Expert Opinion

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Potential therapeutic agents that raise high-density lipoprotein cholesterol levels

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Cardiovascular disease remains one of the leading causes of death in westernised societies. A number of risk factors have been identified that accelerate the risk for cardiovascular disease (CVD), including family history for premature disease (first degree male relative with CVD onset before the age of 55; first degree female relative with CVD onset before the age of 65), hypertension (whether treated or not), age, smoking, diabetes mellitus and low high-density lipoprotein cholesterol (HDL-C) levels. One of the recent changes in the US Adult Treatment Panel guidelines was to increase the lower limit of desirable HDL-C levels (now raised to 40 mg/dL from 35 mg/dL). There have been a few clinical studies demonstrating the benefit of raising HDL-C levels but there are not many therapeutic options that easily accomplish this goal. Research into the understanding of HDL metabolism has yielded a number of potential therapeutic targets. HDL is thought to exert its cardioprotective effects by a number of mechanisms. The predominant one appears to be its participation in the process of reverse cholesterol transport, whereby excess cholesterol from peripheral cells is transported to the liver for disposal via bile acid production. The newer potential targets, among others, include peroxisomal proliferator-activated receptors (PPAR-a, -g and -d), ATP-binding cassette (ABC) transporters, cholesterol ester transfer protein (CETP) and scavenger receptor class B Type I (SR-BI). Among this group, agonists for PPAR-a and PPAR-g have been shown to increase HDL-C levels and are commonly used in the management of patients with Type 2 diabetes mellitus (fibrates and glitazones, respectively). The precise mechanism by which activation of PPAR-g leads to increased HDL-C is still not clearly defined but these agents have been shown to increase expression of ABC transporters and scavenger receptors both in animals and in vitro. An investigational agent, JTT-705, is a CETP inhibitor that has been shown to raise HDL-C levels 34% and without major side effects. The effect of the CETP inhibitor on clinical outcomes is unknown.

Keywords: atherosclerosis, cholesterol, cholesterol ester transfer protein (CETP), coronary artery disease, reverse cholesterol transport

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1. Introduction

It is now well-established that high-density lipoprotein cholesterol (HDL-C) levels are an independent risk factor for cardiovascular disease (CVD) [1]. Results from the Framingham cohort have shown that the incidence of coronary heart disease is inversely correlated with HDL-C [2]. The current US National Cholesterol Education Program (NCEP) guidelines for the management of dyslipidaemia have again emphasised the importance of HDL-C by raising the lower limit to 40 mg/dL [3].

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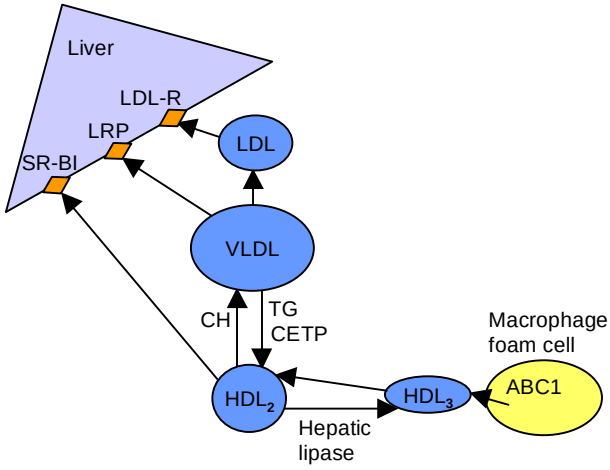


Figure 1. Simplified schematic diagram of reverse cholesterol transport.

ABC: ATP-binding cassette transporter; CETP: Cholesteryl ester transfer protein; CH: Cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; LDL-R: LDL-receptor; LRP: LDL-receptor related protein; SR-BI: Scavenger receptor class B Type 1; TG: Triglycerides; VLDL: Very low density lipoprotein.

