MEDICINE

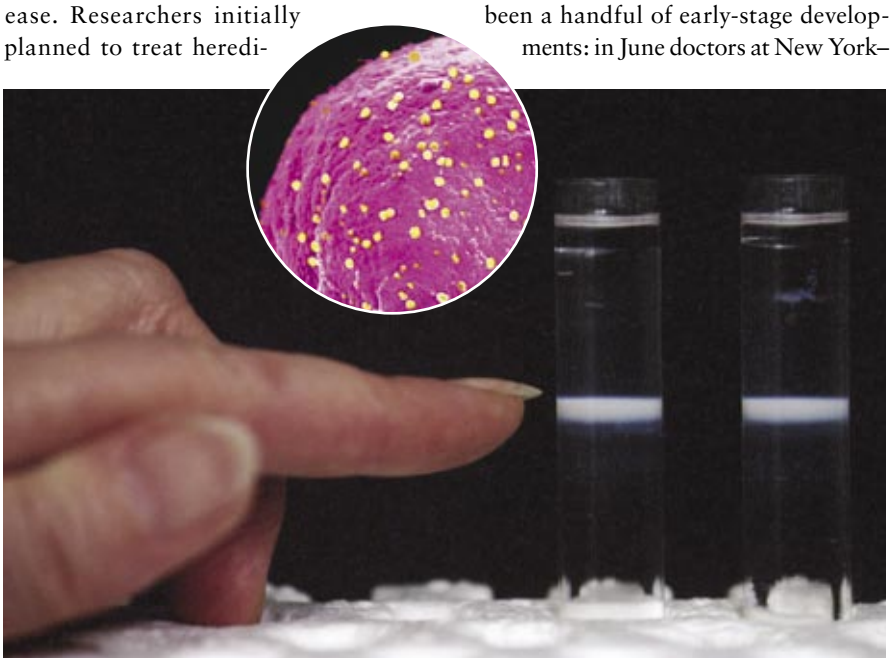
Regaining Lost Luster

New developments and clinical trials breathe life back into gene therapy BY MELINDA WENNER

The past 15 years have been a roller coaster for gene therapy. After being touted in the early 1990s as "the medicine of the future," gene therapy left an 18-year-old dead and three others with leukemia; in July it was tied to the death of a 36-year-old Illinois woman undergoing treatment for rheumatoid arthritis, although further investigation cleared her therapy of the blame. Gene therapy scientists, however, believe they can put the bad news behind them, thanks to a handful of recent developments and others just over the horizon.

Gene therapy describes any treatment in which doctors insert new or modified genes into a person's cells to treat or prevent disease. Researchers initially planned to treat hereditary disorders such as cystic fibrosis, in which normal gene products are deficient, by delivering functional copies of missing genes to cells that need them. Since then, scientists have expanded gene therapy's possible applications to include "training" immune cells to hunt down cancer, building new blood vessels and making the immune system resistant to infection.

"We really don't know the full dimension of what it can do," says Arthur Nienhuis, a hematologist at St. Jude Children's Research Hospital in Memphis and president of the American Society of Gene Therapy (ASGT). In addition to 12 cancer treatments and a heart treatment currently in large phase III clinical trials, there have been a handful of early-stage developments: in June doctors at New York–Presbyterian Hospital announced promising results from a phase I trial for Parkinson's disease; a therapy that has restored sight to 70 congenitally blind dogs is being tested in humans at the University of Pennsylvania; and eight research groups are gearing up to test new HIV treatments. Although no gene therapies have yet been approved by the U.S. Food and Drug Administration, more than 800 trials are ongoing; China has approved two cancer treatments, but their efficacy remains unclear.



SPECIAL DELIVERY: Viruses carrying human genes accumulate in the blue layer of liquid after centrifugation. So modified, the virus can deliver its payload to treat or prevent diseases. The inset shows ordinary adenoviruses (*yellow*) on a red blood cell.

CNRI *Photo Researchers, Inc.* (*scanning electron micrograph*); PHILIPPE ERANIAN *Corbis* (*test tubes*)

