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REVIEW ARTICLE

Prospects for Developing Lipoprotein-based Drug Transporters for Therapeutic Applications

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Abstract

The primary focus of this review is lipoprotein-based drug carriers, more specifically, high-density lipoprotein (HDL) type nanoparticles (NPs). These nanostructures are discussed regarding their suitability for clinical applications, particularly for cancer therapy. Poor solubility and insufficient capability to selectively target malignant tumors represent significant challenges facing many anticancer drugs. Nevertheless, we and others have found that most, if not all, of these difficulties, can be overcome by incorporating drugs into lipoprotein nanocarriers[1]. While not a novel approach, as HDL type NPs have been documented to deliver anticancer agents to cancer cells effectively and tumors[2,3,4,5], including those that, on their own (without facilitation), exhibited less than desirable therapeutic efficacy[6], due to their desirable features (see below), HDL type drug carriers, at least in our view, hold tremendous promise as facilitators of cancer chemotherapy. One of the key aspects of the HDL-type NP-facilitated drug transport is the receptor-mediated uptake of the payload from the NPs[7,8]. Consequently, in this review, major emphasis is placed on monitoring the expression of the scavenger receptor type B1 (SR-B1) as a potentially valuable tool for the pre-treatment selection of patients regarding their suitability for advanced, personalized chemotherapy. The main emphasis in this article is on developing novel cancer therapeutics, while approaches for treating other diseases via lipoprotein nanocarriers are briefly discussed.

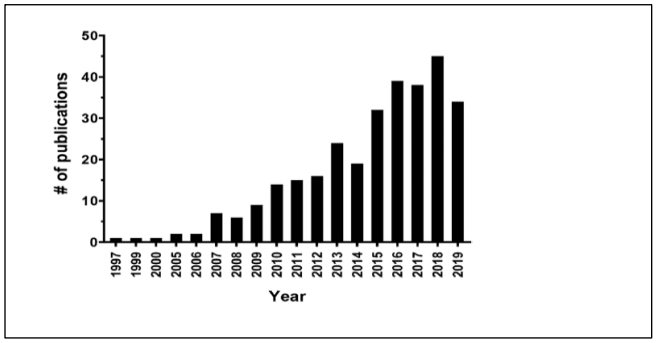
Abbreviations:

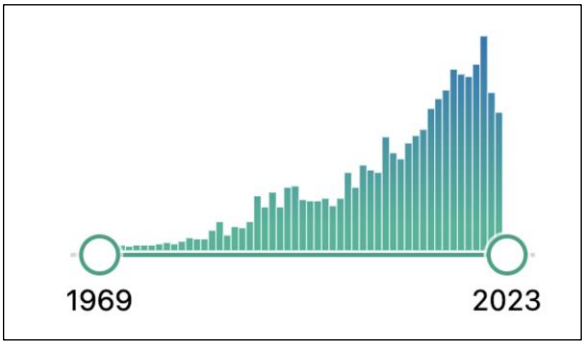
ABCA1	ATP-binding cassette transporter 1
AMD	Age-related macular degeneration
apo A-1	Apolipoprotein A-I
DSS	Disuccinimidyl suberate
HDL	High density lipoprotein
LPS	Lipopolysaccharides
LTA	Lipoteichoic acid
Myr 5A	Myristic acid 5A peptide
NP	Nanoparticle
rHDL	Reconstituted HDL
RPE	Retinal pigmented epithelium
SR-B1	Scavenger Receptor type B1
TNF	Tumor necrosis factor
TLR	Toll-like receptors

EARLIER DRUG DELIVERY STUDIES WITH LIPOPROTEIN-TYPE NANOPARTICLES?

Drug delivery via lipoproteins and HDL were first proposed by Gal et al[9], Counsell et al[10] and Firestone[11]. One of the first studies exploring the lipoprotein-facilitated delivery of drugs was carried out by Kader et al[12,] who showed that drugs incorporated into the lipoprotein carriers formed stable transport complexes and that their ability to suppress the growth of cancer cells was significantly more effective than that of the respective free (unencapsulated) drugs. Similar but substantially more extensive studies were performed by the group of T. Van Berkel[13,14,15,16], including lipoprotein mimetics used for drug delivery.

Among the many studies conducted with lipoprotein drug delivery models, the consistent achievements of three laboratories (led by Drs Gang Zheng, Shad Thaxton and Ann Schwendeman) stand out as major contributors to the advances in lipoprotein-facilitated drug delivery research. According to the studies of Chaudhary et al[3], perhaps not coincidentally, a rapid acceleration occurred since 2007 in lipoprotein drug delivery research, based on the publication activity in this area (Figure 1A). Interestingly, there appears to be a substantial recent decline in this field (Figure 1B) that may be temporary. In our view, the challenges in the commercialization of lipoprotein-based formulations and the tremendous surge in immune therapeutics, offering lucrative alternative financial opportunities for pharmaceutical companies, may be a significant contributors to this trend.





