New Lipid and Lipoprotein Targets for the Treatment of Cardiometabolic Diseases

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Lifestyle and dietary efforts have known benefits for the prevention of cardiovascular disease (CVD) (1,2). In addition, prescriptive approaches for cardiovascular risk reduction include treatment of elevated blood pressure, and anti platelet therapy with low dose aspirin, particularly within subjects at higher risk such as those with known CVD (3,4). Beyond these interventions, our current pharmacopoeia for the prevention and treatment of CVD are in large part based upon manipulation of lipid and lipoprotein targets. The dose-dependent relationship between circulating levels of low density lipoprotein cholesterol (LDL) and incident CVD risks in population studies (5) and the unequivocal benefit of therapies that lower LDL (6,7) have prompted its central role in the approach to risk prediction and preventive strategies. Yet, while high potency statin therapy has proven efficacy for both primary and secondary prevention subjects (6-8), many patients with established CVD have “normal” LDL levels, though likely above ideal (9), often without clear alternative risk factors. Although some experts feel the current LDL target goals are still too high, many subjects cannot even reach these goals, much less the lower treatment goals now being advocated with current agents. Thus, there is significant unmet need for additional agents to help subjects achieve appropriate therapeutic targets. Further, the polygenetic / causal nature of CVD suggests that there are additional factors that play contributory roles in the development and progression of CVD, which have yet to be appropriately leveraged as therapeutic targets. Indeed, subject with CVD are already typically placed on poly-pharmacy, yet substantial residual risk still exists, and few new agents have made it to use in the past decade in patient care for prevention of CVD and its complications. Cardiovascular therapeutics faces significant hurdles, and the demonstration of a new drug with proven efficacy for reduction in hard endpoints (incident heart attack, stroke and death) on top of high potency statin therapy has yet to be realized.

Despite these obstacles, the magnitude of the problem is staggering, and "the prize" for those who usher in the next generation of cardiovascular therapeutics can not be under estimated. While mortality
rates from CVD have reduced, the prevalence of major risk factors like obesity and diabetes are rising. Fully one in three individuals in industrialized societies will be affected by CVD, and approximately one in three subjects will die from CVD (10). With CVD as the single largest cause of morbidity and mortality in industrial societies and the significant health care burden of obesity and diabetes, it is perhaps not too surprising that a multitude of novel therapeutic approaches are under investigation, with many already undergoing early clinical trials in humans.

In this issue, we launch the first installment of a series of review articles for a new JLR Thematic Review Series entitled "New Lipid and Lipoprotein Targets for the Treatment of Cardiometabolic Diseases". In the first review, Bart Staels and colleagues discuss "Bile acid receptors as targets for the treatment of dyslipidemia and cardiovascular diseases"(11). Bile acid sequestrants were among the first lipid lowering agents with proven efficacy in LDL lowering and CVD event risk reduction in use (12). By binding and facilitating gastrointestinal elimination of bile acids, a net reduction in bile acid pool size is achieved, prompting hepatic cholesterol consumption for increased bile acid synthesis. Accompanying increases in hepatic LDL receptor levels promote a net decrease in circulating LDL cholesterol levels. While effective at lowering LDL cholesterol and CVD events, their clinical use has been somewhat limited by side effects (e.g. triglyceride elevations, GI issues). Their widespread use demonstrated numerous additional metabolic effects, particularly in type 2 diabetic subjects, where reductions in fasting glucose and changes in energy metabolism are observed. The two receptors mediating these phenomena, the nuclear farnesoid X receptor (FXR) and the G-protein coupled receptor TGR5, have emerged as novel targets of glucose metabolism, weight loss, and regulation of inflammation. In their review, Dr Staels and colleagues focus on recent advances in the understanding of bile acid metabolism, as well as the role of FXR and TGR5 in lipid, glucose and energy metabolism. Further, they review how both receptors are pharmacological targets under investigation for the treatment of atherosclerotic CVD, as well as a variety of metabolic disorders including cholestasis,
hyperlipidemia, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), obesity, and type 2 diabetes mellitus. Up to date information is provided in the current state of preclinical and clinical studies with various FXR and TGR5 agonists, as well as selective bile acid receptor modulators.

