

## Review Article

Theme: Chemical, Pharmacologic, and Clinical Perspectives of Prodrugs

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# Lipid-Based Carriers for Prodrugs to Enhance Delivery

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**ABSTRACT.** The combination of lipid drug delivery systems with prodrugs offers several advantages including improved pharmacokinetics, increased absorption, and facilitated targeting. Lipidization and use of lipid carriers can increase the pharmacological half-life of the drug, thus improving pharmacokinetics and allowing less frequent dosing. Lipids also offer advantages such as increased absorption through the intestines for oral drug absorption and to the CNS for brain delivery. Furthermore, the use of lipid delivery systems can enhance drug targeting. Endogenous proteins bind lipids in the blood and carry them to the liver to enable targeting of this organ. Drugs with significant side effects in the stomach can be specifically delivered to enterocytes by exploiting lipases for prodrug activation. Finally, lipids can be used to target the lymphatic system, thus bypassing the liver and avoiding first-pass metabolism. Lymphatic targeting is also important for antiviral drugs in the protection of B and T lymphocytes. In this review, both lipid-drug conjugates and lipid-based carriers will be discussed. An overview, including the chemistry and assembly of the systems, as well as examples from the clinic and in development, will be provided.

**KEY WORDS:** drug delivery; fatty acids; glyceride; phospholipid; prodrug.

## INTRODUCTION

Currently, approximately 40% of marketed prodrugs are activated by enzymatic hydrolysis, with alkyl esters being the most common type of prodrug. Lipid modification of a drug has several advantages. First, lipid modification can result in an improved pharmacokinetic (PK) profile, an important determining factor for the success of a drug. Non-protein-bound, small-molecule drugs are subjected to rapid renal clearance from the blood following filtration at the glomerulus. Depending on several factors including the solubility and pKa of the drug and the pH of the urine, drugs may be reabsorbed across the tubular epithelium or excreted in the urine. While hydrophilic compounds are quickly excreted, lipophilic drugs tend to be easily reabsorbed across the tubular epithelium back into circulation, thus prolonging their circulation time (1). Renal clearance of lipophilic drugs is further reduced by the increased binding to plasma proteins, mainly albumin (2,3). Lipid modification also has the advantage of increased absorption across biological barriers, most importantly the gastrointestinal epithelium and blood-brain barrier. Improved oral absorption is commonly achieved by acylation, particularly for antibiotic prodrugs including pivampicillin, talampicillin, and

bacampicillin (4). The absorption of these prodrugs is increased from <50% for the parent drug, ampicillin, to 98–99% (5). For enhanced delivery to the brain, glyceride analogs, such as GABA glycerides and L-dopa diglycerides, have been utilized to increase the passive diffusion through the blood-brain barrier. Additionally, lipid modification can also be used to achieve a controlled release property. For example, highly lipophilic prodrugs of steroids and neuroleptics are slowly released into circulation from the injection site, resulting in a prolonged duration of action (6). In this review, the final advantage of lipid modification, enabling drug targeting, will be discussed.

## LIPID MOIETIES IN TARGETED PRODRUG DESIGN

In this type of prodrug approach, the lipid moiety is covalently attached to the active drug. These prodrugs are designed to target specific sites either via selective absorption, retention, or release of active drug at the target site. In this section, an overview of several different types of lipids, conjugation strategies, and target sites will be provided.

### Types of Lipids and Conjugation Strategies

Various natural lipids carriers are commonly used in the design of lipid prodrugs, including fatty acids, glycerides, and phospholipids. In the design of fatty acid-linked conjugates, the drugs are linked either to the free carboxylate group or to the  $\omega$ -position at the end of the carbon chain. In the conjugation to the carboxylate group, a drug containing an alcohol or amino group

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is linked to the fatty acid, resulting in an ester or amide-linked conjugate, respectively (Fig. 1a). These conjugation strategies generally involve the use of an activating agent, such as *N,N'*-carbonyldiimidazole or carbodiimide, to convert the poor  $-OH$  leaving group to a better one, followed by the addition of an amine- or alcohol-containing drug (7). This approach is the most common method of linking fatty acids and has been utilized for many parent drugs including NSAIDs, ACE inhibitors, angiotensin, nucleosides, and testosterone (8,9). While the conjugation chemistries required for this reaction are relatively straightforward and simple, this approach does not take advantage of the natural fatty acid chemistries. The carboxylate group of a fatty acid is essential for binding to the fatty acid binding site of albumin and for recognition by the fatty acid binding protein for internalization at the cell surface (3). Therefore, conjugation to the  $\omega$ -position is preferable in cases where increased albumin binding and cell membrane transporter properties are preferred. For this method, an  $\omega$ -modified fatty acid, such as amino (10) or thiol (11) analog, is utilized to link to the parent drug. In addition to deciding on the drug linkage site, the chain length of the fatty acid is also an important parameter in the design of prodrugs. Fatty acids have differences in chain lengths (i.e., short chain ( $<C_{10}$ ), medium chain ( $C_{10}$ – $C_{12}$ ), and long chain ( $>C_{12}$ )), which impact various properties of the conjugate. For example, longer-chain fatty acids ( $>C_{14}$ ) generally show increased lymphatic absorption and stability in the circulation compared to shorter chains (12).

