Expert Opinion

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Prospects and challenges of the development of lipoprotein-based formulations for anti-cancer drugs

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This review evaluates drug delivery systems that involve intact plasma lipoproteins or some of their components. These complex macromolecules transport highly water-insoluble compounds (cholesteryl esters and triacylglycerols) in their natural environment – a property that renders them ideal carriers of hydrophobic drugs. Particular emphasis is placed on the application of lipoproteins as drug delivery agents in cancer chemotherapy. The history and present activity regarding lipoprotein-based formulations are reviewed, with the primary focus on the smaller sized (low and high density) lipoprotein-based formulations and their potential clinical and commercial value. The use of both native and synthetic lipoproteins as drug delivery agents are discussed from the standpoint of therapeutic efficacy, as well as commercial feasibility. The advantages of lipoprotein-based drug delivery formulations are compared with other drug delivery models, with the primary focus on liposomal preparations. Finally, an expert opinion is provided, regarding the potential use of lipoprotein-based formulations in cancer treatment, taking into consideration the major advantages (biocompatibility, safety, drug solubility) and the barriers (manufacturing protein components, financial interest, investments) to their commercial development.

Keywords: cancer chemotherapy, drug delivery, lipoprotein, targeting

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1. Introduction

Many intravenously administered pharmaceutical preparations, particularly anti-cancer drugs, perform with less than optimal efficiency because of limited accessibility to target tissues, systemic toxicities and tumor drug resistance [1]. An additional concern about developing new cancer chemotherapeutic agents is the inability of specific drugs to fully penetrate individual tumors [2]. The expectations for adjuvant therapy, despite recent improvements, are thus only modest, as many recurring cancers tend to be fatal because the presently available approaches are unable to eradicate the metastatic lesions [2]. Targeted anti-cancer agents – an advanced version of systemic therapeutic strategies – are considered a promising new frontier for treating cancer, offering perhaps the best hope for victory over this lethal disease [3-5]. Plasma lipoprotein-based nanoparticle carriers, in the present author's view, offer one of the best opportunities for designing and developing effective strategies for treating and eventually curing cancer. Consequently, this review deals with the relative merits of lipoproteins as drug carriers and the challenges involved in their developments as delivery vehicles for anti-cancer agents.

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1.1 Lipoprotein carriers as vehicles for targeted cancer chemotherapy

The structural characteristics and metabolic functions of lipoproteins have been extensively reviewed [6-8] and, thus, will be referred to only briefly here. Plasma lipoproteins are spherical macromolecular complexes of specific apolipoprotein and lipid components (**Figure 1A**) that transport water-insoluble lipids to their specific organ/tissue destinations.

The basic structure of lipoproteins involves an outer protein-phospholipid shell with a lipophilic surface and an interior hydrophobic compartment (**Figure 1A**) for the transport of water-insoluble lipid components (triacylglycerols and cholesteryl esters). This structural arrangement is also eminently favorable for the transport of hydrophobic drugs (e.g., paclitaxel) that are often used in cancer chemotherapy (**Figure 1B**). In the context of being able to transport hydrophobic molecules, lipoproteins are, thus, attractive candidates for delivering anti-cancer agents to tumors, due to their biocompatible components and the opportunity for targeted delivery by receptor-mediated uptake of the drug-loaded low-density lipoproteins (LDLs) by endocytosis [2,10] or by the selective uptake of high-density lipoprotein (HDL) core components [11,12]. Both types of these lipoprotein receptors are overexpressed by malignant cells and tumors [9,12,13-17]. Therefore, lipoproteins are expected to increase the therapeutic efficacy by targeting drugs to tumors that overexpress lipoprotein receptors and, thus, minimize systemic toxicity by shielding the drug from contact with most normal tissues [18]. In this review, the authors limit the discussion to two classes of lipoprotein carriers based on the structure of LDLs and HDLs.