(A) (B)

Figure 1A. Frequency of publications on lipoproteins nanoparticles and cancer from 1998 to November 2019 in PubMed (From: Chaudhary J. et al; Int J Mol Sci. 2019; 20(24):6327.
Figure 1B. Frequency of publications on lipoprotein drug delivery as found on the website https://pubmed.ncbi.nlm.nih.gov.

WHY HDL?

Initially, our laboratory has been working on understanding the mechanisms involved in reverse cholesterol transport for nearly 30 years. Consequently, it was a natural transition for us to explore the potential of HDL-type nanostructures to serve as delivery vehicles for primarily lipophilic anticancer drugs[1]. Our initial efforts were based on a formulation utilizing a spherical lipoprotein model composed primarily of Apolipoprotein A-I (apo A-1) and egg phosphatidylcholine[17]. Subsequently, we demonstrated that a number of drugs, including paclitaxel[17], fenretinide[18] and valrubicin[6], can be incorporated into these reconstituted HDL (rHDL) NPs that exhibited enhanced therapeutic efficacy against cancer cells as compared to their unencapsulated counterpart drugs[5].

In collaboration with Dr. Anil Sood's lab at MD Anderson Cancer, we were also able to show that our rHDL-based formulations, transporting siRNA[4] and microRNA[19], were highly effective in suppressing the growth of human ovarian tumors transplanted into mice, without substantially impacting normal tissues. This tumor-selective toxicity of the delivery process may be crucial to translate these findings into treating patients with solid tumors and perhaps other types of cancers.

We submit that the successes of the rHDL formulations can be attributed to several beneficial characteristics of the rHDL NPs that compare very favorably with the majority, if not all the therapeutic drug delivery approaches[20], including those that have already been cleared for clinical applications[21].

These characteristics of the rHDL NPs include:
Biocompatible components
Small size
Stable and efficient drug incorporation
Tumor selective drug delivery, reducing or eliminating treatment-associated side effects (see Figure 2).

The capability of expanding the therapeutic efficacy via surface modification of the NPs[22].

Favorable pharmacokinetics, based on the residence time of HDL particles in human circulation.

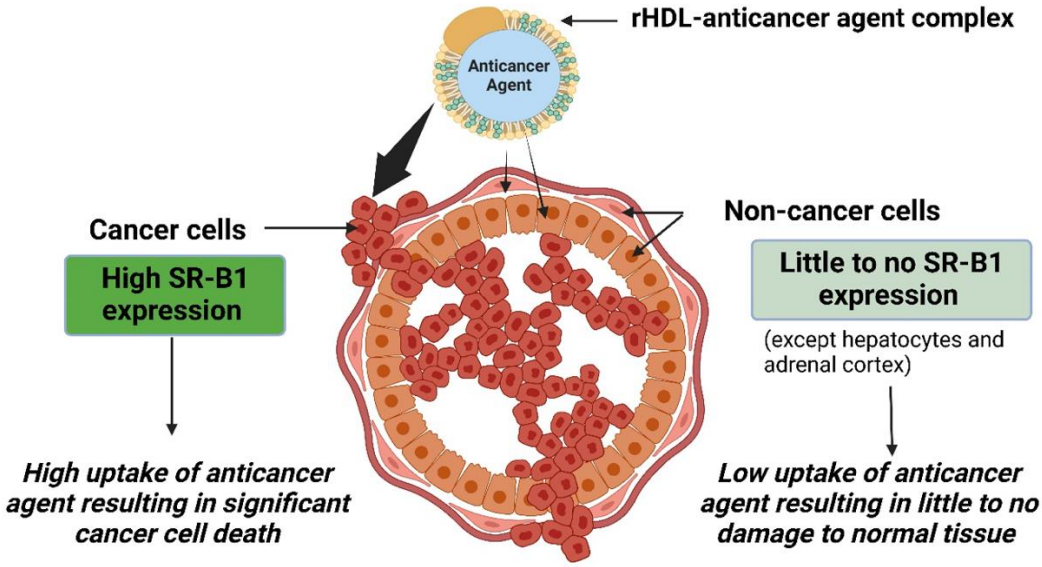


Figure 2. *Receptor-mediated (tumor selective) delivery of the payload transported by rHDL nanoparticles (NPs).* The HDL (SR-B1) receptor is a major facilitator of the uptake of drugs by cancer cells and tumors, from rHDL NPs. This mode of therapeutic delivery is anticipated to be of a significant benefit to patients via avoiding side effects. Image created with BioRender.com

In addition, most injectable drugs are lipophilic; thus, they possess a natural affinity for the core region of circulating lipoproteins, including HDL and reconstituted lipoproteins. Such positioning of the drug payload (cholesteryl esters), in the case of high HDL and similar reconstituted nanostructures, also allows the tumor-selective delivery of the NP's payload via the scavenger receptor type B1 (SR-B1).