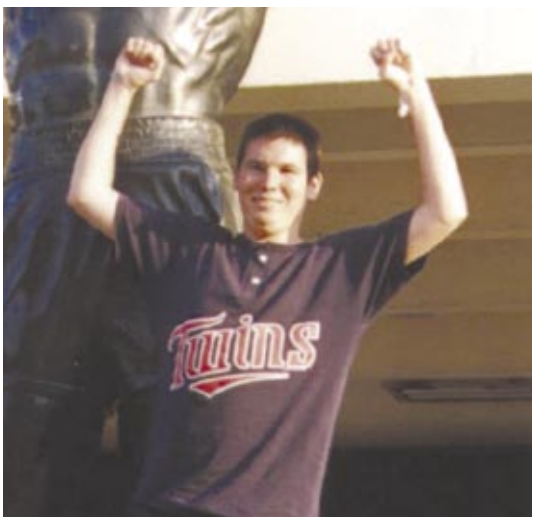
What makes gene therapy so promising also makes it extremely challenging. It can target only those tissues that need it, "which is a major contrast with traditional pharmacotherapy, where you take a pill or receive an injection, and a very, very small portion of the injected or ingested drug actually arrives at the [correct] site," says David Dichek, a cardiologist at the University of Washington. But ensuring that the gene reaches its target is no small feat. Trials can skirt this problem when targeted cells can be injected directly or easily removed—with the latter method, doctors can manipulate isolated cells in the lab and replace them in the patient later. But getting genes to inaccessible targets has been one of the field's biggest hurdles.

Most scientists use modified viruses as "vectors" to deliver gene therapy. Viruses are good at delivering genetic payloads to cells; after all, that is what they do. If scientists strip viruses of their genetic material and replace it with therapeutic genes, viruses will deliver this payload to the cells instead. Different viruses do different things—some attack the liver, others nerves; some insert their DNA into the host genome, others do not—so physicians

can choose those that best suit their purposes and further engineer them if need be. "There's been a lot of effort to steer viruses to go specific places," says Donald Kohn, an immunologist at the Keck School of Medicine of the University of Southern California and Childrens Hospital Los Angeles.

But viruses come with a catch: "Our immune system developed to reject them," Kohn explains. What killed 18-year-old Jesse Gelsinger in 1999 was a powerful immune response to his therapy, not the therapy itself. So even if a vector reaches its target, scientists must ensure that the body does not attack the "infected" cells. Recently scientists have identified a number of ways of achieving this, by using lower therapy doses, pretreating patients with immunosuppressive drugs and masking vectors so immune cells do not notice them. Some scientists also use vectorless "naked" DNA and genes packaged in other ways.

Even if gene therapy conquers these challenges, will it ever overcome its negative reputation? Some scientists maintain that it has never been that unsafe, relatively speaking. "If you compare the safety profile of gene drugs in development versus the traditional small-molecule pharmaceutical drugs, there's no evidence that gene therapy is any more dangerous," says Savio Woo, an oncologist at Mount Sinai Hospital in New York City. Thousands of patients have been treated, and only a few adverse events have been reported, he states; the leukemia that developed in three "bubble boy" patients may have been a side effect specific to the therapeutic gene, which stimulates immune cell growth. "Any time a few cells divide a lot, you always worry about secondary genetic changes, which is how cancers form," notes Mark Kay, a geneticist at Stanford University.



TRIALS AND TRIBULATIONS: The death of Jesse Gelsinger during a gene therapy trial in 1999 gave the field a shock from which it is slowly recovering.

As the field continues to evolve and improve, scientists hope that the public's perceptions of it will, too. "We clearly have had clinical successes, and now we're on the threshold of achieving many more," says ASGT president Nienhuis. "I think we're going to hear a lot about them in the next several years."

Melinda Wenner is a freelance writer based in New York City.

MBR Newscom

FOOD SCIENCE

A Dash of Nutrition

Iron- and vitamin-fortified salt gets set to fight deficiency diseases BY DIANE MARTINDALE

The fortification of salt with iodine is a global success story: with two out of three households in the developing world now consuming iodized salt, an estimated 82 million children are protected from thyroid disease and resultant learning disabilities every year. Still, people suffer from a lack of other micronutrients.

For years, food scientists have looked for a way to fortify iodized salt to combat iron-deficiency anemia, which affects some two billion people, as well as vitamin A deficiency, which afflicts at least 100 million children in poor countries and is the leading cause of blindness among them. Canadian researchers have now developed a practical way to double- and triple-fortify salt, which might also be more acceptable to people than genetically modified foods in tackling malnutrition.

Adding iron to iodized salt is a simple idea that has proved difficult to execute. The chemicals are incompatible: when mixed together, iodine vaporizes and iron degrades. After more than a decade, Levente Diosady, a chemical engineer at the University of Toronto, finally solved the problem by borrowing a technique from the food industry referred to as microen-

Nourishing Soft Drinks?

Besides fortifying salt, Levente Diosady of the University of Toronto has also developed a method to purify rapeseed protein, a by-product of canola oil manufacture. "The protein meal is highly nutritious, but it comes out as black sludge," Diosady explains. His process separates the protein from bitter compounds and then concentrates it into a neutral-tasting powder that contains all the essential amino acids. Similar to soy, the canola protein has the additional quality of being soluble in acidic liquids and hence could supplement soft drinks, which in developing countries are often consumed in lieu of water because of safety concerns. Diosady plans to develop a protein-enriched soft drink called LiveADE.