2. Low-density lipoprotein-type carriers

2.1 Circulating (native) low-density lipoprotein

Initially, Krieger *et al.* [10,19] replaced the core of native LDL with cholesteryl linoleate and concluded that a broad range of hydrophobic compounds, including drugs, may thus be incorporated into LDL [10]. Subsequently, Gal *et al.* [15] proposed the use of LDL as a delivery vehicle for radiological or chemotherapeutic agents to gynecological neoplasms. More recently, Masquelier *et al.* have attempted to use LDL [20] and similar emulsions [21] as a vehicle for delivering chemotherapeutic agents to leukemic cells. Although these studies are promising, having shown solubilization of hydrophobic drugs and the overcoming of drug resistance, to a degree, in leukemic cells [22], the lack of *in vivo* efficacy data suggest that these approaches are still relatively early in their development. Kader and Pater [23] prepared drug-loaded LDL, as well as HDL, and concluded that incorporation of the drug did not change the structure of the lipoprotein particle, and the cytotoxicity of the encapsulated drug increased substantially.

De Smidt and Van Berkel reviewed the methods of preparation and properties of a number of LDL-based drug formulations and concluded that these preparations represent '*an advanced biotechnological system whereby natural endogenous pathways are utilized for site-specific drug delivery*' [24]. Nevertheless, concerns remained regarding the appropriate selection of the drug to be incorporated into LDL, and methods for the encapsulation of hydrophobic drugs into the core of the LDL complex. The design of LDL–drug complexes for the purpose of drug delivery to cells, particularly to cancer cells, has been based on the premise that rapidly proliferating cells and tissues have an enhanced need for cholesterol and, thus, have a higher expression of LDL receptors for increased LDL internalization [9,16,25]. Although this is a rational hypothesis, it has not been proven to be universally correct. Accordingly, although most malignant cells show higher LDL receptor expression than the corresponding normal cells [9,16,25-27] some show decreased expression or abnormal behavior [28-30]. In addition, receptor expression did not always correlate with, internalization of LDL – a key feature of the mechanism for projected applications in chemotherapy [31].

In summary, although cancer cells generally exhibit an increase in LDL receptor function, the overexpression of LDL receptor protein in tumor cells has not been consistently documented.

Vitols *et al.* conducted the most extensive studies, utilizing LDL particles as potential drug carriers in leukemia chemotherapy [25,27,32-36]. Their approach was based on findings that leukemia patients had substantially reduced LDL levels and enhanced LDL receptor activity in leukemia cells [33,35]. These studies led to the incorporation of the lipophilic drugs AD-32 [32] and WB4291 [34] into LDL and the assessment of their respective bio-distributions [32] and anti-leukemia activity [34,36]. Subsequently, several anthracyclin derivatives were studied [37], resulting in LDL–drug complexes with some, but a number of these hydrophobic compounds proved to be difficult to incorporate into LDL. The overall stability of the drug-carrying LDL particle, upon injection into the plasma, proved to be less than satisfactory, with these formulations precluding more extensive *in vivo* and clinical studies [36,38]. Another approach by Lo *et al.* and Fung *et al.* produced LDL–doxorubicin complexes that displayed reduced toxicity to normal tissues, but were nearly as toxic to malignant tumors as the free drug [39], and exhibited reduced drug resistance in R-HepG2 cells [40].

LDL has been used for solubilizing and targeting a number of additional compounds of pharmaceutical interest, including photosenzitizers [41,42], nucleosides [43], isoflavones [44], acrylophenone [45], anti-HIV drugs [46] and fluorescent imaging agents [47]. Nevertheless, the clinical application of native LDL particles as drug delivery agents is complicated by the procedures required for their isolation [24], methods of incorporation of the therapeutic agent [20], and related safety concerns [24,48]. The difficulties encountered in the use of native LDL–drug complexes for therapeutic purposes include the adequate supply of LDL,