EXPANSION OF THE CLINICAL IMPACT OF HDL-TYPE NANOPARTICLES VIA EMPLOYING HDL/APOLIPOPROTEIN MIMETICS.

Artificial constructs mimicking HDL[23,24], including apolipoprotein mimetics[25,26,27], have been considered and investigated for their capabilities toward clinical applications for decades. Nevertheless, despite the numerous clinical trials conducted to treat the consequences of atherosclerosis, there appear to be no clinical trials in progress using lipoprotein-based formulations for cancer therapeutics. Some concerns about using lipoprotein-based formulations for intravenous administration as a therapeutic approach for other diseases (particularly cancer) may arise from the arduous path of several attempts with similar formulations in clinical trials where pharmaceutical companies so far have achieved little success. An additional concern (for HDL-type formulations) has been the availability of apo-A1 and the complexity of the component

profile of many of the formulations, leading to the high costs of the assembly process. These considerations perhaps led to increased activity in the use of apolipoprotein mimetics, exploring the therapeutic potential of several formulations resembling the structure/function and the biological profile of HDL[28,29].

One of the major challenges in the formulation and (industrial) large-scale production of rHDL nanoparticles is the acquisition of sufficient quantities of the major apolipoprotein component apo A-1. Although the commercial scale production of apo A-I has been established and approved for clinical applications[25], these preparations are quite expensive, and their cost may thus hinder their broad applicability. While earlier, our laboratory has been primarily evaluating apo A-I based rHDL nanoparticles[18,19], we recently described an HDL mimetic drug carrier with properties similar to the rHDL/drug nanocomplexes[26]. In collaboration with Dr. Alan T. Remaley of the NHLBI/NIH, we developed a drug carrier based on a lipo-peptide apolipoprotein mimetic that spontaneously assembles into a relatively small diameter (pre-beta HDL-type) spherical structure (Figure 3) upon dissolution in water.

