CLINICAL RESEARCH

Gene Therapists Celebrate a Decade of Progress

It has taken many years, but researchers may have reached a prized goal in gene therapy: lowering the risk of uncontrolled bleeding in patients with hemophilia. At a meeting last week, researchers reported that six patients who received a virus engineered to carry a gene for a blood-clotting protein called factor IX needed fewer transfusions of the protein for as long as 18 months; some didn't require any transfusions. One patient developed an immune response to the viral vector, but this side effect was successfully treated with drugs.

Some researchers say these results mark a watershed for the long-struggling field. At the meeting at the U.S. National Institutes of Health (NIH) in Bethesda, Maryland, gene therapy researchers summarized progress on several fronts. They said they have proved that they can treat at least a half-dozen rare genetic diseases (see table), and that early trials are beginning to find benefits for common diseases as well, including HIV, leukemia, and heart disease.

Most important, gene therapy seems to have overcome a reputation for recklessness it acquired a decade ago after an 18-year-old, Jesse Gelsinger, died in a trial. "It's a different day now," says meeting attendee Theodore Friedmann of the University of California (UC), San Diego, who has followed the field since the 1970s: People recognize that "it really is the right thing to do for some diseases."

To be sure, enthusiasm is not what it was 20 years ago when NIH last held a similar symposium. That event attracted nearly twice as many speakers and attendees (21 speakers and about 400 registrants came this time), noted R. Jude Samulski of the University of North Carolina, Chapel Hill, president of the American Society of Gene and Cell Therapy (ASGCT), a meeting cosponsor. Back then, "excitement clearly exceeded any of the data," Samulski said at the meeting. After the Gelsinger incident, U.S. regulators put many trials on hold; others were canceled.

But in the early 2000s, teams in Paris and Milan demonstrated the first clear-cut benefits from gene therapy, treating children with two different forms of severe combined immunodeficiency disorder (SCID), which make the patient highly vulnerable to infection. Last year, researchers reported success in two patients with another immune disorder, Wiskott-Aldrich syndrome; like SCID patients, they were treated by adding a curative gene to blood stem cells. By now, about 86 patients with these immune deficiencies have been helped this way, Donald Kohn of UC Los Angeles said at the NIH meeting.

Last year also brought good news in a new area: Gene therapy researchers published the first success in treating a patient with β-thalassemia, a blood disorder that is relatively common in South Asia and the Mediterranean region. Eight centers are now setting out to expand on this result, noted Michel Sadelain of Memorial Sloan-Kettering Cancer Center in New York City.

These trials were not without problems, however. In some the viral vector, a retrovirus, which can insert unpredictably in DNA, turned on an oncogene, increasing the risk of cancer. Nine patients, including three with chronic granulomatous disease, another immune disorder, who initially seemed cured by gene therapy later developed a leukemia-like disease, Kohn noted. In response, a U.S.-European consortium has developed alternative "self-inactivating" retroviral vectors that are less likely to turn on other genes. All new trials treating blood cells are using these vectors.

It's a sign of the field's overall health that researchers are going beyond safety testing now. The San Raffaele Telethon Institute for Gene Therapy in Milan, for example, will soon apply to European regulators to conduct a phase III trial needed for regulatory approval of a plan for treating adenosine deaminase deficiency–SCID. Last year, that institute struck a deal with pharmaceutical giant GlaxoSmithKline to commercialize gene therapies for seven disorders. "Gene therapy for rare genetic diseases is really a mature field now," Telethon Institute immunologist Maria-Grazia Roncarolo said at the NIH meeting.

Eye diseases are another success story. In three trials that are "kind of biblical in impact," Friedmann says, eyesight improved, sometimes dramatically, in 28 of 30 patients with Leber's congenital amaurosis, a type of inherited blindness, after gene therapy using an adeno-associated virus (AAV) to deliver a curative gene to the retina. The Children's Hospital of Philadelphia (CHOP) plans to apply this fall to the U.S. Food and Drug Administration to conduct a phase III trial for this treatment. Gene therapy trials for two other blindness diseases are under way. "In the next year and a half, there's going to be a boatload coming out," says Stephen Rose, chief research officer for Foundation Fighting Blindness.

Gene therapy is working for neurologic diseases, too. The San Raffaele Telethon Institute has treated four patients with a devastating brain disorder called metachromatic leukodystrophy, following a report published in 2009 from a team in France that used a similar strategy to halt the progression of a related disease, adrenoleukodystrophy. So far the treatment seems safe and the patients' blood cells are producing the corrected enzyme, Roncarolo reported.

The path to better health has been long and winding for hemophilia B patients. A trial in the early 2000s led by Katherine High of CHOP and Stanford University's Mark Kay resulted in only brief gene expression; patients developed an immune response that destroyed cells with the corrected gene. This trial used AAV to deliver a factor-IX clotting factor gene to the liver. But a new trial led by Amit Nathwani of University College London and Andrew Davidoff of St. Jude Children's Research Hospital in Memphis, Tennessee, has overcome earlier immune problems. These researchers used a different AAV that can be delivered intravenously and may be less likely to trigger an immune reaction. As

Some Gene Therapy Successes

Disorder	Disease type	Patients benefiting	First publication
X-SCID	Immunodeficiency	17/20	2000
ADA-SCID	Immunodeficiency	26/37	2002
Adrenoleukodystrophy	Neurologic	2/4*	2009
Leber's congenital amaurosis	Blindness	28/30	2008
Wiskott-Aldrich syndrome	Immunodeficiency	8/10	2010
β-thalassemia	Hemoglobinopathy	1/1	2010
Hemophilia	Coagulation	6/6	2011?

