Cholesterol Buster

Physicians uncover a new way of reducing high cholesterol in patients resistant to standard drug treatments. **BY LIZ STILLMAN**

As is often the case with those suffering from a rare condition, patients with homozygous familial hypercholesterolemia (FH) have few treatment options available to them. A genetic condition that strikes one in a million individuals, FH causes abnormally high levels of "bad cholesterol," also known as low-density lipoprotein (LDL), in the blood of patients. The LDL deposits in the walls of arteries that feed the heart, making it harder for the blood to flow through them. As a result, FH patients frequently develop heart disease before their 25th birthdays.

Although they help millions of individuals each year, the cholesterol-lowering drugs currently on the market, such as the statins, provide relatively little relief to homozygous FH patients. "Right now the standard care for these patients, LDL apheresis, is at best an invasive, expensive, and temporary solution," says Daniel Rader, a professor of Medicine and Pharmacology at the University of Pennsylvania (Penn) and director of the NCRR-funded Clinical and Translational Research Center. Apheresis is a process of physically removing cholesterol from the blood that must be repeated every one to two weeks in a clinic or hospital.

Rader has spent his career studying factors that regulate the formation and breakdown of lipoproteins—large particles consisting of fats, such as cholesterol and triglycerides, and specialized proteins. In the early 1990s, while in the intramural research program of NIH's National Heart, Lung, and Blood Institute in Bethesda, he was part of a research team that discovered the gene responsible for another rare inherited disease called abetalipoproteinemia. This disease is associated with extremely low quantities of cholesterol and lack of LDL in the blood. The responsible gene encodes a protein, called microsomal triglyceride transfer protein (MTP), that works in the liver to "package" triglycerides and cholesterol with apolipoprotein B to produce LDL in the blood. Without MTP, LDL cannot be produced.

"The discovery of MTP as the genetic basis of abetalipoproteinemia suggested that MTP could be a novel therapeutic target for lowering LDL," Rader asserts. "My extensive experience in working with patients with homozygous FH convinced me that an MTP inhibitor could be useful in these patients." Investigators at the pharmaceutical company Bristol-Myers Squibb developed the first MTP inhibitor, and Rader collaborated with them in an early study to demonstrate its effectiveness in lowering elevated LDL levels in otherwise healthy individuals. But the company decided to stop further development of the drug because of some gastrointestinal and liver-related side effects and concern that it would not compete with statins for the treatment of high cholesterol in the general population. "I then persuaded them to essentially donate it to Penn so that we could continue working with it in our patients with homozygous FH," says Rader.

His persistence is starting to pay off. Taking advantage of the resources available at the Institute for Translational Medicine and Therapeutics (ITMAT) at Penn—one of the first recipients

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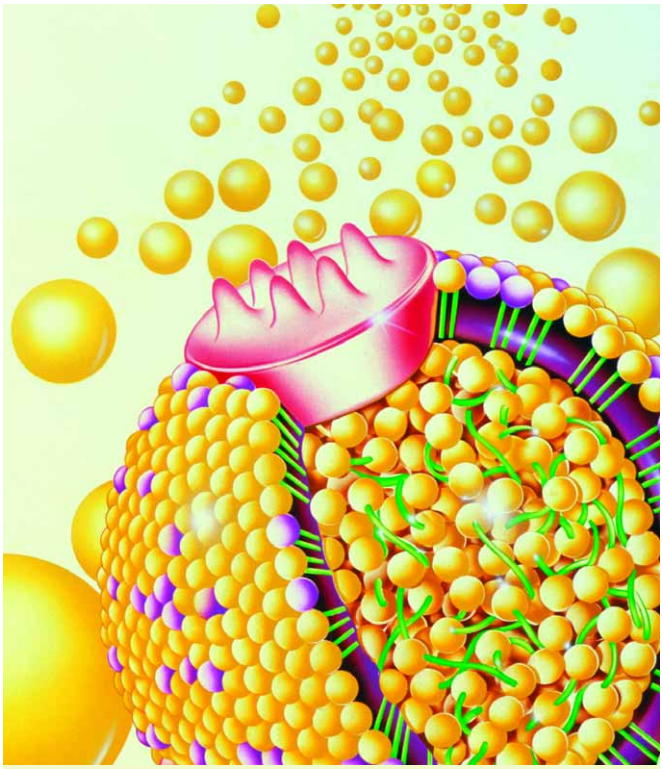
of NCRR's Clinical and Translational Science Awards (CTSAs) launched in October 2006 and supported by additional funding from the Doris Duke Charitable Foundation—Rader carried out a protocol in which the MTP inhibitor was given to six homozygous FH patients at four increasing dosages, each for four weeks.

"The patients were eager to try anything and everything that might lower their cholesterol levels without the need of LDL apheresis," says Marina Cuchel, co-investigator of the study, who was supported through an NCRR-funded K-12 Mentored Clinical Research Scholar Award. "Used to the poor response to conventional drug treatment, they were, like us, amazed at how low their cholesterol levels dropped, especially at the highest dosage of the drug." The treatment led to a remarkable 51 percent reduction in LDL levels, 65 percent reduction in triglyceride levels, and 56 percent reduction in apolipoprotein B levels in the patients' blood. The study also demonstrated that, as investigators had suspected, the MTP inhibitor reduced the production of LDL by the liver.



This illustration shows the structure of a low-density lipoprotein (LDL) particle, a form of cholesterol-carrying lipoprotein found in the blood. Mainly composed of lipids, this complex structure includes a large protein (pink) known as apolipoprotein B, which regulates the metabolism of LDL. Also found in the outer coat are phospholipids (stalked spheres) and free cholesterol molecules (yellow). Within the core, cholesterol molecules (yellow) are attached to fatty acids forming cholesteryl esters (green). Researchers believe that high blood levels of LDL particles lead to increased risk of narrowing of the arteries (atherosclerosis), coronary heart disease, and stroke.

Thanks to the study's success, Cuchel has received funding from the U.S. Food and Drug Administration's orphan drug program to carry out a larger and longer phase III trial of the compound in patients with homozygous FH. "One of the key questions for this next trial is: What are the effects on the liver when we test this drug over long periods of time?" says Cuchel. She hopes that the results will support the approval of this MTP inhibitor as an orphan drug for patients with homozygous FH who do not respond to available cholesterol-lowering treatments. It is also possible that lower doses of the drug might be used in patients at high risk of heart disease who are unable to reach the desired LDL levels with conventional treatments. The drug is being developed with this goal in mind by Aegerion Pharmaceuticals, Inc.

"This translational research shows how investigations into rare genetic diseases can lead to important advances that can influence many more people," says Rader, who, in addition to being ITMAT's associate director and a co-principal investigator (PI) of the Penn CTSA, was previously the PI of a K-12 Mentored Clinical Research Scholar Award from NCRR to prepare and train clinicians for careers in translational research. ■

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ADDITIONAL READING: Cuchel, M., Bloedon, L. T., Szapary, P. O., et al., Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med* 356:148–156, 2007.

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