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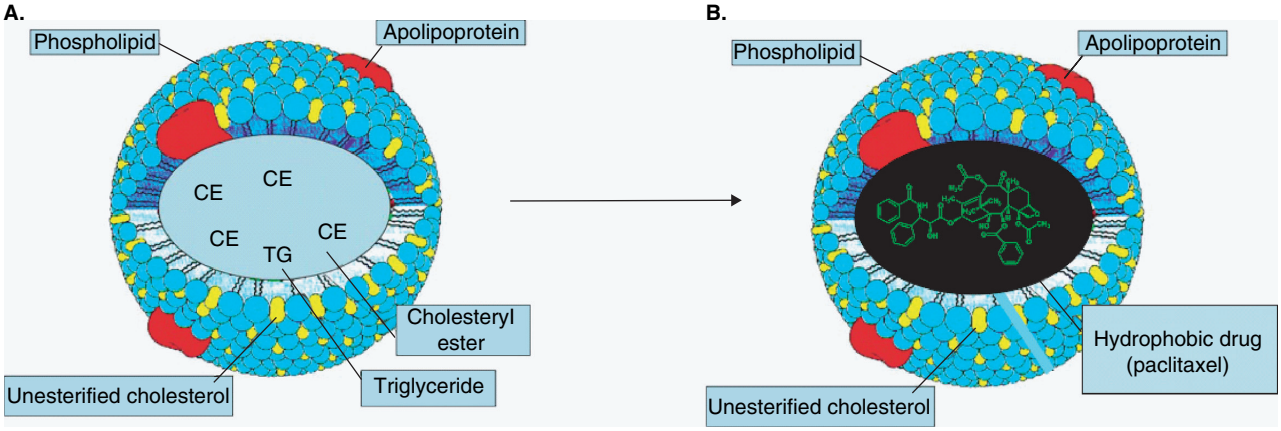

Figure 1. Localization of a hydrophobic drug (paclitaxel) in the core region of a generic lipoprotein.
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and its tendency to aggregate, as have been summarized by Owens *et al.* [49] and Shaw and Shaw [50]. These issues, despite the compelling biological rationale [19,24], render the use of native LDL impractical as a drug delivery agent in a clinical setting. Consequently, alternate strategies have been developed via artificially prepared, reconstituted LDL for the purpose of targeted drug delivery.

2.2 Synthetic (reconstituted) low-density lipoprotein, including apolipoprotein E-containing particles

The major challenge to the design and preparation of reconstituted low-density lipoprotein (rLDL) is the isolation of a soluble lipid-free apolipoprotein B-100 – the major protein component of the circulating LDL complex [7]. Some of the difficulties in involving apolipoprotein B-100 in synthetic formulations are associated with its high molecular weight and its tendency to aggregate upon delipidization. The early attempts to prepare rLDL, the methods for its production and the physical/chemical properties of the resultant particles have been reviewed [51,52]. A number of investigators attempted to prepare synthetic LDL/rLDL as a drug carrier, despite the limitations posed by the availability of apolipoprotein B-100 [7]. Lundberg [16,53,54] combined egg yolk phosphatidylcholine, a hydrophobic drug and apolipoprotein B-100 [15], resulting in a 23-nm rLDL particle that was taken up by the LDL receptor of cultured fibroblasts [16].

Van Berkel and coworkers prepared unilamellar liposomes, containing apolipoprotein E that were taken up by rat tissue LDL receptors [55], and similar particles containing a lipophilic derivative of daunorubicin that were taken up by B16 tumors [56]. By combining egg yolk phosphatidylcholine, triolein, cholesterol and cholesteryl oleate, Maranhao *et al.* developed a protein-free microemulsion (LDE) that was shown to be able to carry lipophilic drugs [57]. These LDE particles acquired apolipoprotein E upon injection into rats and were cleared at a rate similar to LDL. When the LDE particles were loaded with oleoyl-etoposide [58] and oleoyl-paclitaxel [59], studies in mice showed an improvement in the therapeutic efficacy of encapsulated oleoyl-paclitaxel compared with the free drug. The metabolism of the LDE particles was studied in gynecological cancer patients, where the tumor tissue incorporated 3.5-times more paclitaxel-oleate from the LDE particles than normal tissues [60].

To circumvent the need for intact apolipoprotein B in the preparation rLDL–drug complexes. Baillie *et al.* utilized peptides covering the receptor binding region of apolipoprotein B to produce drug-carrying nanoparticles that supported the growth of U937 human lymphoma cells similar to native LDL [61]. More recently, Nikanjam *et al.* [62] prepared a synthetic LDL using peptides representing the lipid binding motif and the LDL-receptor binding domain of apolipoprotein B-100. The fluorescently labeled "nano-LDL" particles [33] were taken up by glioblastoma cells by the LDL receptor-mediated mechanism. The findings of these studies support the concept that targeted delivery of anti-cancer drugs by lipoprotein-type carriers via upregulated receptors in cancer cells and tumors [17,27] is feasible and, thus, could pave the way for clinical studies using these nanoparticles.