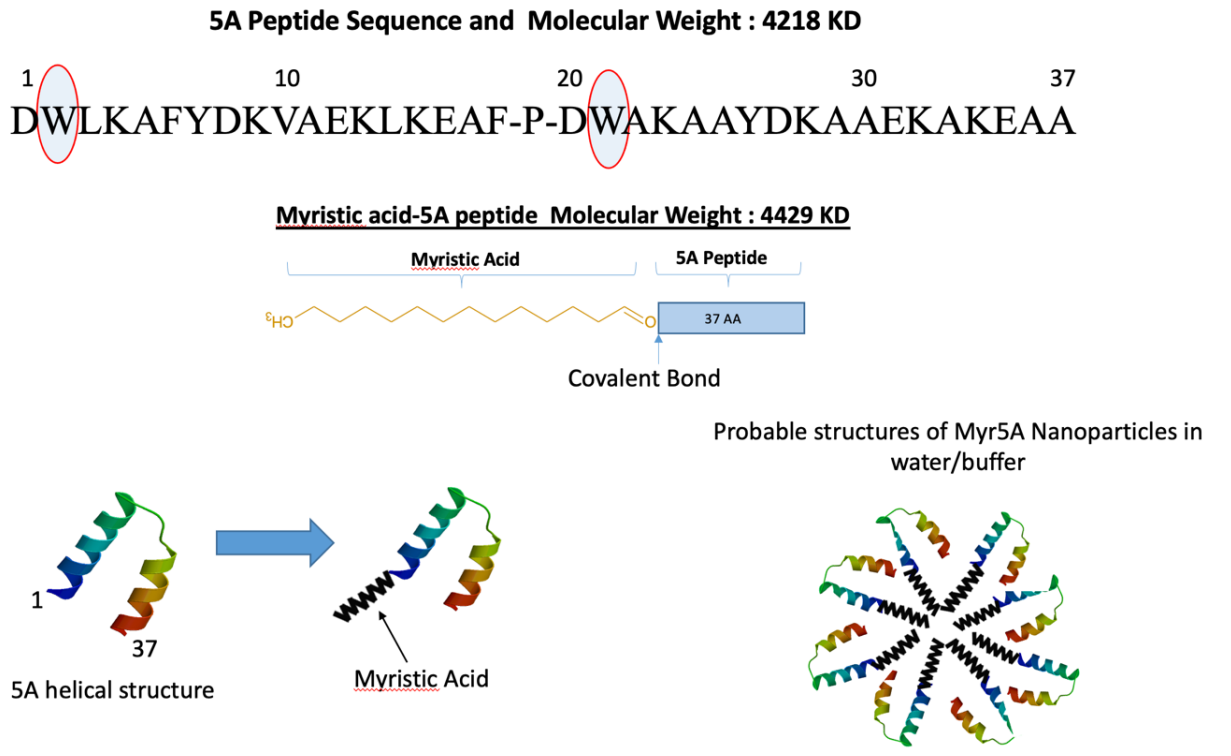


Figure 3. Assembly of the MYR-5A nanostructures from the 5A peptide and myristic acid

Designated as MYR-5A NPs, these nanostructures have already been characterized as effective drug transporters as well as targeted delivery vehicles due to their affinity for the SR-B1 receptor (32). During optimization studies, it was found that the

MYR-5A NPs functioned most effectively if they were subjected to cross-linking by reacting the ε-amino group of the constituent lysine residues with disuccinimidyl-suberate (DSS see Figure 4) after loading the anticancer agent into the NPs. The outcome of this crosslinking process was nearly completely eliminating the leakage of the drug payload, 70% of which was lost during 3 hrs of incubation of the non-crosslinked NPs with human plasma[30].

A highly beneficial feature demonstrated during these initial studies was the close resemblance of the MYR-5A nanostructures to circulating human HDL. Perhaps the most important of these characteristics was the NPs affinity for the SR-B1 receptor, as the SR-B1 antibody could nearly totally block the interaction between the receptor and the NPs. Additional features resembling HDL were found to be the core/surface structural arrangement of the MYR-5A peptide, still leaving room for the drug payload in the interior of the nanoparticle. As mentioned above, the extremely small diameter of the NPs, makes them resemble the native pre-beta HDL particles that tend to be efficient cholesterol removers from tissues.

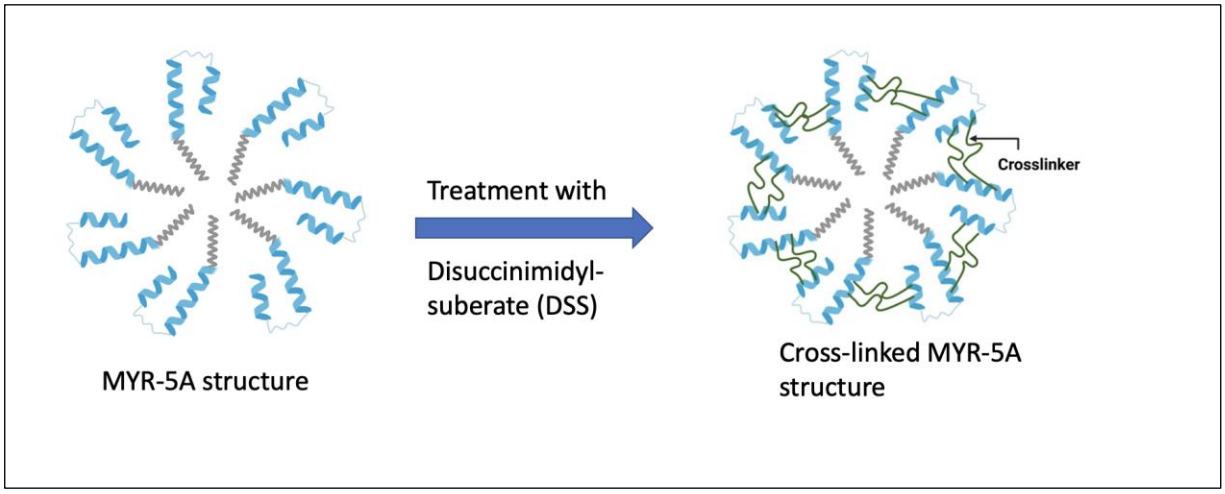


Figure 4. Introduction of crosslinks to protect the therapeutic payload, transported by the MYR-5A nanostructures. Image created with BioRender.com

APPLICATIONS OF LIPOPROTEIN MIMETICS FOR AREAS OUTSIDE CANCER THERAPEUTICS

The information presented in this section, contains examples of potential therapeutic applications for rHDL NPs in a number of different settings. While these examples may not represent self-assembling constructs, in our experience, due to the structural and functional similarities between the rHDLs (made up of natural ingredients) and the MYR-5A NPs, the drug transporting and receptor (SR-B1)-mediated targeting properties are very likely to be nearly identical between the two classes of these nanocarriers. Consequently, the technologies, involving the rHDL NPs are anticipated to be transferable to the MYR-5A NPs as desired.

