Published in final edited form as:
Curr Opin Investig Drugs. 2010 September ; 11(9): 989–996.

Apolipoprotein A-I and its mimetics for the treatment of atherosclerosis

Jonathan D Smith

Abstract

Although statin treatment leads consistently to a reduction in major adverse coronary events and death in clinical trials, approximately 60 to 70% residual risk of these outcomes still remains. One frontier of investigational drug research is treatment to increase HDL, the 'good cholesterol' that is associated with a reduced risk of coronary artery disease. HDL and its major protein apolipoprotein A-I (apoAI) are protective against atherosclerosis through several mechanisms, including the ability to mediate reverse cholesterol transport. This review focuses on the preclinical and clinical findings for two types of therapies for the treatment of atherosclerosis: apoAI-containing compounds and apoAI mimetic peptides. Both of these therapies have excellent potential to be useful clinically to promote atherosclerosis regression and stabilize existing plaques, but significant hurdles must be overcome in order to develop these approaches into safe and effective therapies.

Keywords

Apolipoprotein A-I; HDL; mimetic peptide; reverse cholesterol transport

Introduction

Heart disease remains the most frequent cause of death in the US, with over 50% of heart disease mortality attributed to coronary artery disease (CAD) [1]. Observational epidemiological studies have identified multiple independent risk factors for coronary artery disease, including age, gender, smoking, diabetes, hypertension, and total and LDL cholesterol (LDL-C) levels [2]. Since the Framingham Heart Study, elevated levels of HDL-cholesterol (HDL-C) have been recognized as an independent protective factor against CAD. Moreover, an early meta-analysis of four large prospective American studies (including Framingham) revealed that for every 1 mg/dl increase in HDL-C, a 2 and 3% reduction in CAD risk was observed for men and women, respectively [3].

Additional support for the protective effects of HDL comes from animal models and drug trials. ApoAI overexpression in mouse models of atherosclerosis increases HDL levels and reduces plaque formation and progression significantly [4,5]. Moreover, the Coronary Drug Project clinical trial revealed that participants treated with niacin, the most effective FDA-approved HDL-raising drug, had a 14% decrease in heart attacks or death as a result of CAD, a 27% decrease in non-fatal heart attacks, a 26% decrease in stroke and a 47% decrease in the incidence of heart surgery [6]. This finding has held up with time, and increasing HDL levels has been demonstrated to be effective in reducing CAD risk in subjects with low, medium, or high levels of LDL-C [7].

Address Cleveland Clinic, Department of Cell Biology, Cleveland, OH 44195, USA smithj4@ccf.org.

Although small-molecule drug therapies aimed at increasing HDL are mentioned in this review, the focus is on the administration of apoAI formulations and apoAI mimetic peptides, both of which may impart rapid effects on plaque regression and stabilization. Initial evaluations in a small clinical trial demonstrated that these types of therapies were efficacious [8]. Trial participants receiving injections of an apoAI variant, recombinant $apoAI_{Milano}$ (r-$apoAI_M$), formulated with lipids into reconstituted HDL (rHDL) particles, demonstrated a small, but significant, decrease in coronary artery plaque volume after four weekly treatments, as assessed by intravascular ultrasound (IVUS) [8], thus proving the concept that apoAI therapy can reduce atheroma burden in humans directly. *In vitro* studies comparing the ability of $apoAI_M$ and wild-type (WT) apoAI to act as cholesterol acceptors have reported mixed results [9-11]; thus, an opportunity exists for the development of more effective apoAI-based therapies. This review covers the mechanisms by which HDL is thought to protect subjects from CAD, and the development of apoAI and mimetic peptide therapeutics for the treatment of CAD.

Mechanisms underlying the HDL-mediated reduction in CAD risk

The reverse cholesterol transport (RCT) hypothesis, first described by Glomset [12], proposes that HDL acts as a shuttle to retrieve cholesterol from the periphery and deliver it to the liver, where it can be excreted directly into the bile or metabolized into bile salts before excretion. Both lipid-poor apoAI and HDL are now known to act as acceptors for cellular lipids, and lipid efflux from cells can be mediated via the cell surface proteins ABCA1, ABCG1 and SR-BI [13]. However, there was little direct evidence for the RCT hypothesis *in vivo* until a study conducted by Rader and colleagues was published in 2003 [14]. In this study, a macrophage cell line was loaded with [^{3}H]cholesterol *in vitro* and these cells were then injected into the peritoneal cavity of mice. Increased levels of [^{3}H]cholesterol mobilization from the macrophages to the plasma, liver and fecal compartments were observed in animals that were also treated with recombinant human apoAI adenovirus, thus demonstrating that increased levels of apoAI/HDL can mobilize cholesterol from peripheral tissues for excretion [14]. Subsequent to the initial apoAI/HDL-mediated removal of cholesterol from peripheral cells, there are several more steps in the RCT pathway: the maturation of nascent HDL through cholesterol esterification mediated by the plasma enzyme lecithin-cholesterol acyltransferase (LCAT); the uptake of HDL-C by the liver mediated by SR-BI; the alternate pathway of transferring HDL-C to apoB-containing lipoproteins via the plasma enzyme cholesterol ester transfer protein (CETP) that allows cholesterol trafficking to the liver via the LDL receptor; the metabolism of hepatic cholesterol into bile acids, and the excretion of liver sterols and bile acids into the bile and feces.

HDL/apoAI might exert their anti-atherogenic effects through several other mechanisms. For example, Navab *et al* demonstrated that HDL has anti-inflammatory activity and can inhibit LDL-induced monocyte attachment and transendothelial migration in an endothelial cell vascular smooth muscle cell co-culture system [15]. Moreover, this anti-inflammatory activity could be mediated by the direct antioxidant activity of HDL or minor HDL-associated proteins, such as paraoxonase and platelet-activating factor acetylhydrolase. In addition, Barter and colleagues were the first to demonstrate that HDL has anti-inflammatory activity that inhibits cytokine-induced adhesion molecule expression in endothelial cell cultures [16]. HDL has also been observed to neutralize the proinflammatory activity of C-reactive protein [17]. Some of these effects may be mediated by the HDL-induced stimulation of endothelial cell nitric oxide synthase [18]. For example, Seetharam *et al* reported that HDL promotes endothelial cell migration and vessel re-endothelialization that is mediated by SR-BI [19].

Although HDL is generally protective against CAD, not all HDL is equivalent, leading to the concept of dysfunctional HDL [20,21]. For example, HDL from patients with CAD who had high levels of HDL was determined to exhibit less anti-inflammatory activity and, in some cases, less proinflammatory activity, as compared with HDL derived from healthy control participants, when assayed in the co-culture system, thus indicating that HDL from patients with CAD may be dysfunctional [22]. Conversely, animal models of inflammation exhibit impaired RCT and HDL remodeling [23,24]. Moreover, apoAI is known to be a selective target for oxidative modification by the enzyme myeloperoxidase, which is located in neutrophils, monocytes, plasma and atheroma, creating a covalently modified apoAI with greatly diminished ABCA1-dependent cholesterol acceptor activity [25]. Thus, future apoAI therapies may be designed to be resistant to myeloperoxidase-mediated loss of function.