Like all lipoproteins, HDL consists of a heterogenous population of spherical lipoprotein particles. By weight, it consists predominantly of protein, the major fraction being apolipoprotein A-I (apoA-I). The centre core consists of neutral lipids containing predominantly esterified cholesterol and triglycerides, with the surface lipids consisting of unesterified cholesterol and phospholipids. Associated with HDL particles are important enzymes that influence the physical state of the lipoprotein, including lecithin cholesterol acyltransferase (LCAT) and cholesterol ester transfer protein (CETP).

One of the major mechanisms by which HDL exerts its cardioprotective effect is by participating in reverse cholesterol transport. Figure 1 shows a process whereby cholesterol is removed from peripheral cells and transported to the liver for disposal [4]. Additional beneficial effects of HDL include its ability to reduce oxidation of low density lipoproteins (LDL) and to act as an endotoxin scavenger [5]. The pathway shown in Figure 1 is a simplified schematic of the role of HDL in reverse cholesterol transport. While there has been a great focus on HDL-C *per se*, it should also be emphasised that other components of the HDL particle are thought to influence its antiatherogenicity (apoA-I), as well as its interaction with hepatic receptors (apoE receptor, scavenger receptor class B Type I (SR-BI)) and ATP-binding cassette (ABC) transporters. For instance, subjects with ApoA-I Milano mutations (substitution of cysteine for arginine at position 173) have been shown to have low HDL-C levels and reduced atherosclerotic disease [6]. The low HDL-C levels are due to rapid catabolism of apoA-I and a normal synthetic rate [7].

At the earliest steps in reverse cholesterol transport (for example, in macrophage foam cells), the ABC transporters exert an important effect in mediating cholesterol and phospholipid efflux from the cells [8]. Among the vast members of this family, deficiency of the ABC1 (also known as ABCA1) transporter has been shown to be the causative factor in subjects with Tangier disease, a condition associated with markedly low HDL-C levels [9]. The mechanism for the associated low HDL-C is thought to be due to increased catabolism of apoA-I with a failure to lipidate nascent disc-like HDL particles [10]. The significant role of ABC1 transporters in HDL metabolism was confirmed in mice deficient in ABC1 transporters and in those genetically engineered to overexpress the protein. ABC1 knockout mice have been shown to have low HDL-C levels [11]. The importance of the ABC1 transporters in raising HDL-C in transgenic animals has yielded conflicting results. In a recent study of C57BL6 mice overexpressing human ABC1 transporters and fed a high cholesterol diet, HDL-C increased 2.8-fold and apoA-I increased 2.2-fold while non-HDL-C levels decreased by 53%. The extent of aortic atherosclerotic disease was significantly less in the transgenic mice as compared with the wild type [12]. However, overexpressing ABC1 in the background of apoE deficiency showed no significant changes in HDL-C levels and progression of atherosclerotic lesions [12]. These results contrasted with a recent study by Singaraja *et al.*, in which these investigators also examined the effect of overexpressing ABC1 in the background of apoE deficiency. Singaraja *et al.* found that HDL-C levels were modestly increased and atherosclerotic lesions reduced in the transgenic ABC1/apoE-/- mice compared to apoE-/- mice [13]. The authors also found increased cholesterol efflux from the ABC1/apoE-/- peritoneal macrophages and concluded that raising ABC1 activity was associated with reduced atherosclerosis and qualitative and quantitative changes in HDL [13].

Recent *in vitro* studies have shown that expression of the ABC1 transporters can be regulated by members of the nuclear hormone receptor superfamily, peroxisomal proliferator-activated receptors (PPAR) [14]. Three isoforms of PPARs have been identified: α, γ and δ [15] and they have been shown to play an important role in atherosclerosis [16]. PPAR agonists also influence ABC1 expression via activation of another member of the orphan nuclear hormone receptor superfamily, liver X receptor α (LXR α). LXR α forms a heterodimer complex with retinoid X receptors (RXR), which can then positively regulate expression of ABC1 transporters [17]. Currently available medications, such as fibrates (which primarily act as PPAR-α agonists) and glitazones (which primarily act as PPAR-γ agonists) have been shown to elevate HDL-C levels [18]. *In vitro* studies have shown that rosiglitazone and troglitazone increased LXR α expression and apoA-I mediated cholesterol efflux in human macrophages [19]. It is unknown whether this is the major mechanism by which these agents increase HDL-C levels in patients with Type 2 diabetes mellitus. Novel PPAR agonists are the focus of some of the patent applications presented within this review.