A) Diabetic kidney disease

The incidence of diabetic kidney disease is approaching epidemic proportions in the U.S.[31,32] while currently there is no curative (or preventive) interventional strategy available for this disease. HDL type NPs have been found to be beneficial in treating (or preventing) diabetic kidney disease as shown by Moreira *et al.*[33] and Kronenberg[34], who demonstrated that HDL protected the kidney from injury induced by sepsis and other potentially damaging impacts. In addition, several infusible rHDLs[35]., including CER-001[36] (developed by Abionyx Pharma) have already been tested in humans). Recently, CER-001 was reported to improve the lipid profile and to counter the evelopment of kidney disease in a mouse model of familial lecithin:cholesterol acyltransferase (LCAT) deficiency.

Recently, our research group obtained preliminary data, regarding the effects of the rHDL NPs on the development of diabetic kidney disease in eNOS$^{-/-}$ *dbdb* mice, a well-accepted model for studying type II diabetes[37,38,39]. Following a 4 week-treatment with rHDL NPs, the eNOS$^{-/-}$ *dbdb* mice showed alleviation of renal injury and slower progression of diabetic kidney disease, as indicated by decreased albuminuria, mitigated glomerular injury, and ameliorated renal fibrosis, compared to the untreated controls. Consequently, rHDL, by itself (without transporting a payload) may have protective effects on the development of renal disease in diabetes mellitus.

B) Lipoprotein mimetics for ocular drug delivery

The retina is a specialized tissue of ten distinct layers with three major cell types, including photoreceptors, neuronal, and glial cells. The pigmented epithelium(RPE), makes up the outermost layer of the retina and plays a critical role in maintaining the health of the photoreceptors through phagocytosis. Drug delivery to the neuroretina and RPE is complex and challenging. Various nanoparticles have been broadly investigated to increase bioavailability with the slow and regulated release of treatment molecules and, most importantly, avoid repeated intraocular injections or implantations.

Currently, researchers have utilized systemic, intravitreal (into the vitreous of the eye), and topical administration of drugs to help treat ocular diseases. Topical administration is an alternative to invasive intravitreal injection and the side effects caused by systemic administrations. However, corneal, conjunctival epithelium, and tear film pose biological barriers to topical drug administration (Figure 5). The use of nanoparticle drug carriers to circumvent these barriers has gained momentum in the last two decades. Previous studies by Dang et al.[40], have shown that lipid nanoparticles between the size of 150 and 600 nm can penetrate these barriers and localize in the back of the eye when compared to non-encapsulated conventional drugs. Moreover, rHDL nanoparticles are thought to overcome these biological barriers due to the lipophilicity and small size of the rHDL drug vehicles[41,42,43,44].

The RPE plays a significant role in lipid transport and metabolism through phagocytosis and lysosomal degradation. Moreover, several studies have shown the presence of epithelial lipid transporters such as the scavenger receptor BI (SR-BI) and CD36 on RPE cells. Specifically, previous studies have identified SRB receptors on several cells in the retina, including RPE cells, photoreceptors, retinal ganglion cells (RGCs), and Müller cells. Recent studies have shown that CD36 and SR-BI are responsible for transporting provitamin A carotenoids in the retina. Other studies have shown that RPE and Müller cells uptake circulating low-density lipoproteins (LDL) and can release high-density lipoproteins (HDL) for reverse cholesterol transport. These studies demonstrated that cholesterol could be replaced entirely in the retina every 6-7 days, indicating extensive lipid transport from circulation to the retina via RPE and Müller cells. Currently, there is no proof of the presence of LDL receptors (LDLR) on RPE cells, and intraocular circulation of cholesterol from RPE and Müller cells remains unknown. While extensive lipid transport and efflux occur in the retina, synthetic HDL nanoparticles have yet to be utilized in ophthalmology research[44,45].

Apolipoproteins play a key role in transporting and circulating lipids and cholesterol in the form of lipoprotein carriers, such as LDL and HDL, which carry hydrophobic agents through the blood to periphery tissues. There are several mechanisms for the efflux of cholesterol from cells, including passive diffusion, oxysterol production, reverse cholesterol transport, and apolipoprotein E secretion. The ATP-binding cassette transporter 1 (ABCA1) is responsible for the transport of apolipoprotein A-I (apo-AI), the major apolipoprotein component of HDL, and apolipoprotein E (apoE). Previous studies have reported the localization of ABCA1 to Müller cells, astrocytes, and RPE cells (46). Moreover, ABCA1 and SR-BI activity in RPE cells are related to photoreceptor disk turnover. RPE cells recycle photoreceptor disks through phagocytosis and recycle the lipids by either reverse cholesterol transport through HDL carriers or lysosomal degradation (44,46). This process is vital for the retina's health and for that of the retinal ganglion cells (RGCs) responsible for relaying visual information from the retina to the brain.