HDL-targeted therapies

Although not the main focus of this review, it is relevant to mention HDL-targeted therapies other than apoAI-based therapies. Currently available drugs that increase HDL-C levels include niacin, fibrates and, to a lesser extent, statins (as reviewed in reference [26]). However, niacin has an adverse facial flushing side effect, limiting the use of this inexpensive therapy. CETP inhibition is being developed as another HDL-raising therapy; however, the ILLUMINATE clinical trial of torcetrapib, an oral CETP inhibitor and HDL cholesterol enhancer, was terminated early as a result of increased death and cardiac events observed in the treated patients [27]. Notably, torcetrapib has off-target effects, including increasing blood pressure and altering plasma levels of aldosterone, potassium, sodium and bicarbonate; thus, the failure of this drug cannot be attributed to any potential class effects (common to all CETP inhibitors) on generating dysfunctional HDL. A new small-molecule inducer of apoAI production, RVX-208, is under development by Resverlogix Corp, which induces apoAI mRNA and synthesis in hepatoma cells [28,29]. A phase I study in 18 human subjects found that RVX-208 treatment with varying doses over seven days yielded 10% increases in serum apoAI and HDL-C, a 42% increase in serum prebeta-apoAI (lipid free and lipid poor apoAI),and an 11% increase in the ABCA1-mediated cholesterol acceptor activity of 2% serum (assayed in vitro) [28]. Another HDL-targeted therapy developed by Lipid Sciences Inc involved the selective delipidation of plasma HDL and the reinfusion of the lipid-poor HDL and apolipoproteins; this procedure increased the ABCA1-dependent cholesterol acceptor activity of HDL from human plasma [30]. Moreover, atherosclerotic monkeys treated with 12 weekly infusions of selectively delipidated monkey plasma exhibited a 7% reduction in atheroma volume, as determined by IVUS [30]; however, Lipid Sciences filed for bankruptcy in 2008, and development activities were assumed to be discontinued [31].

ApoAI-based therapies

Preclinical studies of apoAI-based therapies

Since HDL is protective against CAD, a series of studies were performed by several investigators to determine the effects of direct injections of HDL or rHDL, made with different apoAI preparations, on atherosclerosis in various animal models. Badimon *et al* demonstrated that four weekly infusions of rabbit HDL into rabbits fed an atherosclerosis-inducing high cholesterol diet could decrease the progression of aortic atherosclerotic lesions [32]. In a separate study, the same treatment regimen was used on older rabbits with more advanced lesions; despite the continued feeding of the high cholesterol diet, a regression of approximately 50% in the surface area of aortic atherosclerosis and in aortic total cholesterol content was observed [33]. In another study, Nicholls *et al* infused rabbit HDL or rHDL, prepared from palmitoyl-linoleoyl phosphatidylcholine and either rabbit apoAI or human apoAII, to cholesterol-fed and aortic-injured rabbits, and demonstrated that

each of these treatments reduced the lesion area [34]. Other investigators have confirmed the effect of HDL infusions on retarding lesion progression in cholesterol-fed rabbits [35]. However, the effect on lesion regression was not reproducible, which is not surprising in the context of continued feeding of the high cholesterol diet that maintains high levels of LDL-C.

A series of preclinical studies using r-apoAI$_M$, a naturally occurring Arg^{173}Cys variant, have been conducted. Carriers of this variant have lower levels of apoAI and HDL-C, and are protected from carotid atherosclerosis compared with individuals with hypoalphalipoproteinemia [36]. However, apoAI$_M$ carriers have been demonstrated to have a 57% increased prevalence of carotid plaques compared with healthy controls, although the difference was not statistically significant in this study because of the small sample size analyzed [36]. Shah *et al* investigated four groups of apoE-deficient mice, with the baseline group fed a high cholesterol western-type diet (WTD) for 20 weeks, and the control group maintained on this diet for 25 weeks. The treatment groups were fed the WTD from week 20 for 5 weeks and received tail vein injections every other day with either 40 mg/kg apoAI$_M$ in a phospholipid complex (for simplicity, all apoAI phospholipid mixtures are referred to as rHDL) or the equivalent amount of phospholipids [37]. A 59% increase in lesion surface area in the control group (ie, progression) was observed, as compared with a 32% increase in lesion surface area in the phospholipid treatment group. Lesion progression was halted completely in the rHDL-treated mice, and was accompanied by a decrease in the lipid-staining area of the aortic root lesions [37]. In a follow-up study, Shah *et al* delivered a high dose of r-apoAI$_M$ (400 mg/kg), formulated into rHDL particles, as a single infusion to WTD-fed apoE-deficient mice [38]. This treatment led to an acute > 2-fold increase in plasma free cholesterol levels and an increase in HDL-C levels. Aortic root lesions were investigated 2 days after treatment using histology-based assays; treatment with rHDL led to an approximately 40 and 30% decrease in lipid and macrophage content of aortic root lesions, respectively [38]. Another study by this research group demonstrated that r-apoAI$_M$ rHDL injections administered to apoE-deficient mice led to improved endothelium-dependent vasodilation in perfused arteries analyzed *ex vivo*. In addition, the *in vitro* treatment of rabbit arteries with this rHDL also protected against endothelial dysfunction induced by lysophosphatidylcholine [39]. More recently, ETC-216, an r-apoAI$_M$ rHDL formulation made by Esperion/Pfizer was evaluated in cholesterol-fed carotid artery-injured rabbits in a dose-response study of the carotid plaque, as assessed *in vivo* by IVUS [40]. Rabbits were treated every 4 days; after two treatments, the lower doses led to reduced lesion progression, while the higher doses led to lesion regression and a significant reduction in markers associated with plaque instability [40,41]. For undisclosed reasons, Pfizer Inc discontinued the development of ETC-216, and sold the apoAI$_M$ license to The Medicines Company in 2009 [42].