The role of CETP in HDL metabolism has been the focus for many pharmaceutical scientists. As shown in Figure 1, in

addition to raising HDL-C levels, a benefit of inhibiting CETP activity would be the concomitant lowering of LDL and very low density lipoprotein cholesterol levels. Earlier studies have shown that rabbits fed with the CETP inhibitor, JTT-705, had markedly increased HDL-C levels and lower non-HDL-C levels [20]. Studies of human subjects have shown that those with genetic mutations associated with absent or decreased CETP activity had elevated HDL-C levels [21,22]. However, the functional benefit of raising HDL by inhibiting CETP in humans (such as improvement in vascular function or clinical outcomes) is, however, still unknown. Some subjects with CETP mutations have been shown to be at increased risk for atherosclerotic disease [23], while others have not [24,25].

In the liver, near the final steps in reverse cholesterol transport, HDL particles deliver esterified cholesterol from its core for selective uptake by cell surface receptors (scavenger receptor, class BI (SR-BI)). Acton *et al*. [26] first identified SR-BI in 1994 and it is now a well characterised HDL receptor. One of its primary functions is to mediate the removal of esterified cholesterol from the core of the HDL particles and does so without internalising the apoprotein particles [26]. This helps to facilitate the return of the now cholesterol depleted HDL back into the peripheral circulation, wherein it can begin the process of cholesterol delivery anew. SR-BI is expressed in a number of tissues, including adrenal, testes, ovaries and macrophages [27]. In steroidogenic tissue, its role is thought to mediate delivery of cholesterol for hormone production [28,29]; while in macrophages its role is still unclear (some studies suggesting that SR-BI mediates cholesterol efflux [30, 31], while others do not [32, 33]). In animal models, overexpressing SR-BI has been associated with decreased atherosclerosis and lower HDL-C levels [34]. The results from overexpressing SR-BI in mice demonstrate the importance of the fractional clearance of cholesterol ester (CE) derived from HDL in modulating circulating HDL-C levels [35].

In the clinical setting, there exist only a few pharmacological agents that effectively raise HDL-C levels. The most potent of the currently available products is niacin, which can elevate HDL-C levels up to 35% [36]. Compounds such as the fibrates (gemfibrozil and fenofibrate) raise HDL-C levels by ~ 20 – 25%, while statins exert a minimal effect, raising HDL-C levels generally < 10% [37]. Agents used in the management of Type 2 diabetes mellitus, such as the glitazones and metformin, have also been shown to modestly raise HDL-C levels [38].

Despite the modest effects by these agents in raising HDL-C levels, there does exist clinical evidence supporting the benefit of such increases in patients with and without CVD [39, 40]. Because of the dearth of available agents that effectively raise HDL-C levels, a number of compounds are being tested that might potentially be used in the clinical setting. Within the field of HDL metabolism, there exists a justified debate of whether the focus should be on HDL-C by itself, or on the other components that influence HDL structure and function. Those aspects of the debate are beyond the focus of this review, which will concentrate on selected patent applications from 2000 to 2002 and published reports of preclinical and clinical studies of agents that raise HDL-C levels.

2. Experimental and preclinical investigations

2.1 Cholesterol ester transfer protein inhibitors

2.1.1 WO0038722

Scientists from GD Searle & Co. (US) claimed that compound 1 [101], a CETP inhibitor, when combined with an β-hydroxy-βmethyl glutaryl-CoA (HMG-CoA) reductase inhibitor, could be used for the prophylaxis and treatment of hyperlipidaemia. The preferred combination included the CETP inhibitor, 8,9-dihydro-4,6,7a-trihydroxy-5-methoxy-1,8,8,9-tetramethyl-3H-phenaleno[1,2-b]furan-3,7 (7aH)-dione (one of twenty inhibitors), plus mevastatin (one of six HMG-CoA reductase inhibitors that could be used in the combination).

