Cardiovascular Disease Reduction

ApoA-I Enhancement Will Provide Future HDL Therapies

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The recent disappointments of drugs in clinical trails targeting vascular disease have patients, scientists and other interested parties searching for safe, effective and novel therapies. This was no more apparent than at the 2007 American College of Cardiology (ACC) meetings in New Orleans, where a number of drug companies discussed the failure of their clinical candidates. This set the stage for the ACC community to focus on new therapeutics, specifically those targeting high-density lipoprotein (HDL) metabolism and function, in particular apolipoproteinA-I (ApoA-I), the protein component of HDL.

Epidemiological studies, such as the Framingham[1] and Procam[2], have found that high levels of HDL are associated with protection from cardiovascular events. Other more mechanistic studies have shown the importance of additional markers in the cholesterol transport pathway. However, few have yet demonstrated a role in the reduction of atherosclerotic plaque and cardiovascular disease (CVD). This was clearly demonstrated in the ILLUMINATE and ILLUSTRATE trials, where Torcetrapib, a cholesterol ester transfer protein (CETP) inhibitor, increased plasma HDL, but was not shown to be effective at reducing plaque volume. Though inhibiting CETP is an attractive target to increase HDL, it comes with the cost of retarding the atherosclerosis protective pathway, termed reverse cholesterol transport. However, another trial, ARISE, re-affirmed the importance of HDL. Treatment with AGI-1067, a vascular protectant, was shown to be associated with a 14% decrease in HDL and negated any beneficial effects of the drug's anti-inflammatory properties in atherosclerosis. This underscores the difficulty of identifying new drug targets that show efficacy in reducing atherosclerosis.

Remarkably however, three infusion studies with nascent HDL particles (ApoA-I/phospholipids complexes) have been able to demonstrate the prevention and regression of atherosclerosis. A single infusion with recombinant proApoA-I particles resulted in a 34% sustained 10 day increase in cholesterol excretion, with a net removal of 5-7% of total body cholesterol[3]. In a second study, five weekly infusions of ApoA-IMilano demonstrated a significant regression of coronary atherosclerosis[4]. The coronary segment containing the greatest atherosclerotic plaque resulted in an average 11% reduction in atheroma volume[5]. In a recent study by Tardif *et al*, also released at the ACC, researchers describe how treatment with ApoA-I particles had quick and potent effects on reducing plaque volume[6]. On the other hand, aggressive treatment with statins over a period of 2 years resulted in minimal removal of arterial plaque. These studies support the notion that ApoA-I has remarkable potency in removing cholesterol and atherosclerotic plaque.

These results are also supported by numerous epidemiological studies. The Swedish prospective population study, AMORIS, following roughly 175,000 men and women for 6 years demonstrated ApoA-I to be the most potent protection factor against fatal myocardial infarct[7]. The INTERHEART study, an international case control study comparing myocardial survivors with age and gender matched controls, revealed that the ApoA-I/ApoB ratio was the strongest modifiable protective factor[8]. These two studies high-lighting ApoA-I comprise 40 times more subjects than the aforementioned Framingham study where HDL cholesterol was followed. Taken together, these findings demonstrate that ApoA-I is the strongest modifiable risk factor against death from cardiovascular disease, making it a desirable target for therapeutic intervention.

Resverlogix Corp. (RVX) has discovered novel small molecules that increase the production of endogenous ApoA-I. This physiological approach that targets the patients own liver and small intestine to increase the transcription, synthesis, and secretion of ApoA-I, feeds new ApoA-I particles or nascent HDL particles into the reverse cholesterol transport pathway. The parallels with the ApoA-I infusion therapies are obvious. While the former are infusion therapies for short term treatment the Resverlogix small molecules provide permanent ApoA-I increase for chronic treatment. Using this approach, plaque is rapidly removed from the artery to the liver for elimination. As compared to CETP inhibition, which specifically prevents the unloading of cholesterol from HDL to LDL thereby preventing elimination by the body, RVX's approach tips the natural balance in favor of cholesterol elimination. The development of a small molecule drug that increases plasma ApoA-I by enhancing endogenous ApoA-I production has the potential to become a breakthrough therapy for the treatment of cardiovascular disease, either as a stand alone treatment or in combination with the standard of care treatment.

About the author:
Dr. Johansson, M.D., Ph.D. has had a distinguished 28 year career of which the past 12 years have been in small biotechnology and large pharmaceutical companies with expertise in the cardiovascular disease therapeutic area. He has served as Chief Medical Officer at Nuvelo, Inc., VP, Clinical Research and Development at Lipid Sciences, Inc., was Co-founder, VP, Clinical Affairs and Senior Clinical Research Fellow of Esperion Therapeutics, Inc., and headed the Pharmacia cardiovascular group. Dr. Johansson is currently Senior Vice President, Clinical Development for Resverlogix Corp.

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