Although r-apoAI$_M$ was demonstrated to be effective in preclinical atherosclerosis studies and in many other infusion studies that measured non-atherosclerosis endpoints (eg, see references [39,43]), whether r-apoAI$_M$ is superior to WT human apoAI remains unclear. In head-to-head comparisons of RCT in mice after virus-mediated gene transfer, essentially no difference was observed between the two forms of apoAI, although r-apoAI$_M$ led to lower LCAT activity compared with WT human apoAI [44]. Cho and Kim reported a greater decline in lesion areas in WTD-fed apoE-deficient mice 48 h after the infusion of a single dose of pro-apoAI$_M$ rHDL, as compared with WT pro-apoAI; treatment with pro-apoAI$_M$ rHDL was associated with increased plasma apoAI levels, reduced plasma peroxidase levels and a decreased susceptibility of apoAI$_M$ to oxidation *in vitro* [45]. Notably, apoAI$_M$ binds lipids less efficiently than WT apoAI and has a reduced capacity to accept membrane cholesterol [9,46]. In addition, in transgenic mouse models, apoAI$_M$ was secreted less efficiently by the liver than WT apoAI [47,48]. Furthermore, in atherogenic mice, lesions in

apoAI$_M$ transgenic female animals were larger than in WT apoAI transgenic female animals; this effect was not observed in males [47,48]. Other studies compared virus-mediated expression of WT apoAI and apoAI$_M$ directly in apoE-deficient or LDL receptor-deficient mouse hosts and demonstrated that they were equivalent in reducing plaque progression [49,50]. However, one study using apoAI-transduced macrophages reported that apoAI$_M$ reduced lesion progression to a greater extent than WT apoAI in apoE/apoAI double-knockout mice [51].

Clinical trials of apoAI-based therapies

Single infusions of high-dose rHDL, derived from ~1.6 g of recombinant human pro-apoAI, into four patients with low HDL-C led to a 20% increase in HDL-C that persisted for approximately 4 days, and demonstrated a plasma residence time of ~5.5 days [52]. This residence time was similar to that observed in human apoAI tracer studies in which radiolabeled apoAI, which was not in a rHDL format, was mixed with autologous plasma and infused into human participants [53]. The net increase in plasma apoAI levels was similar following infusion of apoAI as rHDL or as a lipid-free preparation [54,55]. Thus, it is unclear whether there is any pharmacokinetic advantage of rHDL formulations compared with lipid-free apoAI. However, there are several potential advantages of the lipid-free form of apoAI, including easier preparation and excellent ABCA1-dependent cholesterol acceptor activity, which rHDL lacks [56].

A series of elegant papers from Miller and colleagues demonstrated that rHDL infusion into humans increases the levels of small preβ-HDL, HDL-C, plasma and lymph apoAI, and plasma CETP, as well as the activities of LCAT and phospholipid transfer protein [54,57-59]. These rHDL infusions were accompanied by an increase in fecal bile acid excretion [60], thus demonstrating increased RCT. Several additional studies with rHDL infusion in humans have demonstrated improvements in glucose metabolism in diabetic patients [61], endothelial function [62-64], anti-inflammatory responses [65-67] and platelet function [68-70].

The key study in this area was the phase II, double-blind, randomized clinical trial of five weekly infusions of placebo or two dosages of the apoAI$_M$ rHDL product ETC-216 in patients (n = 47) with acute coronary syndrome [8]. Atheroma burden was assessed at the beginning and the end of the treatment period by IVUS. Pooling data from the two dosages, ETC-216 treatment led to a significant 4% decrease in atheroma volume, while the atheroma volume increased by 0.14% in the placebo-treated group [8]; this result is noteworthy, considering the short treatment period.

The phase II, randomized, placebo-controlled ERASE clinical trial evaluated four weekly infusions of two doses of CSL-111, a rHDL product prepared from WT plasma apoAI that is being developed by CSL Behring, in patients (expected n = 180) with atherosclerosis [71]. The high dose regimen (80 mg/kg) was discontinued because of abnormal liver function results. IVUS was used to measure effects on plaque volume; although plaque volume decreased by 3.41% in the treated groups, this result was not significantly different from the 1.62% decrease in plaque volume observed in the placebo group [71]. A separate trial investigated the administration of one dose of CSL-111 or placebo to patients with femoral artery claudication (n = 10), 5 to 7 days prior to femoral artery atherectomy [72]. The recovered atheromas were examined histologically for lipid content, macrophage size and VCAM-1 expression, with all three parameters being lower in the rHDL treatment group compared with the placebo group [72]. Although the results suggested that CSL-111 infusion may lead to plaque stabilization, given that the study was limited by a lack of longitudinal data, these effects could not be demonstrated conclusively. CSL Limited is now

recruiting subjects for a phase I safety study of CSL-112, an alternative rHDL formulation [73].

ApoAI mimetic peptides

Segrest *et al* first demonstrated the prominent pattern formed by apoAI residues 41 to 243 in helical wheel plots [74]. In this structure, termed the class A amphipathic α-helix, the hydrophobic residues are on one side, with positively charged residues flanking to, and negatively charged residues opposite of, the hydrophobic residues. This research team also developed a series of synthetic peptides, which were not based on the sequence of apoAI, but on the class A amphipathic helix structure that apoAI residues 41 to 243 formed; 18A is the prototype 18-mer peptide, and 37pA is a dimer of two 18A peptides with a proline spacer [75]. Similar to apoAI, these peptides can spontaneously clarify a phospholipid emulsion of dimyristoylphosphatidylcholine (DMPC), forming disc-like rHDL particles [75]. Additional interest was focused on a series of more hydrophobic analogs with an increasing number of phenylalanine substitutions (referred to as 2F, 3F, 4F and 5F) [76]. Several of these analogs exhibited increased lipid association activity and, when tested in the co-culture assay for LDL-induced monocyte chemotaxis, the 4F peptide demonstrated the strongest anti-inflammatory activity, which appears to be related to the ability of these peptides to absorb oxidized fatty acids [77]. Similar to apoAI, many of these peptides could act as ABCA1-dependent acceptors for cellular cholesterol; however, at high concentrations, these peptides displayed detergent-like properties and could extract cholesterol from cells independent of ABCA1 [78]. Notably, Remaley *et al* demonstrated that the 37pA peptide, which is composed entirely of D-amino acids, retains its ABCA1-dependent cholesterol acceptor activity, while substituting only two D-amino acids for L-amino acids led to a loss of the class A structure and the cholesterol acceptor activity [78]. This result implies that ABCA1 does not need to interact with these peptides in a chiral manner, but that ABCA1 modifies the plasma membrane that permits a productive interaction with class A amphipathic helical peptides resulting in cholesterol efflux.

The 5F peptide (20 μg/day ip) was injected for 16 weeks into C57BL/6 mice fed a cholate-containing high cholesterol atherogenic diet [79]. This treatment significantly reduced aortic root atherosclerosis, while injection with mouse apoAI (50 μg/day ip) was ineffective. To circumvent the need to inject the mimetic peptides and to facilitate oral administration, Navab *et al* prepared the 4F peptide entirely out of D-amino acid, referred to as APP-018 (D-4F); following oral delivery, the peptide could be detected intact in the plasma 4 h later [80]. The oral administration of APP-018 to LDL receptor-deficient or apoE-deficient mice led to substantial reductions in aortic root lesion areas [80]. In addition, oral APP-018 treatment increased small preβ-HDL levels and led to increased anti-inflammatory activity of HDL, with reductions in lipid hydroperoxides [81]. Combined oral APP-018 and statin treatment of apoE-deficient mice with established lesions resulted in the regression of lesions in the aortic root and the entire aorta [82]; however, Li *et al* reported that orally or intraperitoneally administered APP-018 without statin did not inhibit the progression of established lesions in apoE-deficient mice [83].