3. High-density lipoprotein as a drug delivery vehicle

During the initial development of lipoprotein-based drug carrier systems, the primary focus was centered on LDL because of the elegant, detailed characterization of LDL receptor structure and function [63], and the finding that rapidly proliferating cells (cancer cells) had enhanced LDL receptor expression [16,24], resulting in mild hypocholesterolemia in cancer patients [64]. However, recent studies, based on data from 530 cancer patients, revealed that HDL cholesterol levels were impacted to approximately the same extent (-13% for LDL-cholesterol, -12% for HDL-cholesterol) by malignancies [65]. Similar findings were reported for patients with hematologic cancers [66-68],

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small cell lung cancer [69] and colorectal adenoma [70]. The characterization of the receptors (scavenger receptor B1 and CD36, and LIMPII analogous-1 [CLA-1]) that facilitate the selective uptake of cholesterol esters from HDL [71-73] have provided further impetus for the development of HDL-based, targeted drug delivery vehicles [18].

A number of earlier studies indicated that HDL may be an attractive drug carrier, particularly in cancer chemotherapy as the proliferation of adenocarcinoma [74] and other malignant cells have been shown to be accelerated by HDL or HDL components [75,76]. More recently, Pussinen *et al.* have shown that breast cancer cells acquire cholesterol from HDL via the CLA-1 receptor pathway [11], and Cao *et al.* reported that a mutant form of CLA-1 receptor suppressed the growth in a breast cancer cell line [17]. These data, combined with other reports, strongly suggest that the HDL receptors may play a role in the proliferative capacity of cancer cells and tumors that is at least as important as that of the LDL receptor [9,10,27]. Furthermore, the recent focus on HDL receptors in the biology of cancer cells [77,78] provides strong impetus for the development of HDL or HDL-type complexes as anti-cancer drug delivery agents. The concept of the selective targeting of HDL or reconstituted HDL (rHDL) drug complexes to malignant cells and tissues has been supported by data from Cao *et al.*, who showed that, in mice carrying MCF7 (breast) tumors, the tumor cells were expressing markedly higher levels of the CLA-1 receptor compared with the surrounding normal cells [17]. These findings are consistent with earlier data from the present authors' laboratory showing that cancer cells produced substantially stronger immunoblots with an antibody for the scavenger receptor B1 than normal fibroblasts [12]. It has also been shown that the uptake of paclitaxel and cholesteryl esters from rHDL particles was highly correlated ($r^2 = 0.88$; $p = 0.04$), suggesting that paclitaxel was taken up by cancer cells via the HDL receptor mechanism from the rHDL–paclitaxel complex [12].

3.1 Native (circulating) high-density lipoprotein

The utilization of native HDL as a drug delivery vehicle is fraught with the same difficulties as listed for LDL above, namely the difficulty of large scale isolation, bio-safety issues and consequently the excessive cost involved in the development of the HDL–drug formulations [24]. As a result, only a limited number of attempts have been made to incorporate drugs into native HDL [23], and none with the ultimate purpose of therapeutic applications. The following section reviews the application of a more appropriate model, rHDL, for an effective drug delivery system.

3.2 Synthetic (reconstituted) high-density lipoprotein

One of the confounding issues regarding rHDL relates to the exact definition of what is meant by 'rHDL'. The terms 'reconstituted' and 'recombinant' have both been used in the literature, although the former is more predominant recently, as 'recombinant' is now preferred for designating DNA constructs.

The nomenclature is quite clear for all other classes of lipoproteins; however, for rHDL, it is complicated by the nature of HDL metabolism, which has been reviewed in detail recently [79,80]. Specifically, discoidal precursor particles, composed primarily of phosphatidylcholine and apolipoprotein A-I – the major components of HDL – are secreted by the liver [81] and the intestine, and are subsequently rapidly converted to spherical particles [82] via the action of the enzyme lecithin:cholesterol acyltransferase in the blood (**Figure 2**).