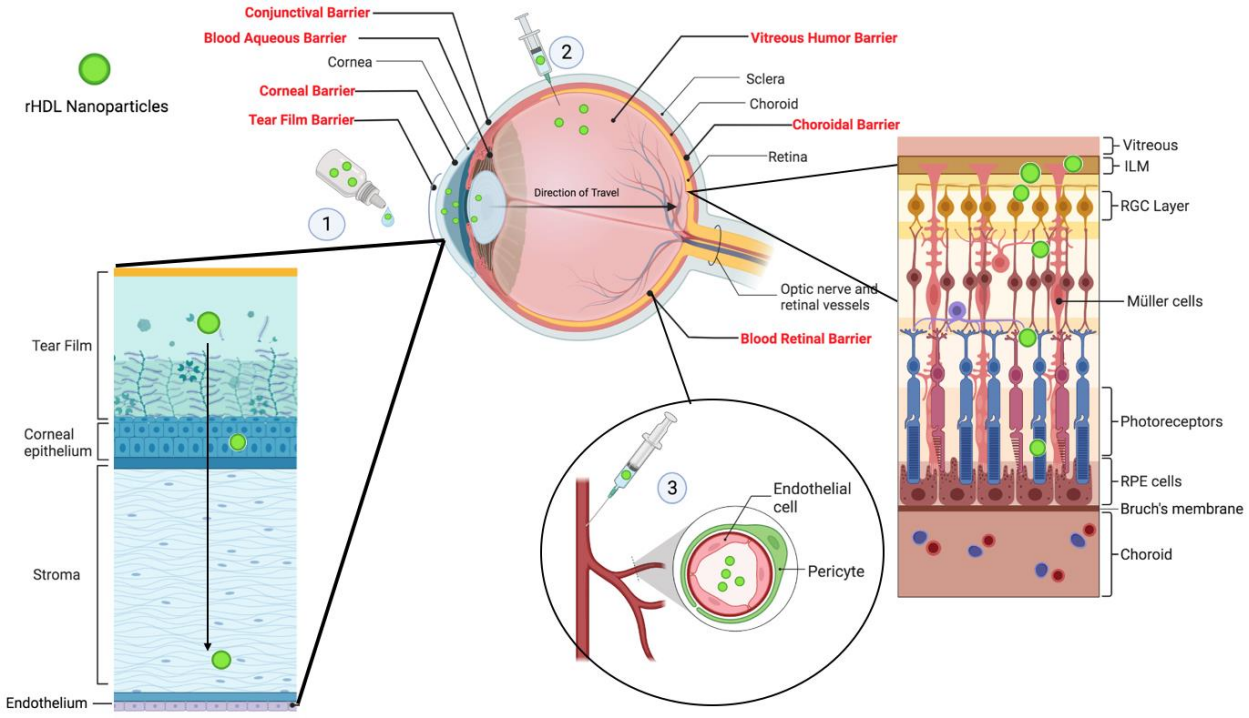


Figure 5. The anatomy of the eye with biological barriers labeled. Green spheres represent rHDL nanoparticle vehicles. 1. Topical administration of nanoparticles with emphasis on the anterior segment of the eye and biological barriers, including the tear film, the cornea, and the conjunctival barrier. 2. Intravitreal administration into the vitreous of the eye. This administration circumvents several barriers; however, nanoparticles will need to penetrate two retina layers, including the inner limiting membrane (ILM), to reach the RGCs and nine layers to reach the RPE cells. 3. Systemic administration of nanoparticles that must penetrate the blood-retina barrier. The figure was prepared using Biorender (https://app.biorender.com/).

The presence of SRB receptors and extensive lipid and cholesterol efflux through the retina provides a unique opportunity for nanoparticle drug delivery, specifically, the rHDL drug delivery platform. The rHDL drug delivery allows several advantages to delivering therapeutic agent-loaded rHDLs to the retina. Based on previous studies with solid lipid nanoparticles, the rHDL vehicle should be able to penetrate the cornea to travel to the back of the eye due to the hydrophobicity and small size of rHDL nanoparticles (49). The nonimmunogenic aspect of the rHDL vehicle also provides an advantage over other conventional nanoparticle formulations for treating eye diseases where neuroinflammation is a significant risk factor. Moreover, RPE cells are critical in transporting HDL cargo from HDL particles outside the retina and recombining the apolipoproteins with the lipids. These HDL-like particles are then released by RPE

ABCA1 on the inside of the retina for binding to SR-B receptors on the photoreceptors, RGCs, and Müller cell. This lipid efflux pathway could be exploited to deliver therapeutic agents to specific cells in the retina that would otherwise be inaccessible by conventional medications. This information suggests that rHDL drug delivery vehicles could theoretically be administered through topical, intravitreal, subretinal, or systematic administration (Figure 5). Topical and systemic delivery is of interest due to the unique features of rHDL nanoparticles enabling them to penetrate through corneal, blood-retina, and blood-aqueous barriers.