These and other preclinical studies of APP-018 led Bruin Pharma Inc to a conduct a phase I clinical trial in patients (n = 50) with CAD, who were administered a single oral dose of placebo or APP-018 (30, 100, 300 or 500 mg) [84]. The agent was detected in plasma at low levels, suggesting limited bioavailability; however, the two highest doses were associated with an increased anti-inflammatory activity of patient-derived HDL [84]. Novartis AG licensed APP-018 from Bruin Pharma in 2005 [85], but no subsequent development has been reported.

Various other amphipathic peptides have been developed based on apoAI, apoE and apoJ, or on purely structural constraints, similar to peptide 18A. Although many of these peptides appear to be promising, most have not advanced significantly in animal models. For example, Sethi *et al* developed a 37pA analog referred to as 5A [86]. The acute administration of a 5A lipid complex to mice increased RCT, and chronic intravenous or intraperitoneal administration of the 5A lipid complex to apoE-deficient mice significantly decreased the aortic surface atherosclerosis lesion area [87]. Another peptide, designated ATI-5261, is being investigated by Artery Therapeutics Inc. Daily intraperitoneal injection of this apoE-derived peptide for 6 weeks into LDL receptor-deficient mice led to a 30% reduction in aortic root lesion area, without affecting plasma cholesterol [88]. Similarly, the treatment of apoE-deficient mice with this peptide by intraperitoneal injection every other day led to a 45% decrease in lesion area [88]. In addition, Navab *et al* recently demonstrated that niclosamide complexed to 4F or an apoJ peptide protected the compounds from degradation and allowed oral delivery [89]. Oral treatment of the niclosamide-4F complex and a statin for 6-months resulted in lesion regression in aged apoE-deficient mice [89].

Conclusion

HDL is protective against CAD by several proposed mechanisms including reverse cholesterol transport, which has led to great interest in the development of therapeutics based upon apoAI and mimetic peptides. Preclinical studies have demonstrated the proof of principal that infusion of rHDL or mimetic peptides can lead to increased levels of HDL and reverse cholesterol transport, and decreased atherosclerosis. A landmark clinical study demonstrated that weekly infusions of ETC-216 (rHDL made from $apoAI_M$) into human CAD subjects led to small but significant reduction in atheroma volume. A clinical trial using CSL-111 (rHDL made with wild type apoAI) also trended towards decreased atheroma volume, although these results were not statistically significant. Although, $apoAI_M$ has demonstrated the most therapeutic benefit, the preponderance of evidence suggests that this variant is no better than WT apoAI, thereby creating an opportunity for the development of new apoAI variants that are resistant to becoming dysfunctional. Another challenge in this area is to determine the optimal apoAI formulation for use as a therapeutic; for example, whether rHDL is superior to lipid-free apoAI has not been clearly demonstrated. An additional barrier to the use of apoAI as a therapeutic is the difficulty in producing endotoxin-free recombinant apoAI. Several apoAI mimetic peptides have been developed as potential therapeutics, and although there have been no clinical trials looking at atheroma volume with these peptides, there is a precedent for the use of peptides as drugs with several peptides having been FDA-approved as drugs in other disease areas. Given that these mimetics have more ABCA1-indpendent detergent-like properties than apoAI, these peptides may be more prone to non-specific side effects than apoAI therapeutics. In conclusion, apoAI and mimetic peptides offer great promise for the treatment of CAD. These developing therapies may be used together with statins to shrink, remodel, and stabilize existing plaques.

Acknowledgments

Research in Jonathan D Smith's laboratory is supported in part by NIH grants RO1-HL66082 and P01-HL098055.

References

•• of outstanding interest

• of special interest

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De SG, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010; 121:948–954. [PubMed: 20177011]
2. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998; 97:1837–1847. [PubMed: 9603539]
3. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DJ, Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989; 79:8–15. [PubMed: 2642759]
4. Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E- deficient mouse. Proc Natl Acad Sci U S A. 1994; 91:9607–9611. [PubMed: 7937814]
5. Paszty C, Maeda N, Verstuyft J, Rubin EM. Apolipoprotein AI transgene corrects apolipoprotein E deficiency-induced atherosclerosis in mice. J Clin Invest. 1994; 94:899–903. [PubMed: 8040345]
6. Cornary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA. 1975; 231:360–381. [PubMed: 1088963]
7. Brown BG, Zhao XQ. Nicotinic acid, alone and in combinations, for reduction of cardiovascular risk. Am.J.Cardiol. 2008; 101:58B–62B. [PubMed: 18157966]
8 ••. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA. 2003; 290:2292–2300. [PubMed: 14600188] [A seminal study demonstrating that an apoAI therapeutic can reduce atheroma volume in humans after a short treatment period.]
9. Bielicki JK, McCall MR, Stoltzfus LJ, Ravandi A, Kuksis A, Rubin EM, Forte TM. Evidence that apolipoprotein AIMilano has reduced capacity, compared with wild-type apolipoprotein A-I, to recruit membrane cholesterol. Arterioscler.Thromb.Vasc.Biol. 1997; 17:1637–1643. [PubMed: 9327756]
10. Favari E, Gomaraschi M, Zanotti I, Bernini F, Lee-Rueckert M, Kovanen PT, Sirtori CR, Franceschini G, Calabresi L. A unique protease-sensitive high density lipoprotein particle containing the apolipoprotein A-I(Milano) dimer effectively promotes ATP-binding Cassette A1-mediated cell cholesterol efflux. J.Biol.Chem. 2007; 282:5125–5132. [PubMed: 17164237]
11. Weibel GL, Alexander ET, Joshi MR, Rader DJ, Lund-Katz S, Phillips MC, Rothblat GH. Wild-type ApoA-I and the Milano variant have similar abilities to stimulate cellular lipid mobilization and efflux. Arterioscler. Thromb. Vasc. Biol. 2007; 27:2022–2029. [PubMed: 17615385]
12. Glomset JA. The plasma lecithins:cholesterol acyltransferase reaction. J. Lipid Res. 1968; 9:155–167. [PubMed: 4868699]
13. Yvan-Charvet L, Wang N, Tall AR. Role of HDL, ABCA1, and ABCG1 transporters in cholesterol efflux and immune responses. Arterioscler Thromb Vasc Biol. 2010; 30:139–143. [PubMed: 19797709]
14. Zhang Y, Zanotti I, Reilly MP, Glick JM, Rothblat GH, Rader DJ. Overexpression of apolipoprotein A-I promotes reverse transport of cholesterol from macrophages to feces in vivo. Circulation. 2003; 108:661–663. [PubMed: 12900335]
15. Navab M, Imes SS, Hama SY, Hough GP, Ross LA, Bork RW, Valente AJ, Berliner JA, Drinkwater DC, Laks H. Monocyte transmigration induced by modification of low density lipoprotein in cocultures of human aortic wall cells is due to induction of monocyte chemotactic protein 1 synthesis and is abolished by high density lipoprotein. J Clin.Invest. 1991; 88:2039–2046. [PubMed: 1752961]
16. Cockerill GW, Rye KA, Gamble JR, Vadas MA, Barter PJ. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler.Thromb.Vasc.Biol. 1995; 15:1987–1994. [PubMed: 7583580]