2.1.2 WO0018721

Scientists from Monsanto (US) claimed the specified compound 2 [102], 3-(N-[3-2(,3Dichlorophenoxy)phenyl]-N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino)-1,1,1-trifluoropropan-2-ol, along with 144 additional compounds as CETP inhibitors. These compounds are novel substituted polycyclic aryl and heteroaryl tertiary 2-heteroalkylamine derivatives.

In vitro assays examined the ability of the various compounds to inhibit CETP activity in human plasma. Results showed that the IC_{50} value for the specified compound was 0.56 μM, with the range of the other compounds being 0.88 – 500 μM.

2.1.3 WO0017164

Scientists from Pfizer Products, Inc. (US) claimed novel 4-carboxyamino-2-substituted-1,2,3,4-tetrahydroquinoline derivatives as CETP inhibitors (compound 3) [103]. The authors claimed the invention could be used for the treatment of the following:

- atherosclerosis
- peripheral vascular disease
- dyslipidaemia
- hyperbetalipoproteinaemia
- hypoalphalipoproteinaemia
- hypercholesterolaemia
- hypertriglyceridaemia
- familial hypercholesterolaemia
- cardiovascular disorders
- angina
- ischaemia
- cardiac ischaemia
- stroke
- myocardial infarction
- reperfusion injury
- angioplastic restenosis
- hypertension
- vascular complications of diabetes
- obesity or endotoxaemia.

The invention could also be combined with the following:

- HMG-CoA reductase inhibitors
- a squalene synthetase inhibitor
- MTP/apoB secretion inhibitor
- a PPAR activator
- a bile acid re-uptake inhibitor
- a cholesterol absorption inhibitor
- a fibrate
- niacin
- an ion exchange resin
- an antioxidant
- an acyl-CoA cholesterol acyltransferse (ACAT) inhibitor
- a bile acid sequestrant.

The suggested dosage of the inhibitors was 0.01 – 10.0 mg/kg/day, with a preference of 0.1 – 5.0 mg/kg/day. No biological data were presented.

2.1.4 *WO0140190*

The compound, ethyl (2*R*, 4*S*)-4-[N-(3,5-bis-trifluoromethyl-benzyl)-N-(methoxy-carbonyl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylate (compound 4) [104], from Pfizer Products, Inc. (US) was claimed as a CETP inhibitor. The suggested dosage range was 0.01 – 100 mg/kg/day, although no biological data were presented.

2.1.5 *WO0211710*

Scientists from Pfizer Products, Inc. (US) claimed that compound 5, a solid dispersion of 10% (2*R*,4*S*)-4-(N-[3,5-bis(trifluoromethyl)benzyl]methoxycarbonylamino)-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline-1-carboxylic acid ethyl ester and cellulose acetate phthalate [105], is a CETP inhibitor. This formulation was thought to improve the bioavailability of the CETP inhibitor.

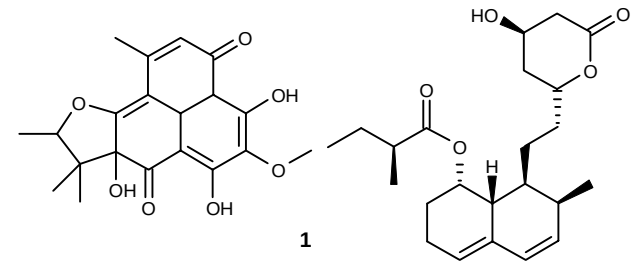
2.1.6 *WO02059077*

Scientists from Takeda Chem. Ind. Ltd (Japan) claimed that compound 6, N-[(1*RS*,2*SR*)-2-hydroxy-2-[4-phenoxyphenyl]-1-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]ethyl]-6,7-dihydro-5H-benzo[a]cycloheptene-1-carboxamide [106], is a CETP inhibitor. The compound was the most potent CETP inhibitor with an IC_{50} value of 0.0084 μM.