*Includes a patient treated too recently to see benefit

TABLE SOURCES: D. KOHN, N. CARTIER-LACAVE, U. REISS, W. HAUSWIRTH, NIH GENE THERAPY SYMPOSIUM, 26 SEPTEMBER, 2011; *LANCET* **374**, 1597 (2009); *NEJM* **358**, 2231 (2008); *NATURE* **467**, 318 (2010)

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Ulrike Reiss of St. Jude reported at the meeting, levels of factor IX reached 1% to 8% of normal levels in the six patients, high enough that two patients could cut back on their twice- or thrice-weekly infusions of factor IX, and four could go off infusions altogether.

Even so, one patient who got the highest dose did experience immune effects: As in the previous trial, the patient's T cells targeted the capsid, or protein coat, of the viral vector, causing liver enzymes to rise. But this time, researchers controlled the reaction by giving the patient prednisolone, a widely used steroid, for several weeks until the capsids degraded and cleared. However, prednisolone may not be acceptable for hemophilia patients with hepatitis, says High, a trial collaborator. The treatment also won't work for the 30% of patients with preexisting immunity to AAV8. And gene therapy will be more challenging for the more common form of the disease, hemophilia A, which involves a larger gene that cannot be delivered as easily with AAV.

Still, this trial and the eye studies show the promise of AAV vectors for gene therapy, High says. To have achieved success with hemophilia "feels great," she says. "It's much more fun to think about" obstacles to treating more patients "rather than how to get it to work," High says.

Researchers at the meeting pointed to many hurdles that still lie ahead: the "morass" of multistage reviews these protocols face, particularly in the United States; long timelines for some patients to show benefits; and scarce funding for rare diseases. But researchers are optimistic enough that the ASGCT is working on a list of 10 diseases that it hopes will be successfully treated with gene therapy within the next 7 years. Says Samulski, "Now we're where everyone wanted to be 10 years ago." **–JOCELYN KAISER**

NOBEL PRIZE IN PHYSICS

Curious Cosmic Speed-Up Nabs Nobel Prize

Thirteen years ago, two teams of astronomers and physicists independently made the same stark discovery: Not only is the universe expanding like a vast inflating balloon, but its expansion is speeding up. At the time, many scientists expected that the gravitational pull of the galaxies ought to slow the expansion down. Today, researchers from both teams shared the Nobel Prize in physics for that dramatic observation, which has changed the conceptual landscape in cosmology, astronomy, and particle physics.

Half of the $1.45 million prize will go to Saul Perlmutter of Lawrence Berkeley National Laboratory and the University of California, Berkeley, who led the Supernova Cosmology Project. The other half will be shared by Brian Schmidt of the Australian National University in Weston Creek, who led the High-z Supernova Search Team, and Adam Riess of Johns Hopkins University and the Space Telescope Science Institute in Baltimore, Maryland, who worked on High-z. "I'm really happy for them," says Yannick Mellier of the Institute for Astrophysics in Paris. "It's a huge discovery that has impact in all of physics."

Both teams traced the expansion of the universe back through time using stellar explosions called type Ia supernovae. Because all such supernovae explode with essentially the same brightness, astronomers can use them as "standard candles": They can tell how far away a supernova is by measuring its apparent brightness from Earth. They can also tell how long ago the stellar bomb went off by measuring how much its light has been stretched to longer, redder wavelengths by the expansion of space. Using different supernovae, both teams found that the expansion of the universe is accelerating. "We thought we must be making some mistake," Schmidt says. "But the mistake refused to go away."

Other evidence soon bolstered the case for the accelerating expansion and some sort of "dark energy" to power it. A few years later, measurements of the afterglow of the big bang—the so-called cosmic microwave background—indicated that 70% of the stuff in the universe had to be dark energy. Studies of clusters of galaxies show that their growth has slowed over the 14-billion-year age of the universe, as if space-stretching dark energy were impeding it.

Exactly how surprising the discovery of the accelerating expansion was remains a matter of debate. By the late 1990s, cosmologists had begun to suspect that the universe contained a large amount of dark energy and only a little matter, says Simon White, a theorist at the Max Planck Institute for Astrophysics in Garching, Germany. In contrast, Schmidt recalls that the debate was between theorists who claimed the universe's expansion should be slowing a lot and observers who found no evidence for that.

Cosmologists, astrophysicists, and particle physicists must still explain what dark energy is. Much effort focuses on how the density of dark energy changes as space expands. If dark energy is an inherent part of space, the density should remain constant. If dark energy is something *in* space, then it should become more dilute. The question comes down to using further astronomical observations to determine whether a single parameter in the cosmological "equation of state" is exactly –1, indicating dark energy is part of space, or something like –0.93, indicating that dark energy is something in space. Currently the value of this parameter is consistent with –1 with an uncertainty of about 10%.

Will scientists ever know what dark energy is? "That's not a sure thing," White says. "The problem is that you can't prove by observations that a parameter is exactly minus one."

Each team comprised about 20 scientists. "This is another example of what a shame it is that the Nobels can't recognize teams," says Martin Rees of the University of Cambridge in the United Kingdom. "It sends the wrong signal." White notes that Robert Kirshner of Harvard University was the thesis adviser for Schmidt and Riess and got them started on the prize-winning project.

Oddly, Edwin Hubble, who in the 1920s discovered that the universe is expanding, never won a Nobel Prize. **–ADRIAN CHO**

With reporting by Daniel Clery.

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