17. Wadham C, Albanese N, Roberts J, Wang L, Bagley CJ, Gamble JR, Rye KA, Barter PJ, Vadas MA, Xia P. High-density lipoproteins neutralize C-reactive protein proinflammatory activity. Circulation. 2004; 109:2116–2122. [PubMed: 15078800]
18. Mineo C, Yuhanna IS, Quon MJ, Shaul PW. High density lipoprotein-induced endothelial nitric-oxide synthase activation is mediated by Akt and MAP kinases. J Biol.Chem. 2003; 278:9142–9149. [PubMed: 12511559]
19. Seetharam D, Mineo C, Gormley AK, Gibson LL, Vongpatanasin W, Chambliss KL, Hahner LD, Cummings ML, Kitchens RL, Marcel YL, Rader DJ, Shaul PW. High-density lipoprotein promotes endothelial cell migration and reendothelialization via scavenger receptor-B type I. Circ. Res. 2006; 98:63–72. [PubMed: 16339487]
20. Navab M, Reddy ST, Van Lenten BJ, Anantharamaiah GM, Fogelman AM. The role of dysfunctional HDL in atherosclerosis. J. Lipid Res. 2009; 50(Suppl):S145–S149. [PubMed: 18955731]
21. Smith JD. Dysfunctional HDL as a diagnostic and therapeutic target. Arterioscler. Thromb. Vasc. Biol. 2010; 30:151–155. [PubMed: 19679832]
22. Ansell BJ, Navab M, Hama S, Kamranpour N, Fonarow G, Hough G, Rahmani S, Mottahedeh R, Dave R, Reddy ST, Fogelman AM. Inflammatory/antiinflammatory properties of high-density lipoprotein distinguish patients from control subjects better than high-density lipoprotein cholesterol levels and are favorably affected by simvastatin treatment. Circulation. 2003; 108:2751–2756. [PubMed: 14638544]
23. McGillicuddy FC, de la Llera MM, Hinkle CC, Joshi MR, Chiquoine EH, Billheimer JT, Rothblat GH, Reilly MP. Inflammation impairs reverse cholesterol transport in vivo. Circulation. 2009; 119:1135–1145. [PubMed: 19221221]
24. Annema W, Nijstad N, Tolle M, de Boer JF, Buijs RV, Heeringa P, van der Giet M, Tietge UJ. Myeloperoxidase and serum amyloid A contribute to impaired in vivo reverse cholesterol transport during the acute phase response but not group IIA secretory phospholipase A(2). J.Lipid Res. 2010; 51:743–754. [PubMed: 20061576]
25. Zheng L, Nukuna B, Brennan ML, Sun M, Goormastic M, Settle M, Schmitt D, Fu X, Thomson L, Fox PL, Ischiropoulos H, Smith JD, Kinter M, Hazen SL. Apolipoprotein A-I is a selective target for myeloperoxidasecatalyzed oxidation and functional impairment in subjects with cardiovascular disease. J Clin.Invest. 2004; 114:529–541. [PubMed: 15314690]
26. Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease: current and future therapies. J.Am.Coll.Cardiol. 2010; 55:1283–1299. [PubMed: 20338488]
27. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B. Effects of torcetrapib in patients at high risk for coronary events. N.Engl.J.Med. 2007; 357:2109–2122. [PubMed: 17984165]
28. Bailey D, Jahagirdar R, Gordon A, Hafiane A, Campbell S, Chatur S, Wagner GS, Hansen HC, Chiacchia FS, Johansson J, Krimbou L, Wong NC, Genest J. RVX-208: a small molecule that increases apolipoprotein A-I and high-density lipoprotein cholesterol in vitro and in vivo. J.Am.Coll.Cardiol. 2010; 55:2580–2589. [PubMed: 20513599]
29. McNeill E. RVX-208, a stimulator of apolipoprotein AI gene expression for the treatment of cardiovascular diseases. Curr. Opin. Investig. Drugs. 2010; 11:357–364.
30. Sacks FM, Rudel LL, Conner A, Akeefe H, Kostner G, Baki T, Rothblat G, Llera-Moya M, Asztalos B, Perlman T, Zheng C, Alaupovic P, Maltais JA, Brewer HB. Selective delipidation of plasma HDL enhances reverse cholesterol transport in vivo. J. Lipid Res. 2009; 50:894–907. [PubMed: 19144994]
31. Lipid Sciences Inc. Lipid Sciences: Form 8K. October 03. 2008 2008 Press ReleaseRef Type: Report
32 •. Badimon JJ, Badimon L, Galvez A, Dische R, Fuster V. High density lipoprotein plasma fractions inhibit aortic fatty streaks in cholesterol-fed rabbits. Lab Invest. 1989; 60:455–461. [PubMed: 2927083] [The earliest study to demonstrate a benefit of HDL infusion in an animal model of atherosclerosis.]

33 •. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. J. Clin. Invest. 1990; 85:1234–1241. [PubMed: 2318976] [Demonstrated that HDL infusions could lead to lesion regression in rabbits.]