2.2 ATP-binding cassette transporters

2.2.1 *EP-1096012-A*

Investigators from Aventis Pharma SA claimed the use of various nucleic acid sequences of the human ABC1 gene for potential use in therapeutic and diagnostic applications [107]. The claim relates to ABC1 cDNAs and their use for detecting polymorphisms and mutations of the ABC1 gene, in particular for screening for human subjects that might have Tangier disease. The invention also relates to ABC1 cDNAs that encode the full-length ABC1 protein. Among the many examples, investigators claimed that a novel ABC1 cDNA included a newly identified 5′-region containing 244 additional



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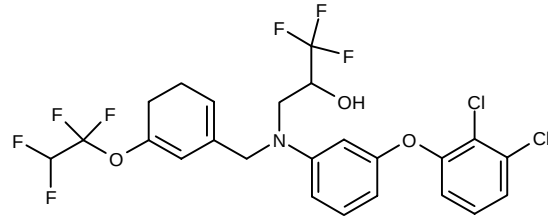

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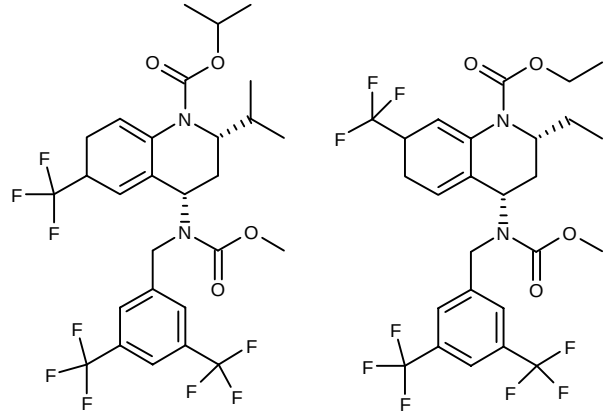

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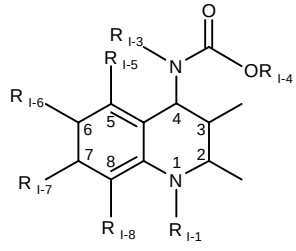
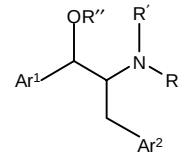
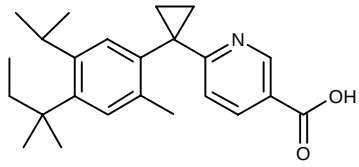


5 R = H, or fully saturated, partialy unsaturated, or fully unsaturated
1 – 6 membered branched or straight carbon chains



6 Ar^1 = optionally substituted aromatic ring group
Ar^2 = substituted aromatic ring group
OR'' = optionaly blocked hydroxy
R = acyl
R' = H or optionally substituted hydrocarcyl

5′ nucleotides and the true initiation ATG codon. Examples of some of the 15 nucleic acids presented were the following: tissue distribution of ABC1 gene transcripts, analysis of the gene expression profile forTangier disease, production of normal and mutated ABC1 proteins, production of antibodies directed against the mutated ABC1 polypeptides, correction of the cellular phenotype of Tangier disease, isolation and



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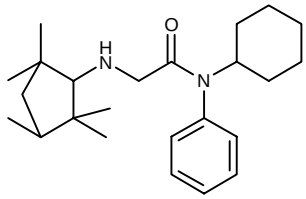

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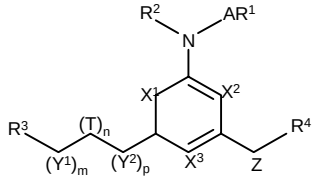

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characterisation of genomic fragments of the ABC1 gene and use of THP-1 macrophages expressing IL-1 β to screen for agonist and antagonist molecules of the ABC1 protein.

