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