34. Nicholls SJ, Cutri B, Worthley SG, Kee P, Rye KA, Bao S, Barter PJ. Impact of short-term administration of high-density lipoproteins and atorvastatin on atherosclerosis in rabbits. Arterioscler. Thromb. Vasc. Biol. 2005; 25:2416–2421. [PubMed: 16141405]

35. Miyazaki A, Sakuma S, Morikawa W, Takiue T, Miake F, Terano T, Sakai M, Hakamata H, Sakamoto Y, Natio M. Intravenous injection of rabbit apolipoprotein A-I inhibits the progression of atherosclerosis in cholesterol-fed rabbits. Arterioscler. Thromb. Vasc. Biol. 1995; 15:1882–1888. [PubMed: 7583568]

36. Sirtori CR, Calabresi L, Franceschini G, Baldassarre D, Amato M, Johansson J, Salvetti M, Monteduro C, Zulli R, Muiesan ML, Agabiti-Rosei E. Cardiovascular status of carriers of the apolipoprotein A-I(Milano) mutant: the Limone sul Garda study. Circulation. 2001; 103:1949–1954. [PubMed: 11306522]

37 •. Shah PK, Nilsson J, Kaul S, Fishbein MC, Ageland H, Hamsten A, Johansson J, Karpe F, Cercek B. Effects of recombinant apolipoprotein A-I(Milano) on aortic atherosclerosis in apolipoprotein E-deficient mice. Circulation. 1998; 97:780–785. [PubMed: 9498542] [The first demonstration that rHDL derived from apoAIM could reduce atherosclerosis in a mouse model, leading the way for the subsequent clinical trial of this apoAI variant.]

38. Shah PK, Yano J, Reyes O, Chyu KY, Kaul S, Bisgaier CL, Drake S, Cercek B. High-dose recombinant apolipoprotein A-I(milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein e-deficient mice. Potential implications for acute plaque stabilization. Circulation. 2001; 103:3047–3050. [PubMed: 11425766]

39. Kaul S, Coin B, Hedayiti A, Yano J, Cercek B, Chyu KY, Shah PK. Rapid reversal of endothelial dysfunction in hypercholesterolemic apolipoprotein E-null mice by recombinant apolipoprotein A-I(Milano)-phospholipid complex. J. Am. Coll. Cardiol. 2004; 44:1311–1319. [PubMed: 15364338]

40. Parolini C, Marchesi M, Lorenzon P, Castano M, Balconi E, Miragoli L, Chaabane L, Morisetti A, Lorusso V, Martin BJ, Bisgaier CL, Krause B, Newton RS, Sirtori CR, Chiesa G. Dose-related effects of repeated ETC-216 (recombinant apolipoprotein A-I Milano/1-palmitoyl-2-oleoyl phosphatidylcholine complexes) administrations on rabbit lipid-rich soft plaques: in vivo assessment by intravascular ultrasound and magnetic resonance imaging. J. Am. Coll. Cardiol. 2008; 51:1098–1103. [PubMed: 18342229]

41. Ibanez B, Vilahur G, Cimmino G, Speidl WS, Pinero A, Choi BG, Zafar MU, Santos-Gallego CG, Krause B, Badimon L, Fuster V, Badimon JJ. Rapid change in plaque size, composition, and molecular footprint after recombinant apolipoprotein A-I Milano (ETC-216) administration: magnetic resonance imaging study in an experimental model of atherosclerosis. J. Am. Coll. Cardiol. 2008; 51:1104–1109. [PubMed: 18342230]

42. The Medicines Company. The Medicines Company acquires ApoA-I Milano From Pfizer. December 22. 2009 Press Release

43. Cimmino G, Ibanez B, Vilahur G, Speidl WS, Fuster V, Badimon L, Badimon JJ. Up-regulation of reverse cholesterol transport key players and rescue from global inflammation by ApoA-I(Milano). J. Cell Mol. Med. 2009; 13:3226–3235. [PubMed: 19120689]

44. Alexander ET, Weibel GL, Joshi MR, Vedhachalam C, Llera-Moya M, Rothblat GH, Phillips MC, Rader DJ. Macrophage reverse cholesterol transport in mice expressing ApoA-I Milano. Arterioscler. Thromb. Vasc. Biol. 2009; 29:1496–1501. [PubMed: 19661486]

45. Cho KH, Kim JR. A reconstituted HDL containing V156K or R173C apoA-I exhibited anti-inflammatory activity in apo-E deficient mice and showed resistance to myeloperoxidase-mediated oxidation. Exp. Mol. Med. 2009; 41:417–428. [PubMed: 19322022]

46. Alexander ET, Tanaka M, Kono M, Saito H, Rader DJ, Phillips MC. Structural and functional consequences of the milano mutation (R173C) in human apolipoprotein A-I. J. Lipid Res. 2009

47. Parolini C, Chiesa G, Gong E, Caligari S, Cortese MM, Koga T, Forte TM, Rubin EM. Apolipoprotein A-I and the molecular variant apoA-I(Milano): evaluation of the antiatherogenic effects in knock-in mouse model. Atherosclerosis. 2005; 183:222–229. [PubMed: 16285990]

48. Parolini C, Chiesa G, Zhu Y, Forte T, Caligari S, Gianazza E, Sacco MG, Sirtori CR, Rubin EM. Targeted replacement of mouse apolipoprotein A-I with human ApoA-I or the mutant ApoA-IMilano. Evidence of APOA-IM impaired hepatic secretion. J. Biol. Chem. 2003; 278:4740–4746. [PubMed: 12471038]

49. Lebherz C, Sanmiguel J, Wilson JM, Rader DJ. Gene transfer of wild-type apoA-I and apoA-I Milano reduce atherosclerosis to a similar extent. Cardiovasc.Diabetol. 2007; 6:15. [PubMed: 17475009]

50. Feng Y, Van CE, Jacobs F, Lievens J, Snoeys J, De GB. Wild-type apo A-I and apo A-I(Milano) gene transfer reduce native and transplant arteriosclerosis to a similar extent. J. Mol. Med. 2009; 87:287–297. [PubMed: 19066833]

51. Wang L, Sharifi BG, Pan T, Song L, Yukht A, Shah PK. Bone marrow transplantation shows superior atheroprotective effects of gene therapy with apolipoprotein A-I Milano compared with wild-type apolipoprotein AI in hyperlipidemic mice. J. Am. Coll. Cardiol. 2006; 48:1459–1468. [PubMed: 17010811]

52 •. Carlson LA. Effect of a single infusion of recombinant human proapolipoprotein A-I liposomes (synthetic HDL) on plasma lipoproteins in patients with low high density lipoprotein cholesterol. Nutr Metab Cardiovasc Dis. 1995; 5:85–91. [The first demonstration that high-dose rHDL infusions in humans could increase HDL-C levels.]

53. Ikewaki K, Rader DJ, Schaefer JR, Fairwell T, Zech LA, Brewer HB Jr. Evaluation of apoA-I kinetics in humans using simultaneous endogenous stable isotope and exogenous radiotracer methods. J.Lipid Res. 1993; 34:2207–2215. [PubMed: 8301239]

54 ••. Nanjee MN, Doran JE, Lerch PG, Miller NE. Acute effects of intravenous infusion of ApoA1/phosphatidylcholine discs on plasma lipoproteins in humans. Arterioscler.Thromb.Vasc.Biol. 1999; 19:979–989. [PubMed: 10195926] [The first demonstration that rHDL infusion in humans could lead to increased fecal bile acid excretion.]

