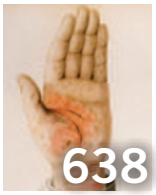
Airing concerns:
Critics question impact of malaria drug subsidy program



Psore point:
New biologic drugs for psoriasis help quell the immune system

Hearing test:
Drugs to prevent hearing loss enter clinical development

Hopes soar as cholesterol plummets with new drug class

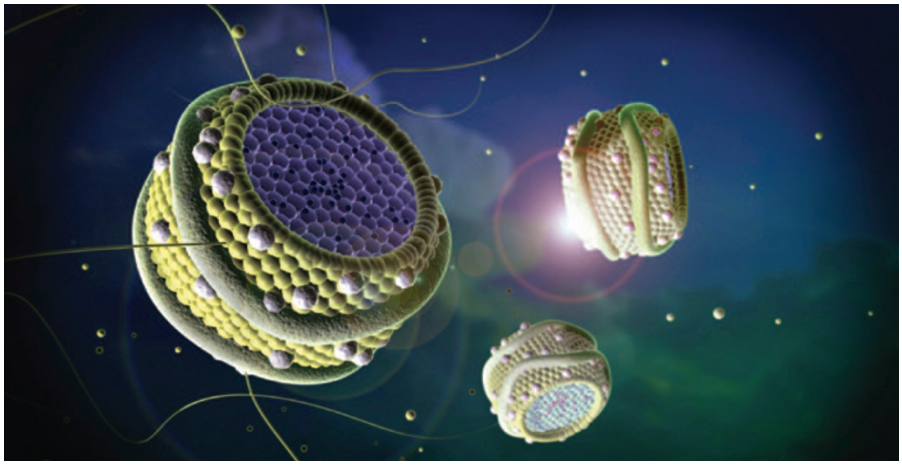
Statin drugs such as the blockbuster Lipitor (atorvastatin) typically reduce the levels of artery-clogging cholesterol in the bloodstream by 30–40%, with comparable reductions in the risk of cardiovascular disease in most people. But other interventions are needed to further drive down the amount of this 'bad' cholesterol, also known as low-density lipoprotein (LDL), in individuals at the highest risk of developing heart attacks and stroke. Now, researchers have published the first data from human trials showing that a combination of statins and new drugs directed against a key regulator of cholesterol metabolism can help bring people's cholesterol levels into the long-sought sweet spot.

"These agents are achieving LDL reductions that you don't even see at the highest dose of statins," says cardiologist Evan Stein, director of the Metabolic and Atherosclerosis Research Center in Cincinnati, Ohio. "So they are a real alternative for patients who can't tolerate statins and give substantial additional reductions for patients who are maxed out on statins and still not reaching target—and that's a lot of patients."

The leading drug in this new class is a monoclonal antibody that Stein is investigating. In March, Stein and his colleagues reported phase 1 data showing that the drug—REGN727, which is being co-developed by Regeneron Pharmaceuticals of Tarrytown, New York and the French drug giant Sanofi—reduced blood levels of LDL cholesterol by up to 61% compared with placebo in people concurrently taking Lipitor (*N. Engl. J. Med.* **366**, 1108–1118, 2012). A few days later, at the American College of Cardiology meeting in Chicago, a team that included Stein presented the results of a 183-person, phase 2 trial of REGN727 showing a similarly steep reduction in cholesterol concentrations with only one serious adverse event (*J. Am. Coll. Cardiol.* doi:10.1016/j.jacc.2012.03.007, 2012).

That same week, Thousand Oaks, California–based Amgen also announced phase 1 data for a similar agent, dubbed AMG 145, which reduced average cholesterol levels by up to 75% in study subjects on stable doses of statins.

Both the Amgen and Regeneron-Sanofi drugs work by inhibiting an enzyme called proprotein convertase subtilisin/kexin type 9 (PCSK9), which normally destroys LDL receptors on the surface of liver cells and thereby makes it hard for those cells to remove cholesterol from the blood. Statins, in contrast, work mainly by inhibiting an enzyme that helps make cholesterol; unfortunately, they also increase the production of PCSK9, which attenuates their LDL-lowering potential.



3D4Medical / Photo Researchers, Inc.

Statin alive: Adding new medicines could kickstart current cholesterol drugs.

Different strokes for different folks

Amgen is currently launching several phase 2 trials of AMG 145, whereas Sanofi and Regeneron are recruiting for a pivotal phase 3 study of REGN727. Several other large companies, including Pfizer, Merck and Novartis, also have PCSK9-directed antibodies in or nearing phase 1 development. But not every drugmaker is using the same toolkit to go after PCSK9. A number of smaller firms also have experimental antisense therapies in early clinical or late-stage preclinical development.

Last month, Alnylam Pharmaceuticals of Cambridge, Massachusetts announced updated results from a 32-person trial testing an RNA interference-based therapeutic that reduced LDL levels in the blood by up to 50%. And in the February issue of *Molecular Therapy* (**20**, 376–381, 2012), Marie Lindholm and her colleagues at Santaris Pharma in Denmark published monkey data showing a comparable silencing technique involving locked nucleic acid–modified oligonucleotides cut cholesterol levels in half.

Santaris's human trials to date have proven lackluster, though, and in October of last year the company halted clinical testing owing to poor efficacy data. "We are currently looking to bring forth a backup candidate with a better therapeutic index," Lindholm says. Similarly, in 2010, New Jersey's Bristol-Myers Squibb and California's Isis Pharmaceuticals stopped a phase 1 study of another PCSK9-targeted antisense therapy, and the two drugmakers are now working to advance a more potent antisense inhibitor.

However antisense approaches ultimately fare, antibodies will probably be the first to market, with the drugs projected to generate billions of dollars in revenue for their manufacturers. Yet with several top-selling statins, including Lipitor, now available as cheap generics costing as little as $1 per day, analysts worry over whether people will embrace the PCSK9-directed antibodies, which, if approved, will probably be priced at $20,000 or more per year.

"The potential choice might boil down to dirt-cheap generic statin or dirt-cheap generic statin plus PCSK9 antibody," says Mike Mitchell, a healthcare analyst at Seymour Pierce, a London-based investment bank. "Suddenly, the economic profile of altering an individual's LDL changes dramatically."

David Holmes