(i) Potential application of lipoprotein mimetics in ocular therapy

Glaucoma is characterized by a progressive loss of RGCs due to increased intraocular pressure (IOP). While lowering IOP is currently the only modifiable risk factor for glaucoma, progressive RGC loss can persist in patients with controlled IOP. Moreover, previous studies have indicated that neuroinflammation *via* immunological surveillance by astrocytes and microglia also plays a crucial role in RGC death. Therefore, researchers have shifted their focus to neuroprotection strategies adjunct to controlling IOP to prevent glaucomatous neurodegeneration[45,46]. Significant limitations of current glaucoma therapies are poor bioavailability and delivery barriers into the eye. The development of an efficient ocular drug delivery system is thus critical for the treatment not only of glaucoma but also other eye diseases. Previous studies have identified SR-B receptors on RGCs, photoreceptors, and RPE cells[41].

Furthermore, while RPE cells seem to express most SR-B receptors, they are present on both the apical and basal sides, indicating that RPE cells can allow HDL into and out of the retina. This provides a unique opportunity to administer neuroprotective agents encapsulated in rHDL nanoparticles through the front (topically) and back of the eye intravitreally, sub-retinally, or systemically). Moreover, endogenous HDL can also act (by itself) as a neuroprotective agent by removing excess lipids and cholesterol from the photoreceptors and ganglion cells through reverse cholesterol transport. Excess lipids and cholesterol can cause plaque if accumulated or reactive oxygen species if metabolized by lipid peroxidase[47]. Finally, SR-BI signaling through HDL interactions can activate nitric oxide synthase leading to the inhibition of apoptosis.

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people over 50. It is estimated that 1.8 million people currently have AMD, and more than 7 million are at substantial risk of developing AMD and consequently losing vision. Most AMD patients have the dry form of the disease, characterized by extracellular deposits called drusen underneath the RPE, which culminates in the atrophy of the central retina, specifically the macula. Approximately 15% of AMD-affected patients present the disease's exudative (wet) form. Wet AMD is characterized by new vessels growing from the choroid through Bruch's membrane into the macula region. Leaky vessels cause

edema and damage to the retinas, leading to loss of central vision. Lipid metabolism plays a critical role in the pathogenesis of AMD[48]. For instance, the genetic variations in ABCA1, SR-B1, and apo E, the gene products that all impact HDL homeostasis, have been shown to influence the risk of AMD by increasing excess lipid materials in the eye (53). A recent study showed that a buildup of HDL and LDL in the RPE and Burch's membrane adjacent to the RPE cells could be a risk factor for AMD. Therapeutic mimetic peptide 5A (which mimics apo A-I) was used to compete with binding sites of endogenous HDL, thereby decreasing the buildup of HDL and the subsequent visual damage caused by the accumulation of lipid materials. The rHDL drug delivery platform could be used similarly to that described by Kelly et al[48], without a need for a therapeutic payload as rHDL, by itself, apparently can perform as a therapeutic agent.

Previous studies have shown that synthetic HDL nanoparticles can be administered topically to the eye and found to localize to the posterior of the eye to treat AMD. Moreover, synthetic HDL nanoparticles can be altered to aid in the optimal delivery of therapeutic agents showing how versatile the rHDL drug delivery system can be. In a study by Suda et al[49] researchers fused apo A-I with cell-penetrating peptides to enhance the corneal penetration of topical HDL eye drops. This study also demonstrated that synthetic HDL could be altered to produce a therapeutically active rHDL eye drop to treat retinopathies such as AMD. Consequently, rHDL is likely to be optimized to facilitate drug delivery to target tissues and overcome biological barriers that tend to hinder the delivery of unencapsulated drugs. Moreover, these studies suggested that rHDL drug delivery vehicles may be administered *topically* as a viable treatment option for retinopathies, including glaucoma and AMD.

C) Lipoprotein mimetics utilized in immunotherapeutics, vaccine delivery and as anti-inflammatory agents.