55. Nanjee MN, Crouse JR, King JM, Hovorka R, Rees SE, Carson ER, Morgenthaler JJ, Lerch P, Miller NE. Effects of intravenous infusion of lipid-free apo A-I in humans. Arterioscler. Thromb. Vasc. Biol. 1996; 16:1203–1214. [PubMed: 8792776]

56. Cuchel M, Lund-Katz S, Llera-Moya M, Millar JS, Chang D, Fuki I, Rothblat GH, Phillips MC, Rader DJ. Pathways by which reconstituted high-density lipoprotein mobilizes free cholesterol from whole body and from macrophages. Arterioscler Thromb Vasc Biol. 2010; 30:526–532. [PubMed: 20018934]

57. Hovorka R, Nanjee MN, Cooke CJ, Miller IP, Olszewski WL, Miller NE. Mass kinetics of apolipoprotein A-I in interstitial fluid after administration of intravenous apolipoprotein A-I/lecithin discs in humans. J. Lipid Res. 2006; 47:975–981. [PubMed: 16401881]

58. Kujiraoka T, Hattori H, Ito M, Nanjee MN, Ishihara M, Nagano M, Iwasaki T, Cooke CJ, Olszewski WL, Stepanova IP, Egashira T, Miller NE. Effects of intravenous apolipoprotein A-I/phosphatidylcholine discs on paraoxonase and platelet-activating factor acetylhydrolase in human plasma and tissue fluid. Atherosclerosis. 2004; 176:57–62. [PubMed: 15306175]

59. Kujiraoka T, Nanjee MN, Oka T, Ito M, Nagano M, Cooke CJ, Takahashi S, Olszewski WL, Wong JS, Stepanova IP, Hamilton RL, Egashira T, Hattori H, Miller NE. Effects of intravenous apolipoprotein A-I/phosphatidylcholine discs on LCAT, PLTP, and CETP in plasma and peripheral lymph in humans. Arterioscler. Thromb. Vasc. Biol. 2003; 23:1653–1659. [PubMed: 12893687]

60. Nanjee MN, Cooke CJ, Garvin R, Semeria F, Lewis G, Olszewski WL, Miller NE. Intravenous apoA-I/lecithin discs increase pre-beta-HDL concentration in tissue fluid and stimulate reverse cholesterol transport in humans. J.Lipid Res. 2001; 42:1586–1593. [PubMed: 11590214]

61. Drew BG, Duffy SJ, Formosa MF, Natoli AK, Henstridge DC, Penfold SA, Thomas WG, Mukhamedova N, de Court, Forbes JM, Yap FY, Kaye DM, van HG, Febbraio MA, Kemp BE, Sviridov D, Steinberg GR, Kingwell BA. High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. Circulation. 2009; 119:2103–2111. [PubMed: 19349317]

62. Spieker LE, Sudano I, Hurlimann D, Lerch PG, Lang MG, Binggeli C, Corti R, Ruschitzka F, Luscher TF, Noll G. High-density lipoprotein restores endothelial function in hypercholesterolemic men. Circulation. 2002; 105:1399–1402. [PubMed: 11914243]

63. Bisoendial RJ, Hovingh GK, Levels JH, Lerch PG, Andresen I, Hayden MR, Kastelein JJ, Stroes ES. Restoration of endothelial function by increasing high-density lipoprotein in subjects with isolated low high-density lipoprotein. Circulation. 2003; 107:2944–2948. [PubMed: 12771001]

64. Nieuwdorp M, Vergeer M, Bisoendial RJ, op 't RJ, Levels H, Birjmohun RS, Kuivenhoven JA, Basser R, Rabelink TJ, Kastelein JJ, Stroes ES. Reconstituted HDL infusion restores endothelial function in patients with type 2 diabetes mellitus. Diabetologia. 2008; 51:1081–1084. [PubMed: 18389214]

65. Pajkrt D, Lerch PG, van der Poll T, Levi M, Illi M, Doran JE, Arnet B, van den Ende A, ten Cate JW, van Deventer SJ. Differential effects of reconstituted high-density lipoprotein on coagulation, fibrinolysis and platelet activation during human endotoxemia. Thromb.Haemost. 1997; 77:303–307. [PubMed: 9157586]

66. van Leuven SI, Birjmohun RS, Franssen R, Bisoendial RJ, de KH, Levels JH, Basser RL, Meijers JC, Kuivenhoven JA, Kastelein JJ, Stroes ES. ApoAI-phosphatidylcholine infusion neutralizes the atherothrombotic effects of C-reactive protein in humans. J.Thromb.Haemost. 2009; 7:347–354. [PubMed: 18983488]

67. Pajkrt D, Doran JE, Koster F, Lerch PG, Arnet B, van der Poll T, ten Cate JW, van Deventer SJ. Antiinflammatory effects of reconstituted high-density lipoprotein during human endotoxemia. J.Exp.Med. 1996; 184:1601–1608. [PubMed: 8920850]

68. Lerch PG, Spycher MO, Doran JE. Reconstituted high density lipoprotein (rHDL) modulates platelet activity in vitro and ex vivo. Thromb.Haemost. 1998; 80:316–320. [PubMed: 9716159]

69. Calkin AC, Drew BG, Ono A, Duffy SJ, Gordon MV, Schoenwaelder SM, Sviridov D, Cooper ME, Kingwell BA, Jackson SP. Reconstituted high-density lipoprotein attenuates platelet function in individuals with type 2 diabetes mellitus by promoting cholesterol efflux. Circulation. 2009; 120:2095–2104. [PubMed: 19901191]

70. Patel S, Drew BG, Nakhla S, Duffy SJ, Murphy AJ, Barter PJ, Rye KA, Chin-Dusting J, Hoang A, Sviridov D, Celermajer DS, Kingwell BA. Reconstituted high-density lipoprotein increases plasma high-density lipoprotein anti-inflammatory properties and cholesterol efflux capacity in patients with type 2 diabetes. J. Am. Coll. Cardiol. 2009; 53:962–971. [PubMed: 19281927]

71 ••. Tardif JC, Gregoire J, L'allier PL, Ibrahim R, Lesperance J, Heinonen TM, Kouz S, Berry C, Basser R, Lavoie MA, Guertin MC, Rodes-Cabau J. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA. 2007; 297:1675–1682. [PubMed: 17387133] [Describes a clinical trial in which rHDL infusions led to decreased atheroma volume, but did not achieve statistical significance compared with the placebo.]

72 ••. Shaw JA, Bobik A, Murphy A, Kanellakis P, Blombery P, Mukhamedova N, Woollard K, Lyon S, Sviridov D, Dart AM. Infusion of reconstituted high-density lipoprotein leads to acute changes in human atherosclerotic plaque. Circ.Res. 2008; 103:1084–1091. [PubMed: 18832751] [Describes a clinical trial indicating plaque stabilization after rHDL infusion in humans, although this trial was not a longitudinal study.]