2.2.2 *WO0078972*

Scientists from CV Therapeutics, Inc. (US) claimed the use of ABC1 polypeptides and nucleic acids, recombinant vectors, host cells and methods to produce the polypeptides [108]. The claim relates to methods to screen compounds that increase cholesterol efflux and ABC1 expression and activity, and for kits and compositions that measure the ability of a compound to alter ABC1-dependent cholesterol efflux. Among the 18 examples shown, investigators claimed that;

- patients with Tangier disease had absent apoA-I mediated cholesterol efflux from cultured fibroblasts
- 175 genes showed a 2.5-fold decreased expression and 375 genes showed at least a 2.5-fold increased expression in Tangier disease cells
- overexpressing the human ABC1 gene caused an increase in apoA-I mediated cholesterol efflux from murine macrophage cells
- ligands for the LXR and RXR nuclear receptors increased ABC1 gene expression in murine macrophages
- receptor gene assays can be used to test compounds that regulate ABC1 gene expression.

2.2.3 *WO0034461*

Scientists from the University of Texas (US) claimed that compound 7 [109] could affect cholesterol levels by modulating the expression of LXR α, RXR and ABC1. The specified compound, LG-100268, a RXR ligand, inhibited cholesterol absorption in LXR α wild type and knockout mice at a dose as low as 1.4 mg/kg body weight. LG-100268 did not affect bile acid production or excretion but increased ABC1 RNA expression in mouse intestinal tissues. Increasing ABC1 expression is thought to increase HDL cholesterol levels.

2.2.4 *WO0055318*

Scientists from the University of British Columbia (Canada) claimed that nucleic acids encoding ABC1 polypeptides could be used for the diagnosis and treatment of abnormal cholesterol regulation [110]. The invention also outlined methods for screening compounds that increased ABC1 activity, with such compounds potentially being used in patients with Alzheimer's disease, Niemann-Pick disease, Huntington's chorea, X-linked adrenoleukodystrophy and cancer.

2.2.5 *WO0246141*

Scientists from CV Therapeutics, Inc. (USA) claimed that compound 8, 2-(adamant-1-ylamino)-N-cyclohexyl-N-phenyl-acetamide [111], increased ABC1 expression in a pGL3 luciferase assay.

2.2.6 *WO0246172*

Scientists from CV Therapeutics, Inc. (US) claimed that the specified compound 9, 6-[4-(tert-butyl)phenoxymethyl]-4-pentylthio-1,3,5-triazin-2-amine [112], increased ABC1 expression in a pGL3 luciferase assay.

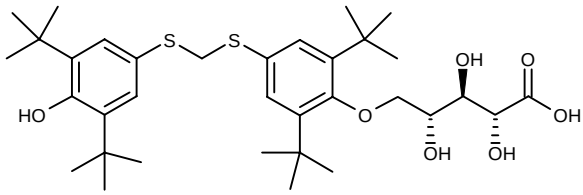
2.3 Other mechanisms

2.3.1 *WO0177072*

Scientists from Atherogenics, Inc. (US) claimed that compound 10 [113], an ether derivative of probucol, substantially increased the levels and function of HDL cholesterol. The mechanism of action was thought to occur by increasing the half-life of apoA-I, increasing the function of the scavenger receptor class B, types I and II (increasing the selective uptake of cholesteryl esters from HDL) and increasing the affinity of HDL particles to hepatic receptors.

Hamsters were fed a high cholesterol diet (0.5% cholesterol plus 10% coconut oil) for 1 week and then the specified compound was added to the hypercholesterolaemic chow at a dose of 150 mg/kg/day for an additional 2 weeks. HDL cholesterol levels increased by 30%, while the compound did not affect LDL cholesterol levels.

In vitro effects of the compound were assessed in cultured HepG2 cells. Cells were incubated with the specified compound (12.5 and 25 μM) for 24 – 48 h. ApoA-I accumulated in the liver cells by 123% (12.5 μM) and 133% (25 μM). Compound 10 also increased the selective uptake of cholesteryl esters from HDL into the HepG2 cells by 109%. Probucol, as a control, decreased apoA-I accumulation by



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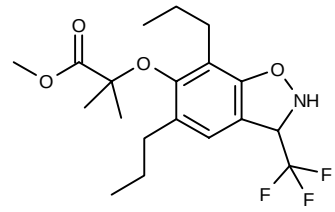

