Genetics provide blueprint for new heart disease therapies

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Advances in the understanding of the genetics of coronary artery disease, or CAD, will revitalize the field and lead to more therapeutic targets for new medicines to combat this common disease, suggests a genetics expert from the Perelman School of Medicine at the University of Pennsylvania in a Perspective article in the new issue of *Science Translational Medicine*.

Daniel J. Rader, MD, chair of the Department of Genetics and associate director of the Institute for Translational Medicine and Therapeutics, asserts that the lagging search for new heart medicines could be jump-started by a wide-angle hunt for relevant genetic variants in humans.

According the America Heart Association, the death rate from heart disease has fallen about 39 percent during the past 10-most-recent years for which statistics are available. Still, heart disease is the number-one cause of death in the United States, killing almost 380,000 people a year.

Although progress has been made in decreasing the risk of heart disease, with the single greatest contribution made by statins to reduce levels of low-density lipoprotein cholesterol (LDL-C) in millions of people, the burden of the disease remains high. "Despite this clear unmet need, however, many biopharmaceutical companies have begun to back away from efforts to discover and develop therapies for this prevalent disease," writes Rader, citing seven drugs that have failed in phase 3 clinical trials in the last three to five years.

The single biggest issue facing the development of new therapeutics for heart disease is confidence before expensive human trials are underway that the target of a new drug has a high probability of success in reducing disease. Animal models of atherosclerosis, however, have not proven reliable at predicting new therapies that are effective in humans. In contrast, Rader says, basing drug targets on human genetics can provide greater confidence that a therapeutic targeted to a particular pathway will show clinical benefit in reducing major cardiovascular events in people. As with recent successes in cancer immunotherapy, a targeted, personalized approach to developing new treatments has proved attractive to big pharma.

Human genetic data strongly support the concept that reducing LDL-C by any means is associated with a lower cardiovascular risk. This association is consistent with LDL-C being a causal factor in the development of cardiovascular disease. Indeed, the discovery that mutations in the gene PCSK9 reduce LDL-C and protect against CAD launched a major effort to develop inhibitors of PCSK9, which markedly reduce LDL-C and are in late-stage clinical development.

Similar genetic data for triglycerides were recently published, suggesting that specific proteins regulating this blood chemical might be viable therapeutic targets. On the other hand, human genetic data provide little support for raising high-density lipoprotein cholesterol (HDL-C) because genetic variants associated with increased HDL-C are not generally associated with decreased cardiovascular risk.

Although circulating biomarkers such as LDLs and triglycerides, commonly measured in standard blood lipid panels, are useful for guiding drug development programs focused on reducing CAD, Rader contends that many of the genetically validated targets for CAD will not have well-established circuiting biomarkers. "Some of the most interesting new targets for atherosclerotic cardiovascular disease are

likely to come from genetic studies of common and rare variants, comparing individuals with early disease with those who are free of disease," says Rader.

He cites studies of common variants associated with CAD that have yielded nearly 50 discrete genetic loci genome-wide that are statistically significantly associated with CAD. Less than a third are associated with such traditional risk factors as LDL-C levels or blood pressure, leaving more than 30 loci with no association with traditional measureable risk factors.

Rader cites a 2011 *Lancet* study, performed in collaboration with Penn colleague Muredach P. Reilly, MBBCH, MSCE, associate professor of Medicine and Pharmacology, that identified a new locus, ADAMTS7, a gene already implicated in arthritis, which was associated with the risk of developing CAD.

ADAMTS7 is a metalloproteinase, an enzyme expressed in blood vessels. Rader suggests that if it could be shown that genetically reduced activity of ADAMTS7 protects against CAD, this would provide compelling support for the concept of pharmacologically inhibiting this enzyme: "Situations like this, in which loss-of function gene variants are associated with protection from CAD, are particularly compelling because they suggest that pharmacologic inhibition of those proteins might be expected to reduce risk."

The wealth of new genetic discoveries over the past several years, combined with additional ones likely to come, has provided potential new targets and has caught the attention of the biopharmaceutical industry, notes Rader. Indeed, the Accelerating Medicines Partnership, a partnership between the National Institutes of Health and 10 biopharmaceutical companies (Rader co-led the working group for type 2 diabetes), was recently formed to leverage human genetics to discover

and validate new therapeutic targets.

More information: "New Therapies for Coronary Artery Disease: Genetics Provides a Blueprint," by D.J. Rader, *Science Translational Medicine*: stm.sciencemag.org/lookup/doi/ … scitranslmed.3008535

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