73. 2010. http://clinicaltrials.gov/ct2/show/NCT01129661

74. Segrest JP, Jones MK, De LH, Brouillette CG, Venkatachalapathi YV, Anantharamaiah GM. The amphipathic helix in the exchangeable apolipoproteins: a review of secondary structure and function. J.Lipid Res. 1992; 33:141–166. [PubMed: 1569369]

75 ••. Anantharamaiah GM, Jones JL, Brouillette CG, Schmidt CF, Chung BH, Hughes TA, Bhown AS, Segrest JP. Studies of synthetic peptide analogs of the amphipathic helix. Structure of complexes with dimyristoyl phosphatidylcholine. J Biol Chem. 1985; 260:10248–10255. [PubMed: 4019510] [Describes the design and properties of class A amphipathic peptides.]

76. Datta G, Chaddha M, Hama S, Navab M, Fogelman AM, Garber DW, Mishra VK, Epand RM, Epand RF, Lund-Katz S, Phillips MC, Segrest JP, Anantharamaiah GM. Effects of increasing hydrophobicity on the physical-chemical and biological properties of a class A amphipathic helical peptide. J Lipid Res. 2001; 42:1096–1104. [PubMed: 11441137]

77 •. Van Lenten BJ, Wagner AC, Jung CL, Ruchala P, Waring AJ, Lehrer RI, Watson AD, Hama S, Navab M, Anantharamaiah GM, Fogelman AM. Anti-inflammatory apoA-I-mimetic peptides bind oxidized lipids with much higher affinity than human apoA-I. J.Lipid Res. 2008; 49:2302–2311. [PubMed: 18621920] [Describes the mechanism by which mimetic peptides may reduce

atherosclerosis in animal models at levels significantly less than endogenous plasma apoAI levels.]

78 ••. Remaley AT, Thomas F, Stonik JA, Demosky SJ, Bark SE, Neufeld EB, Bocharov AV, Vishnyakova TG, Patterson AP, Eggerman TL, Santamarina-Fojo S, Brewer HB. Synthetic amphipathic helical peptides promote lipid efflux from cells by an ABCA1-dependent and an ABCA1-independent pathway. J Lipid Res. 2003; 44:828–836. [PubMed: 12562845] [Demonstrated that mimetic peptides composed of D-amino acids are ABCA1-dependent cholesterol acceptors, and that mimetic peptides have both specific and non-specific acceptor activities.]

79 ••. Garber DW, Datta G, Chaddha M, Palgunachari MN, Hama SY, Navab M, Fogelman AM, Segrest JP, Anantharamaiah GM. A new synthetic class A amphipathic peptide analogue protects mice from diet-induced atherosclerosis. J.Lipid Res. 2001; 42:545–552. [PubMed: 11290826] [The first demonstration of a mimetic peptide reducing atherosclerosis in an animal model.]

80. Navab M, Anantharamaiah GM, Hama S, Garber DW, Chaddha M, Hough G, Lallone R, Fogelman AM. Oral administration of an Apo A-I mimetic Peptide synthesized from D-amino acids dramatically reduces atherosclerosis in mice independent of plasma cholesterol. Circulation. 2002; 105:290–292. [PubMed: 11804981]

81 ••. Navab M, Anantharamaiah GM, Reddy ST, Hama S, Hough G, Grijalva VR, Wagner AC, Frank JS, Datta G, Garber D, Fogelman AM. Oral D-4F causes formation of pre-beta high-density lipoprotein and improves high-density lipoprotein-mediated cholesterol efflux and reverse cholesterol transport from macrophages in apolipoprotein E-null mice. Circulation. 2004; 109:3215–3220. [PubMed: 15197147] [The first demonstration that the oral administration of APP-018 (D-4F) can reduce atherosclerosis in an animal model.]

82. Navab M, Anantharamaiah GM, Hama S, Hough G, Reddy ST, Frank JS, Garber DW, Handattu S, Fogelman AM. D-4F and statins synergize to render HDL antiinflammatory in mice and monkeys and cause lesion regression in old apolipoprotein E-null mice. Arterioscler.Thromb.Vasc.Biol. 2005; 25:1426–1432. [PubMed: 15845909]

83. Li X, Chyu KY, Faria Neto JR, Yano J, Nathwani N, Ferreira C, Dimayuga PC, Cercek B, Kaul S, Shah PK. Differential effects of apolipoprotein A-I-mimetic peptide on evolving and established atherosclerosis in apolipoprotein E-null mice. Circulation. 2004; 110:1701–1705. [PubMed: 15353488]

84 ••. Bloedon LT, Dunbar R, Duffy D, Pinell-Salles P, Norris R, DeGroot BJ, Movva R, Navab M, Fogelman AM, Rader DJ. Safety, pharmacokinetics, and pharmacodynamics of oral apoA-I mimetic peptide D-4F in high-risk cardiovascular patients. J.Lipid Res. 2008; 49:1344–1352. [PubMed: 18323573] [Describes a phase I clinical trial of oral APP-018 (D-4F) in humans, revealing low bioavailability.]

85. Novartis, AG. Novartis shows dynamic momentum in industry-leading pipeline. January 20. 2005 Press Release

86. Sethi AA, Stonik JA, Thomas F, Demosky SJ, Amar M, Neufeld E, Brewer HB, Davidson WS, D'Souza W, Sviridov D, Remaley AT. Asymmetry in the lipid affinity of bihelical amphipathic peptides. A structural determinant for the specificity of ABCA1-dependent cholesterol efflux by peptides. J.Biol.Chem. 2008; 283:32273–32282. [PubMed: 18805791]

87. Amar MJ, D'Souza W, Turner S, Demosky S, Sviridov D, Stonik J, Luchoomun J, Voogt J, Hellerstein M, Sviridov D, Remaley AT. 5A Apolipoprotein Mimetic Peptide Promotes Cholesterol Efflux and Reduces Atherosclerosis in Mice. J.Pharmacol.Exp.Ther. 2010

88. Bielicki JK, Zhang H, Cortez Y, Zheng Y, Narayanaswami V, Patel A, Johansson J, Azhar S. A new HDL mimetic peptide that stimulates cellular cholesterol efflux with high efficiency greatly reduces atherosclerosis in mice. J.Lipid Res. 2010 In Press.

89 •. Navab M, Ruchala P, Waring AJ, Lehrer RI, Hama S, Hough G, Palgunachari MN, Anantharamaiah GM, Fogelman AM. A novel method for oral delivery of apolipoprotein mimetic peptides synthesized from all L-amino acids. J.Lipid Res. 2009; 50:1538–1547. [PubMed: 19225094] [Describes a novel method that allows for the oral delivery of peptides composed of L-amino acids.]