# New avenues for LNS gene transfer

Lesch-Nyhan syndrome (LNS) sits high on the heap of most likely candidates for the first human gene transfer therapy. A neurologic disorder, LNS is the result of a single mutated gene that codes for a protein known as hypoxanthine phosphoribosyltransferase (HPRT). And restoring just 1 percent of normal HPRT levels may be enough to reduce a patient's LNS symptoms from compulsive self-mutilation to those of but a simple case of gout.

Gene therapy involves inserting a normal gene that will synthesize the needed product in order to correct a genetic or acquired disease. Of the two types of gene therapy, most research is concentrated on somatic-cell transfer, which targets the synthesis of the cell and affects only the patient. The other type, germ-cell transfer, enables the patient to pass the new gene to offspring.

Much of the work toward achieving somatic-cell transfer in humans with LNS has been done using retroviruses, which are viruses that use RNA and synthesize it into DNA, in a process called reverse transcription. Through this method, an RNA gene coded with HPRT is transcribed into DNA and integrated into the host chromosomal DNA.

But one team of researchers now thinks what will be needed to correct LNS is a viral transfer that uses DNA rather than RNA. Led by Thomas D. Palella and William N. Kelley, researchers at the University of Michigan in Ann Arbor suggest that using the herpes simplex virus type 1 (HSV-1) will aid the transfer and expression of HPRT in deficient neuronal cells. Palella presented his findings last week at the American Rheumatism Association meeting in Washington, D.C.

Part of the reason the team chose this carrier virus, or vector, says Palella, is because it will go directly to the central nervous system, whereas retroviruses cannot be directed there. In addition, retroviruses require replicating cells for integration, and cells in the central nervous system do not replicate. HSV-1, which is the type of herpes associated with cold sores, infects a cell by crawling up the cell's axon and harboring in the cell until activated. Because HSV-1 is incurable, researchers would somehow have to rid it of its disease effects before using it in gene transfer therapy.

The group, which has submitted its findings to a scientific journal for review, reports success in survival of human HPRT genes cloned in HSV-1 and transferred into rat neuronal cells. To make the recombinant virus, researchers took the thymidine kinase gene from the HSV-1 genome and cloned it with HPRT. The recombinant virus then successfully infected all cells receiving it. After 20 and 30 hours, the infected rat cells showed HPRT activity at levels comparable to those seen in a naturally occurring HPRT cell line.

Because herpes is a disease-causing virus, rat cells responded by killing 80 percent of the naturally occurring herpes viral vectors infecting them. In contrast, 80 percent of the recombinant viral vectors were still alive in the rat cells after 30 hours, although researchers had done nothing to alter the disease effects of HSV-1. Part of this, Palella says, may be because interrupting the thymidine kinase chain automatically limits the disease effects of the HSV-1 genome.

Palella and his colleagues would like next to insert HPRT into other viral genes in the HSV-1 genome to see how well the genes express the HPRT. The researchers also are looking into integrating promoters into a gene and then administering certain metals or steroids to help regulate levels of HPRT expression.

Palella emphasizes that his team's report is preliminary and that there are many hurdles to overcome before HPRT gene transfer in humans can be realized. "In the gene transfer world, we're swimming upstream," says Palella, "or at least against the current." — *K. Hartley*

## STSers win MacArthurs

Four of the 32 MacArthur Fellows announced this week are former winners of the Westinghouse Science Talent Search (STS), which is administered by Science Service. The prestigious MacArthur Fellowships, known as the "genius awards," are presented each year to individuals in the arts and sciences. From 1981, when the awards were established, to 1986, the list had included four former winners of STS, in which the nation's top high school science students submit research projects for competition.

The four former STS winners who have won 1987 MacArthurs (and the amounts of their awards) are:

- Robert Axelrod, 44, professor of political and public policy at the University of Michigan — $275,000.
- Robert Coleman, 32, mathematics professor at the University of California at Berkeley — $215,000.
- Eric Lander, 30, a mathematician with expertise in genetics, biology and business, at the Harvard University Graduate School of Business Administration — $205,000.
- David Mumford, 50, a mathematician at Harvard University — $305,000.

Lander was the top STS scholarship winner in 1974; Mumford was among the top 10 in 1953; Axelrod (1961) and Coleman (1972) were among the top 40 winners. □

# Launch score: Nature 3, NASA 0

As a thunderstorm was raging over NASA's Wallops Island, Va., launch facility on the night of June 9, officials waited in a blockhouse to launch a group of sounding rockets in a study of lightning's effects on the ionosphere. The NASA team never got a chance. Instead, for the first time in more than 13,000 launchings since operations began at Wallops in 1945, the lightning itself took over the job.

As the NASA personnel waited for the storm to pass over the site, expecting to conduct the firing about two and a half hours later, the lightning ignited a small, payload-equipped Orion sounding rocket and two smaller test rockets, sending all three on their way. The test rockets, intended to help the launch team check out its tracking radar, apparently followed their planned routes, climbing to about 15,000 feet and 2½ miles downrange before dropping into the Atlantic Ocean. The Orion, which had not yet been elevated to its intended liftoff angle, took off almost horizontally, traveling about 300 feet before hitting the water.

No one was injured in the incident, and three other rockets were unaffected. This week, an investigating committee was working to determine the cause of the mishap. The Orion rocket that was launched, for example, had had its "igniters" installed and its firing cables connected, though they were deliberately short-circuited and grounded at the launch-control cubicle as a standard safety precaution. One possibility being evaluated was that the launch was triggered by a current induced in the cables by the lightning. Yet a pair of Super-Loki rockets that did not take off at all had been in the same state of readiness, possibly differing from the Orion only in their igniter configurations.

NASA estimates that the total value of the equipment "destroyed" in the affair is less than $50,000, not atypical for operations at Wallops Island, where old military rockets and other such equipment are often used. But Ron Sawyer, head of the facility's Safety and Quality Assurance Engineering Branch, notes that experience gained from investigating last week's incident could turn out to be important if it helps prevent lightning-triggered launchings on other occasions or at other facilities, where the stakes could well be higher. The investigators even include a representative from the space shuttle program.

Lightning has affected NASA's liftoffs before — in March, for example, it destroyed an already ascending Atlas-Centaur rocket — but "to my knowledge," says Sawyer, this is the only time anywhere it has done the actual launching.

— *J. Eberhart*