Scientific publications [83,84], as well as patent disclosures [201] have referred to both discoidal and spherical particles occasionally as rHDL [83,84], but while some prefer to specify the nature of the lipoprotein complex by inserting discoidal or spherical designation before rHDL [85,86]. This unsystematic, alternative naming of rHDL particles can result in considerable confusion and misunderstandings, during the review of scientific articles, grants and patent proposals. The reader is, thus, alerted to the alternate naming of rHDL particles used by many of the articles referred to in this review.

For the purpose of formulating drug delivery complexes, spherical-shaped particles have a clear advantage over other configurations, as these have a defined core region to accommodate the drug to be transported (**Figure 1**). Although other interactions are possible between the hydrophobic drug and specific lipid components within the lipoprotein structure, the localization of the lipophilic drugs in the core region is preferred, due to enhanced stability of the rHDL–drug complex. Van Berkel and coworkers were the first to report on comprehensive studies of spherical 'neo-high density lipoproteins' that were proposed for use as drug delivery vehicles [87,88]. They incorporated the lipophilic prodrug iododeoxyuridine into neo-HDL and found that the molecular characteristics of the neo-HDL–drug complex were similar to that of circulating apolipoprotein E-free HDL [88]. Studies from the present authors' laboratory have shown that a stable rHDL–drug complex could be prepared by combining Taxol® (Bristol-Myers Squibb) and the components from circulating HDL [12] via a procedure similar to that described by Van Berkel and coworkers [88]. The rHDL–Taxol complex was taken up by cancer cells, apparently by a receptor-mediated mechanism, resulting in the killing of the cancer cells by the incorporated drug [12]. A more advanced rHDL formulation, containing paclitaxel, has been developed recently that has substantially increased drug-carrying capacity and cytotoxicity toward several cancer cells [91]. Recent studies by Lou *et al.* resulted in the preparation of rHDL–aclacinomycin complexes that were intended for hepatoma chemotherapy [89]. The rHDL-aclacinomycin complexes were shown to have a molecular diameter and molecular weight similar to native HDL [89]. Lou *et al.* also

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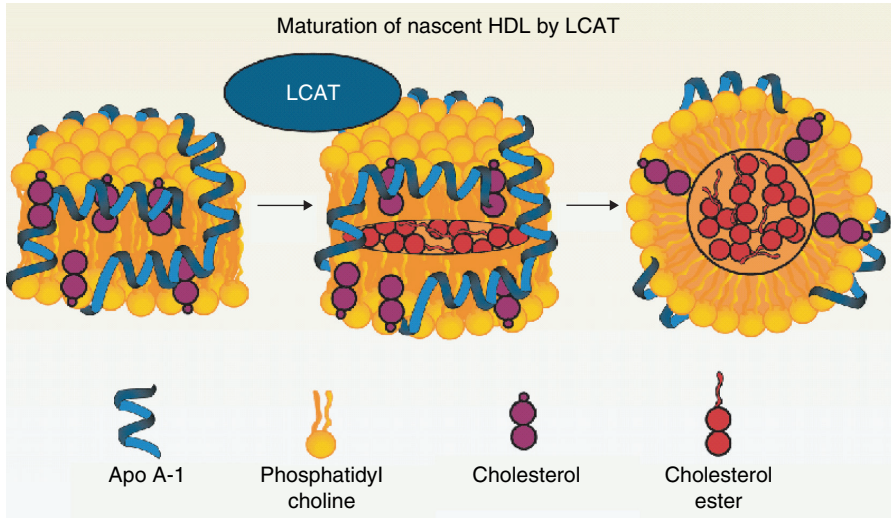

Figure 2. Transformation of the discoidal precursor (nascent) HDL to its stable, spherical configuration via the accumulation of cholesteryl esters, catalyzed by lecithin–cholesterol acyltransferase.

Reproduced from ALEXANDER ET, BHAT S, THOMAS MJ *et al.*: Apolipoprotein A-I helix 6 negatively charged residues attenuate lecithin-cholesterol acyltransferase (LCAT) reactivity. *Biochemistry* (2005) **44**(14):5409-5419.

Apo A-1: Apolipoprotein A-I; HDL: High-density lipoprotein; LCAT: Lecithin–cholesterol acyltransferase.

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reported that the rHDL-aclacinomycin complex was taken up more avidly by hepatoma cells than normal cells, thus, providing preliminary evidence for the selective targeting potential of their formulation [89]. In another attempt to use synthetic HDL complexes for the delivery of pharmaceutical agents, Oda *et al.* incorporated amphotericin B into apolipoprotein A-I-containing discoidal particles that exhibited strong *in vitro* and *in vivo* antifungal activity [90].