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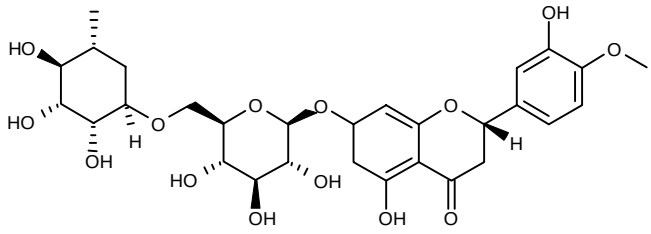

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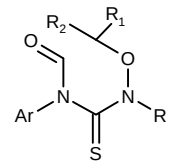

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23% but increased selective cholesteryl ester uptake from HDL by 29%.

Additional experiments suggested that the specified compound enhanced selective cholesteryl ester uptake from HDL via hepatic scavenger receptor class BI/BII receptors.

2.3.2 *WO0160807*

Aryloxyacetic acids are claimed as agonists of PPAR-α and/or PPAR-γ [114] (Merck Co., USA). Compound 11 and similar structures are claimed to be useful in the treatment or prevention of Type 2 diabetes mellitus, hyperglycaemia, dyslipidaemia, hyperlipidaemia, hypertriglyceridaemia, atherosclerosis, obesity, vascular restenosis, inflammation and other PPAR-α and/or PPAR-γ mediated diseases. No biological data are shown in the application.

2.3.3 *WO0023073*

Scientists from the Korea Institute of Science and Technology claimed that compound 12 [115] is a bioflavonoid that elevated HDL-C levels. The main purpose of this invention was to isolate and characterise natural products that would raise HDL-C without causing adverse side effects. The specified compound, hesperidin, along with others, such as hesperitin, naringin, naringenin, diosmin, rutin, quercetin, apigenin, luteolin, kaemferol, eridictyol and neohesperidin dihydrochalcone could be isolated from either citrus peel, vegetables or grains.

The efficacy of the bioflavonoids was at a concentration of 0.1 mg/kg/day. The authors stated that the bioflavonoids, naringin, naringenin, hesperidin, hesperetin, diosmin, neohesperidin dihydrochalcone, quercetin or rutin did not induce toxicity or mitogenicity in mice at a dose of 1000 mg/kg/day.

Data were presented in which 40, 3 week old Sprague–Dawley rats, were randomised to 4 dietary groups (AIN-76 chow diet containing 1% cholesterol, the same diet plus 0.1% hesperetin or 0.1% naringin or 16.7% citrus peel extract) for 8 weeks. As compared with the control diet, the ratio of HDL/total cholesterol increased by 27, 52 and 67% in the hesperetin, naringin and citrus peel extract, respectively. However, much of the effect was due to decreased total cholesterol (15, 31 and 36% in the hesperetin, naringin and citrus peel, respectively) as compared with an isolated increase in HDL-C levels (16, 8, 12%, respectively).

Results are also presented for 2 men in their fifties who were treated with daily oral doses of naringin and hesperidin (10 mg/kg/day) for 2 months. As compared to baseline levels, HDL-C levels increased by 18 and 19%, respectively.

The mechanism of action for the bioflavonoids in elevating HDL-C levels is apparently unknown.

2.3.4 *WO0228845*

Scientists from American Home Products Corp. (US) claimed that compound 13, 4-(5-chloro-2-methylphenyl)-2-methyl-3-thioxo-1,2,4-oxadiazinan-5-one [116] and other similar compounds significantly raised HDL-C levels.

The biological effect of the compounds were tested in male Sprague–Dawley rats fed a rodent chow diet supplemented with 0.25% cholic acid and 1.0% cholesterol plus compounds (100 mg/kg/day) for 8 days. HDL cholesterol levels increased by 60 – 236% with 10 of the compounds, with the specified compound increasing HDL by 236%. The mechanism of action is apparently unknown.