Recently, the impact of endogenous HDL in immunotherapies and as vaccine carriers have been explored by Gracia et al. to evaluate HDL's lymphatic bio-distribution and pharmacokinetics after subcutaneous administration to thoracic lymph-cannulated and non-lymph-cannulated rats[50]. Their findings suggest that the optimized HDL-type nanoparticles could be successfully applied to lymphatic-targeting for therapeutic applications. Many rHDL nanostructures may be specifically targeted by attaching targeting molecules to their exteriors. An example is the treatment of infections via selectively approaching pathogens vs. normal/healthy cells, utilizing GM1 ganglioside as a targeting agent[51]. Various glycoconjugates, similar to GM1, have been reported to also play a role in facilitating viral infections, including Sendai virus[52], rabies virus[53], influenza[54], HIV[55], rotavirus[56], rabies[53] and polyomaviruses[57]. By engineering nanoparticle constructs where these glycol-conjugate molecules are embedded in rHDL, the pathogen could be to bind the nanoparticles decorated with decoys, instead of the cell surface receptors. While this pathogen-decoy strategy is not

novel, the rHDL NP has more potential to succeed in capturing the pathogenic agents than the alternative approaches that have been attempted so far.

Numerous studies have shown that lipoproteins bind microorganisms or structures derived from microorganisms[58]. Reconstituted HDLs have shown a protective effect against severe communicable diseases even without additional modifiers. Endotoxin (LPS), from gram-negative bacteria, or lipoteichoic acid (LTA), from gram-positive bacteria, is shown to bind with HDL when incubated with whole blood from healthy humans. This binding to HDL inhibits the ability of LPS and LTA to interact with toll-like receptors (TLR) and activate macrophages[59]. Endotoxemia, as well as the stimulated immune response caused by lipopolysaccharides (LPS), can lead to whole-body inflammation, specifically, a condition known as septic shock. Casas et al[60] demonstrated beneficiary effects of rHDL treatment in a rabbit model of Gram-negative bacteremia. The effects of rHDL on LPS responsiveness in humans in a double-blind, randomized, placebo-controlled crossover study, suggest that rHDL may inhibit LPS effects in humans *in vivo* by binding and neutralizing LPS. In addition, rHDL administration has also been reported to reduce CD14 expression in monocytes[61]. In other studies, with human and animal subjects, rHDLs were shown to reduce the production of tumor necrosis factor (TNF) in response to challenges by endotoxins, originating from Gram-negative bacteria. Elevated levels of TNF indicate an aggressive/exaggerated immune response resulting in septic shock (a high-risk condition). In addition, the endotoxins. HDLs have been shown to bind and neutralize the LPS molecules, released as a result of normal immune function, potentially preventing further inflammation. Furthermore, a unique feature of HDLs is their effectiveness against smooth and rough LPS types, characterized by the presence or absence (respectively) of an O-antigen. The infection may be lethal if a specific antibody against this O-antigen is absent. Because of the lipid moiety of HDL (and rHDL) binds and neutralizes LPS via a nonspecific mechanism, HDLs can alleviate the dangers of sepsis by serving as a quick and universal entrapper and thus treatment against some inflammatory phenomena.

FUTURE OPPORTUNITIES AND CHALLENGES FOR HDL MIMETICS IN HUMAN THERAPEUTICS

As mentioned at the beginning of this article, lipoproteins have long been known (since the 1980s) for their drug transporting properties (9-11) since the 1980s. The subsequent recognition of the anti-inflammatory potential of lipoproteins (64) has even further enhanced the interest and activity toward the development of eventually clinically applicable formulations, based on their many favorable potentially therapeutic properties (1,4,5,7). Perhaps then, it might be more than a little surprising to find that first clinical trial, utilizing the targeted drug transporting properties (resulting in safe tumor selective delivery of the payload) of lipoprotein mimetic formulations is yet to be completed. Consequently, this type of therapeutic delivery process is not likely to reach the clinic anytime soon.

The state of the current pharmaceutical market is frantic at best as the participating companies continue their surge toward developing a multitude of new products, even though the therapeutic outcomes for many of these products tend to be marginal in terms of lengthening the patients' lifespan or even providing major benefits, in terms of improving quality of life. The prospects for developing profitable lipoprotein-based formulations is challenging for two main reasons:

1. The main (apolipoprotein) ingredient is essential and costly to prepare.
2. Perhaps even more important is the overcrowding of the intellectual property market, regarding lipoprotein therapeutics.

Our laboratory, jointly with Dr. AT Remaley of the NHLBI, has developed a novel HDL type formulation with potentially highly effective HDL drug delivery profile (28) and with a highly likely reduction in production costs. Additional new information on these types of formulations has been forthcoming from several laboratories. With these changes, one would hope (primarily for the patients'sake) that this therapeutic modality will soon gain the sufficient financial interest and support, to begin its march toward clinical utilization.

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Disclosure Statement
None

Conflict of Interest
None

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