Gene therapy takes on a cholesterol defect

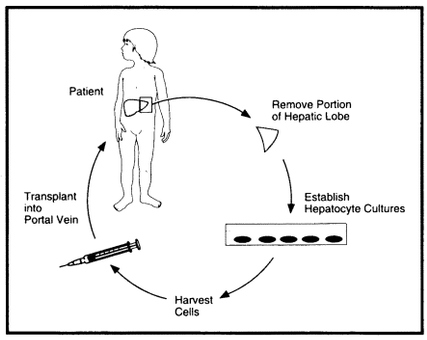
In the first account of successful gene therapy published in a scientific journal, a U.S. team reports it has partially corrected an inherited form of high cholesterol.

Their patient is a French Canadian woman whose medical history is a chilling reminder of the limits of conventional medicine. This woman suffered a heart attack at age 16. She underwent bypass surgery at age 24. Yet her condition continued to worsen.

In June 1992, the woman made medical history by undergoing experimental gene therapy at the University of Michigan Medical Center in Ann Arbor. James M. Wilson and the other researchers responsible for that procedure have since moved to the University of Pennsylvania Medical Center in Philadelphia. In the April NATURE GENETICS they describe a moderate lowering of cholesterol concentrations in this patient's blood with gene therapy, an effect that has lasted 21 months.

This work represents "a genuine step forward in the slow road to successful somatic gene therapy," comments David Weatherall in an editorial that appears in the same issue. "It suggests that, ultimately, it will be possible to correct genetic diseases which are expressed primarily in liver cells," says Weatherall, of the University of Oxford in England.

This patient and others with the rare disorder known as familial hypercholesterolemia inherit mutant versions of genes that code for a liver cell receptor. With the resulting flawed receptors, liver cells can't clear low density lipoprotein (LDL) cholesterol from the bloodstream.



University of Pennsylvania Medical Center

LDL cholesterol sticks to artery walls, clogging the vessels. Particularly at risk are people, like Wilson's patient, who inherit two copies of the defective gene and thus have astonishingly high concentrations of LDL cholesterol.

The procedure, which was approved by federal health officials, involves removing about 10 percent of the patient's liver and culturing those cells in the laboratory. The researchers used a crippled virus to insert healthy copies of the cholesterol-lowering receptor gene into the cultured liver cells. They then injected the cells into the patient's bloodstream (see illustration).

Some of those cells set up shop in the liver, where the inserted genes turned on and started directing the production of the normal cholesterol-clearing receptor. The woman's LDL cholesterol dropped from 448 milligrams per deciliter (mg/dl) – a concentration measured before gene therapy but while receiving a cholesterol-lowering drug – to 366 mg/dl.

This reading is about three times higher than it should be. Gene therapy also seemed to enhance the patient's response to lovastatin, a drug that works in part by spurring clearance of LDL.

The woman's cholesterol concentrations still put her at risk of a heart attack, Wilson cautions. Yet his team hopes that the experimental therapy will slow the dangerous deposition of plaque and thus buy this patient time. Indeed, X rays of the patient's coronary arteries indicate that her atherosclerosis has not progressed since the procedure.

The team has treated four other patients with this disorder. The researchers have yet to release data on any lipid benefits for those patients. – *K.A. Fackelmann*

First image: Ida's moon stars on film

Early last month, NASA scientists reported that the Galileo spacecraft had probably made the first direct detection of a moon orbiting an asteroid (SN: 3/12/94, p.164). Now they're sure. A complete image, relayed by the craft on March 15 and released by the space agency last week, shows that a tiny moon circles the asteroid 243 Ida.

The picture reveals that the moon, informally dubbed Ida 2, measures about 1.5 kilometers wide and lies roughly 100 km from the center of the asteroid. Data from Galileo's near-infrared mapping spectrometer indicate that the moon, like Ida, has a high proportion of silicates. If images of Ida to be radioed between now and June also show the moon, researchers could determine the satellite's orbital period. This, in turn, would reveal the density of Ida and its similarity to that of certain classes of meteorites.

The moon seems to resemble the asteroid it orbits, but researchers debate whether the tiny rock is more akin to a daughter or a sister of Ida.

Based in part on the asteroid's assumed lineage, some scientists favor the sister scenario, notes Clark R. Chapman of the Planetary Science Institute in Tucson.

Ida belongs to the Koronis family of asteroids, apparently created when a collision shattered a larger parent body into 100 or more pieces. Chapman speculates that Ida 2 may represent a small fragment of the Koronis family – a tiny sister of Ida – that because of its proximity and similar velocity becomes gravitationally bound to the asteroid.

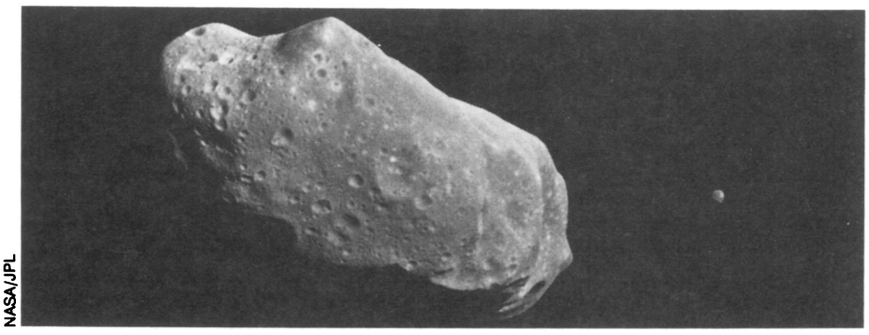

NASA/JPL

Image taken by the Galileo craft shows a moon orbiting asteroid 243 Ida.

Alternatively, the moon may represent a true daughter of Ida – a chip off the old asteroid knocked free long after the creation of the Koronis family. In this scenario, a projectile rammed into Ida, gouging out a small chunk of material that became locked in orbit around the asteroid, much the way scientists believe our moon formed from Earth. However, researchers note that most chunks would either fall back on the asteroid or escape its gravity entirely.

Scientists say it's unlikely that Ida 2 is a relic of the creation of the solar system. A fragment that old would probably have been shattered long ago by collisions in the asteroid belt.

Galileo found a moon after imaging only two asteroids from space. However, it remains unclear whether most asteroids, or just those that belong to families, have moons. Some scientists recording the decline in light when an asteroid passes in front of a star have reported a brief "blinkout" before or after the actual eclipse. They have attributed these blinkouts to asteroid moons. The discovery of Ida 2 may lend more credibility to these reports, the Galileo team says. – *R. Cowen*