Essentially, all the drugs that have been incorporated into LDL- or HDL-based vehicles, including those quoted in this review [12,15,88-90], are substantially lipophilic and, thus, resemble cholesteryl esters (the native lipoprotein core component; **Figure 1**) regarding their solubility properties. In the present authors' experience, a helpful way to define the potential to incorporate specific drugs into lipoprotein-type vehicles is to refer to their octanol/water partition coefficient (XlogP) [91]. The respective values for most compounds, including anti-cancer drugs my be found at [301]. In the present authors' opinion, compounds with an XlogP value > 1 are reasonable candidates for incorporation into synthetic HDL nanopartices. The tendency to be incorporated into the core of the lipoprotein particles improves as the XlogP value exceeds 3.

3.3 The efficacy of high-density lipoprotein-type carriers for anti-cancer agents

The targeted delivery of anti-cancer agents via lipoprotein carriers is based on the concept that cancer cells and tumors have a higher expression of lipoprotein receptors [9,14,18,27], due to their increased need for cholesterol to promote rapid proliferation [64]. Clinical studies have shown that HDL cholesterol levels, as with LDL cholesterol, were lower in a group of cancer patients than in normal controls [66-70]. Recent animal studies are in agreement with the above clinical data showing that the HDL receptors were over-expressed in breast cancer cells compared with surrounding normal cells [17]. In addition, Pussinen *et al.* [11] have shown earlier that breast cancer cells acquired cholesteryl esters from HDL via the CLA-1 receptor, indicating that HDL receptors may play an essential role in regulating the growth of cancer cells/tumors and, thus, support the hypothesis that the selective targeting of anti-cancer agents delivered via HDL-type formulations is feasible [27]. Earlier findings from the present authors' laboratory showed that cancer cells produced substantially stronger immunoblots with an scavenger receptor B1 antibody than normal fibroblasts, and that the respective uptakes of paclitaxel and cholesteryl esters were highly correlated when delivered by rHDL nanoparticles, suggesting a receptor-mediated pathway for the entry of paclitaxel into cancer cells [12].

4. Enhanced targeting of lipoprotein–drug complexes via covalent modification

Although, as emphasized earlier, the receptor-mediated uptake of drugs from lipoprotein complexes by cancer cells and tumors is a major advantage over other types of formulations, the interaction of lipoprotein nanoparticles with normal tissues resulting in side effects due to the enhanced delivery of a cytotoxic agent is a potential concern. A recent strategy developed by Zheng *et al.* [92] addressed this problem by masking the native receptor interaction between the lipoprotein and its target cells via attaching specific surface ligands to the lipoprotein–drug

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complex with exceptionally high affinity for cancer cells and presumably malignant tissues. This strategy is based on the hypothesis that the delivery of anti-cancer drugs to cancer cells and tumors can be substantially enhanced by the interaction between a homing molecule (e.g., folate, antibodies) that is attached to the lipoprotein carrier. Such an approach could provide essentially unlimited opportunities for specifically targeting lipoprotein/drug complexes to individual types of malignant tumors and, thus, could revolutionize cancer chemotherapy.

5. Comparison of lipoprotein-mediated drug delivery with other formulations

Due to the tremendous variety of drug delivery formulations, it is only possible to evaluate a limited number of these. The major emphasis, therefore, will be on selected applications of liposomes, lipophilic pro-drugs and serum albumin-containing formulations using the application of paclitaxel in cancer chemotherapy as a model. Paclitaxel is a hydrophobic compound that requires emulsification/solubilization for intravenous administration [92]. The most widely used formulation (Taxol) contains the emulsifier Cremophor EL® (BASF), which has an undesirable impact in chemotherapy, due to numeous side effects [92,93]. Since the initial marketing of Taxol, several alternate formulations were developed, primarily to eliminate the Cremophor component and to increase the solubility and targeting of paclitaxel. Among the major preparations containing paclitaxel are liposomal formulations, nanoparticles and microemulsions [94-99], prodrugs, antibody conjugates [100-106] and an albumin complex [107,108] that for the most part have been shown to have superior biological activity and anti-tumor potential to Taxol.