The complex world of peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists is elegantly summarized by Drs Gregory Schwartz and colleagues in their review entitled "PPAR-γ as a Therapeutic Target in Cardiovascular Disease: Evidence and Uncertainty" (13). Both fundamental basic science aspects of PPAR-γ functions in multiple cell types and pathways are discussed, along with results of seminal clinical trials for different agents within this class of drugs. The varied biological effects of distinct full PPAR-γ agonists are described, along with summaries of major clinical trials with these agents in diabetes subjects, and among subjects with CVD. Ongoing pivotal clinical trials with PPAR-γ activators in patients with CVD are also summarized. In addition, some new PPAR-γ activators under development are reviewed, including both dual PPAR-α/γ agonists, and selective partial PPAR-γ agonists, in the hope that these latter agents provide the established beneficial insulin sensitizing effects of this class of drugs, but without the adverse effects observed.

Drs Philip Barter and Kerry Anne Rye extensively review the rapidly evolving world of cholesterol ester transfer protein inhibitors in their article entitled "Cholesterol ester transfer protein (CETP) inhibition as a strategy to reduce cardiovascular risk" (14). In addition to an extensive review of the mechanism and biological function of CETP in lipoprotein metabolism, Drs Barter and Rye detail the impact of CETP on lipoprotein composition, concentration and structure, and genetic and clinical evidence linking CETP to atherosclerosis in animals and humans. Drs Barter and Rye then extensively review the current state of the field with various small molecule CETP inhibitors, including recent...
results of clinical trials. They start with the seminal clinical outcomes trials with torcetrapib, and a thorough discussion of on and off target effects of the drug. They next review the recent results of trials with dalcetrapib, and then discuss ongoing and potential planned clinical trials with other CETP inhibitors including anacetrapib and evacetrapib. Finally, controversies and unanswered questions related to CETP inhibition are discussed.

Drs Robert Rosenson and Diana Stafforini provide a thorough review of a novel therapeutic target in phase III clinical studies in humans in their manuscript entitled "Modulation of oxidative stress, inflammation, and atherosclerosis by lipoprotein-associated phospholipase A2" (15). They begin by reviewing evidence demonstrating lipoprotein-associated phospholipase A2 (Lp-PLA2) as both a novel diagnostic marker for CVD risks, and a potential therapeutic target for atherosclerotic CVD. The biology, structure, cellular sources and regulation of Lp-PLA2 are initially reviewed, along with the multitude of clinical studies examining Lp-PLA2 mass and activity in various clinical cohorts of subjects across the spectrum of CVD. Genetic studies of Lp-PLA2 in animal models and humans are then reviewed. Finally, the current state of preclinical studies, and past and ongoing clinical trial data with darapladib, the first Lp-PLA2 inhibitor to be tested in humans, is extensively reviewed and discussed.

Lecithin cholesterol acyl transferase (LCAT) is the focus of the review by Drs Sandra Kunnan and Miranda van Eck entitled "Lecithin-cholesterol acyl transferase: Old friend or foe in atherosclerosis"(16). Over half a century ago, Glomset identified LCAT as the key protein mediating cholesterol esterification and "plasma fatty acid transferase" activity (17). Over the ensuing 50 years, numerous studies have focused on LCAT as a pivotal enzyme in HDL maturation and remodeling; yet its role in reverse cholesterol transport and atherosclerotic CVD remains in debate. In this review, the structure, function, and role of LCAT in atherosclerosis in multiple animal models and humans are
extensively discussed. In addition, insights into the role of LCAT in CVD and other processes through genetic studies are discussed. Finally, efforts to increase LCAT levels by a variety of strategies as a novel CVD therapeutic are reviewed.

These are exciting times in the cardiometabolic pharmacology arena, with a large number of novel therapeutic targets under investigation. We hope that the readers of JLR enjoy the present and future series of review articles that will be forthcoming in the Thematic Review Series "New Lipid and Lipoprotein Targets for the Treatment of Cardiometabolic Diseases".
REFERENCES