3. Clinical investigations

3.1 Cholesterol ester transfer protein inhibitors

To date, there has been only one human study that examined the effects of a CETP inhibitor on lipid levels. In a recent publication by de Grooth *et al.* [41] investigators examined the safety and efficacy of the CETP inhibitor, JTT-705 (Japan Tobacco, Inc.), in a randomised, double-blind, placebo-controlled study of 198 subjects. Investigators reported that JTT-705 inhibited CETP activity by forming a disulfide bond with the protein

and that in previous animal studies the compound effectively increased HDL-C, lowered LDL-C levels and decreased atherosclerotic lesions [20]. In this Phase II study, following a 4 week run-in phase, study subjects entered the active treatment phase and were randomised to either placebo, JTT-705 300 mg once daily, 600 mg once daily or 900 mg once daily for 4 weeks. After this active treatment phase, subjects were monitored for another 4 week period, making the duration of the study a total of 12 weeks. CETP activity decreased by 37.2% at the end of the active treatment phase in subjects taking the 900 mg dose. HDL-C levels increased in a dose-dependent manner, with a maximum rise of 34% in subjects taking the 900 mg dose. LDL-C levels decreased modestly in the high dose group (7%), while triglyceride levels were unchanged. The compound was well-tolerated, with no changes noted in hepatorenal function, although investigators thought the compound might be associated with symptoms of diarrhoea.

3.2 ATP-binding cassette transporters and other agents

To date, no clinical data have been reported.

4. Expert opinion

Low HDL-C levels are clearly an independent risk factor for premature coronary artery disease. Although a number of therapeutic agents are available for the treatment of hypercholesterolaemia and hypertriglyceridaemia, the number of agents that primarily elevate HDL-C levels is still limited.

The evidence that such an endeavour is worth pursuing is admittedly limited. There have been a few large scale clinical trials that addressed the benefit of raising HDL-C levels. Men with known CAD who were participants in the Veteran's Administration High-density lipoprotein Intervention Trial (VA-HIT) study were treated with either placebo or gemfibrozil 600 mg, twice daily for a period of ~ 5 years [39]. Participants treated with gemfibrozil had a significant risk reduction in non-fatal myocardial infarction, stroke and need for revascularisation procedures that were attributed to an 8% increase in HDL-C levels [39].

Nonetheless, despite the lack of a large body of clinical data, the basis for targeting various candidate proteins involved in HDL metabolism (CETP, ABC transporters, PPARs and SR-BI) appears sound. The recent study by de Grooth *et al*. [41] showed a significant increase in HDL-C levels in study subjects treated with the CETP inhibitor. At the highest dose the compound was also effective in lowering LDL-C levels. One of the major issues will be to assess clinical outcomes in subjects treated with CETP inhibitors. Among the many outstanding questions regarding the increased HDL-C induced by CETP inhibition are whether HDL will enhance reverse cholesterol transport, inhibit LDL oxidation and aggregation, induce regression or delay progression of atherosclerotic disease in subjects treated with the inhibitors.

The potential for agonists of ABC transporters and PPARs as therapeutic agents in raising HDL-C also appears attractive. The glitazones are a class of compounds that are currently used in the treatment of Type 2 diabetes mellitus, with a favourable impact on the lipid profile as well. This class of drug has been shown to regulate the expression of the various PPARs, scavenger receptors (CD36 and SR-BI) and ABC1 transporters [16,17]. It is currently unknown whether the major impact of the glitazones in raising HDL-C levels is attributed to these effects or to other mechanisms.

In summary, there remains a pressing need to identify new therapeutic agents that target HDL and concomitantly improve clinical outcomes.

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Patents

Patents of special note have been highlighted as of considerable interest (••) to readers.

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•• This patent application was well written and presented a thorough background in the area of LXR regulation of ABC1 expression. The studies with compound LG-100268, were well done and offer promise for clinical use.

110. UNIV. OF BRITISH COLUMBIA *ET AL.*: WO0055318 (2000).

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•• This patent application was well written and brought a new and refreshing perspective to the use of probucol in treating dyslipidaemia. The results with the ester derivative of probucol offer exciting future possibilities of treating patients with dyslipidaemia.

114. MERCK: WO0160807 (2001).

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