These lipoprotein-based formulations offer potentially enhanced performance over the above alternatives, due to their natural components that render them biodegradable and help to avoid rapid removal by the reticuloendothelial system [24,50]. The biological compatibility and safety [24,48,50] are also important issues that favor lipoproteins over other delivery systems, as several formulations containing HDL components have been already been safely injected into human subjects [109-114]. Lipoprotein formulations tend to have substantially smaller molecular diameters than most liposomal drug preparations. This may be a considerable advantage, as smaller liposomes have been considered to be superior drug delivery agents based on their pharmacokinetic properties [115]. Another important issue favoring lipoproteins over other formulations is targeting, as both LDL and HDL drug complexes are known to deliver their pharmaceutical load via receptor-mediated mechanisms that are known to be overexpressed in cancer cells compared with normal cells [9,12,17,27]. This 'magic bullet'-like capability [18] applies particularly to the comparison of lipoproteins to one of the recently developed paclitaxel formulations. Abraxane or ABI-007, a paclitaxel serum albumin complex, has been shown to be considerably more effective than Taxol due to an increase in the maximum tolerated dose and the reduction of sides effects, particularly hypersensitivity [107,108]. Nevertheless, it appears that additional therapeutic benefits may accrue via the lipoprotein delivery of paclitaxel and other hydrophobic drugs, as Edwards *et al.* have shown that the delivery of omega-3 fatty acids to cancer cells produced markedly stronger inhibitory and apoptotic responses when facilitated by LDL compared with serum albumin [116].

6. Conclusions

Despite many potential advantages over other drug delivery systems, the therapeutic applications of lipoproteins and synthetic lipid–protein complexes resembling lipoproteins continues to lag behind all other formulations. Although lipoprotein preparations are biologically compatible and offer superb targeting potential via receptor-mediated mechanisms, the difficulty in obtaining the polypeptide starting material has so far been a major obstacle in the development of lipoprotein-based pharmaceutical formulations. Perhaps the use of peptide fragments, representing the receptor binding regions of specific apolipoproteins, may be useful. This approach would allow the design and preparation of synthetic lipoproteins to facilitate the scaling up of this process to the production level and allow the pharmaceutical manufacture of lipoprotein–drug formulations.

7. Expert opinion

Pharmaceutical formulations utilizing native and especially synthetic lipoproteins have the potential to perform favorably compared with most alternative drug delivery systems, especially for cancer chemotherapy. The main advantages in favor of lipoprotein-based formulations are their functional capacity to transport hydrophobic drugs, their biocompatible components, relative stability in the blood circulation and their track record of having already been safely injected into human subjects [109-114]. Regarding their utilization in cancer chemotherapy, an additional major advantage favoring lipoprotein-based formulations is their vast targeting potential, via receptor-mediated mechanisms that are overexpressed in cancer cells versus normal cells. Furthermore, an enhanced targeting strategy may be employed by attaching ligands to the apolipoprotein component(s) of the lipoprotein complex to home in on overexpressed surface antigens that characterize specific cancer cells and tumors. This type of approach could eventually lead to individualized therapy and, thus, revolutionize cancer treatment.

Although nearly 25 years have passed since Counsell and Pohland first proposed the use of lipoproteins as delivery vehicles for diagnostic and therapeutic agents [13], there are presently no lipoprotein-based formulations in clinical use or in clinical trials. Since the original proposal to utilize native or synthetic lipoproteins as drug delivery vehicles,

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several patent applications have been filed to protect inventions in this area [117]. Some of these involve the use of peptide fragments, representing the receptor binding regions or other specific domains of apolipoproteins. Using this approach may allow the efficient production of synthetic lipoproteins and its scaling up to the industrial level.

From the financial/business point of view, an additional advantage in the utilization of lipoprotein type carriers as drug delivery agents lies in the potential for not only developing formulations with emerging pharmaceuticals, but the revitalization of numerous highly efficient compounds that had been set aside due to their poor solubility properties. Nevertheless, although the scientific data predict a bright future, until a major commitment is forthcoming from pharmaceutical companies to facilitate their development, lipoprotein-based formulations may remain the best kept secret in the drug delivery arena.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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