends to introduce legislation next month combining most of the government's nonmedical civilian research into a single Department of Science. Walker believes the move, which has tacit backing from House Speaker Newt Gingrich (R–GA), would boost the field's power and prestige while lowering costs (*Science*, 17 March, p. 1587). But the plan is already getting poor reviews from the research community, and it may not go far enough for freshmen lawmakers intent on more radical cuts, say congressional aides.

The new department, according to a draft version of the bill obtained by *Science*, would include four complete agencies—the current Department of Energy, Environmental Protection Agency, National Aeronautics and Space Administration, and National Science Foundation (NSF)—five science-related organizations in the Commerce Department, and the Interior Department's U.S. Geological Survey (see table). The massive new department would be split into five areas—research, technology, energy, space, and the environment—each headed by an undersecretary who would report to the Secretary of Science. The consolidation would eliminate 5000 jobs from a current work force of about 78,000 at those agencies, House staffers say. It would also abolish the White House Office of Science and Technology Policy (OSTP) led by presidential science adviser John Gibbons.

Gibbons, not surprisingly, is unenthusiastic—he says the National Science and Technology Council, run by his office, already provides such coordination. But the science adviser struck a conciliatory note this week by saying that the council may need to be strengthened and that Walker's proposal "bears a lot of discussion."

Past proposals to create a Department of Science have been nonstarters, in part because of "the unfortunately bad feedback we get from the scientific community," says Representative George Brown (D–CA), ranking minority member of the science panel. Each bureaucracy and discipline fiercely defends its turf, notes Brown, who says he "will be very cautious" before backing Walker's legislation.

Part of the opposition comes from a fear that a single department would be more vulnerable to budget cutters than the current lineup of agencies. "It's a bad idea," says Erich Bloch, former NSF director, now at the private Council on Competitiveness in Washington. "It would mean too many eggs in one basket; it would be one big target."

Research administrators also reject the argument that consolidation would save money. "[The idea] is the figment of someone's imagination," says Kumar Patel, the president of the American Physical Society and a physicist at the University of California, Los Angeles. While a single department could boost the prestige of science, he says, "the downside risks are too high." Pulling science out of mission agencies could weaken its contribution to the U.S. economy, he says, and having separate sources of funding "has allowed us to progress rapidly in several different fields."

Although Walker's proposed department wouldn't include the National Institutes of Health, biomedical researchers see a downside for their discipline, too: By scrapping OSTP, the proposal would leave them without an obvious advocate in the White House. "We feel strongly that it's important to have a public policy voice on biomedical research in OSTP," says Frankie Trull, president of the National Association for Biomedical Research. There will also likely be debate over just how much would be saved. A veteran staffer notes, for example, that the bill does not take into account the high cost of consolidating the agencies.

Whatever savings are calculated may not be enough for some budget-cutters, however. Freshmen Representatives Todd Tiahrt (R–KS) and Sam Brownback (R–KS) plan to introduce a bill by May that sets forth their blueprint for a streamlined government. "No one is sure what the end result will be, but it could well be we propose eliminating agencies rather than simply replacing them" with a new organization, says Brownback's press secretary, Jackie McClaskey. Says Walker: "We're in the process of talking."

Few in the science community question Walker's motives in pushing for a streamlined new department. But many are worried that his colleagues, who do not necessarily share his interest in science and have pledged to lower spending, might use his proposal as a vehicle for a more radical downsizing of science. Says one congressional aide: "The obvious question is whether this is all a smoke screen to kill programs."

–Andrew Lawler

ONE BIG HAPPY FAMILY?

Agency	Personnel	1995 Budget
Department of Energy	20,000	$17.5 billion
National Aeronautics and Space Admin.	23,000	$14.4 billion
Environmental Protection Agency	14,000	$7.2 billion
National Science Foundation	1,221	$3.4 billion
U.S. Geological Survey (Interior)	2,768	$571 million
Commerce Department:		
National Oceanic and Atmospheric Admin.	13,000	$1.9 billion
National Institute of Standards and Technology	2,000	$855 million
Patent and Trademark Office	914	$82 million
National Technical Information Service	378	$78 million
National Telecommunications & Information Admin.	378	$30 million

SOURCE: OFFICE OF MANAGEMENT AND BUDGET