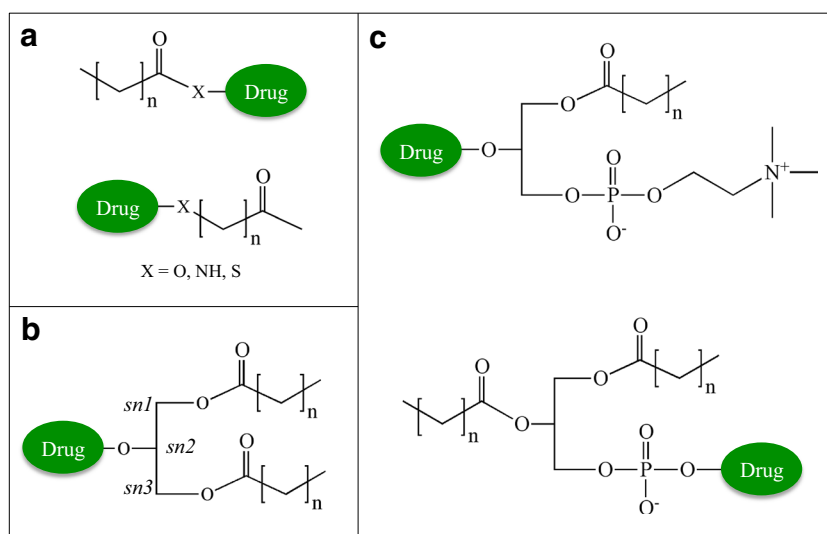
Similar to fatty acids, glyceride prodrugs also take advantage of natural biosynthetic pathways. Glyceride conjugates are linked to orally administered drugs in order to (i) reduce gastric damage of certain drugs (e.g., NSAIDs including aspirin, indomethacin, ibuprofen (13–15)) by preventing their release in the stomach, (ii) reduce enzymatic degradation in the intestines (16), (iii) target the lymphatic route (9), or (iv) enhance their delivery through the blood-brain barrier (17). The *sn*-2 monoglyceride, specifically, remains intact in the intestines prior to absorption and is therefore the major site of drug attachment (Fig. 1b). In this approach, drugs containing a

carboxylate group are linked to the glyceride via an ester bond. The conjugation chemistry is also similar to fatty acid conjugation, involving the use of an activating agent or acid halide (e.g., chloride) derivative (18,19).

In phospholipid-linked prodrugs, the drugs are either attached to the phosphate group or to the glycerol backbone (Fig. 1c). Drugs linked to the phosphate group are generally antiviral nucleoside analogs. These prodrugs take advantage of the release of the drug inside the cell in a monophosphate form, bypassing possible deficiencies in nucleoside kinase activity. Examples of this type of approach will be discussed in “Tumor Targeting of Anticancer Drugs.” Drugs attached to the glycerol backbone utilize the natural absorption pathway for phospholipids to cross the intestinal lumen or blood-brain barrier (20). Following absorption, the prodrug can be incorporated into the lipoprotein assembly pathway, which will also be described in a later section.

### Tumor Targeting of Anticancer Drugs

Examples for the use of lipid modification to generate prodrugs for anticancer therapies are slightly different from other targeting methods in that they are not using active targeting. Since a majority of anticancer agents are hydrophilic molecules, they rely on active ligand transport mechanisms to be efficiently internalized into cells (e.g., folate receptor, nucleoside transporters). However, rapid development of resistance to therapy often occurs via downregulation of these receptors (21). Lipid modification can enhance passive transport of these hydrophilic drugs mediated by the lipid moiety (22). The resultant drugs no longer require active ligand transport mechanisms and are therefore able to overcome transport resistance barriers. Another drug resistance mechanism is enhanced the efflux of certain drugs by transporters including the p-glycoprotein (P-gp) or multidrug resistance (MDR) transporters (21). Lipid conjugation can also lead to a reduction in the amount of drug effluxed out of the cell by these transporters, resulting in increased

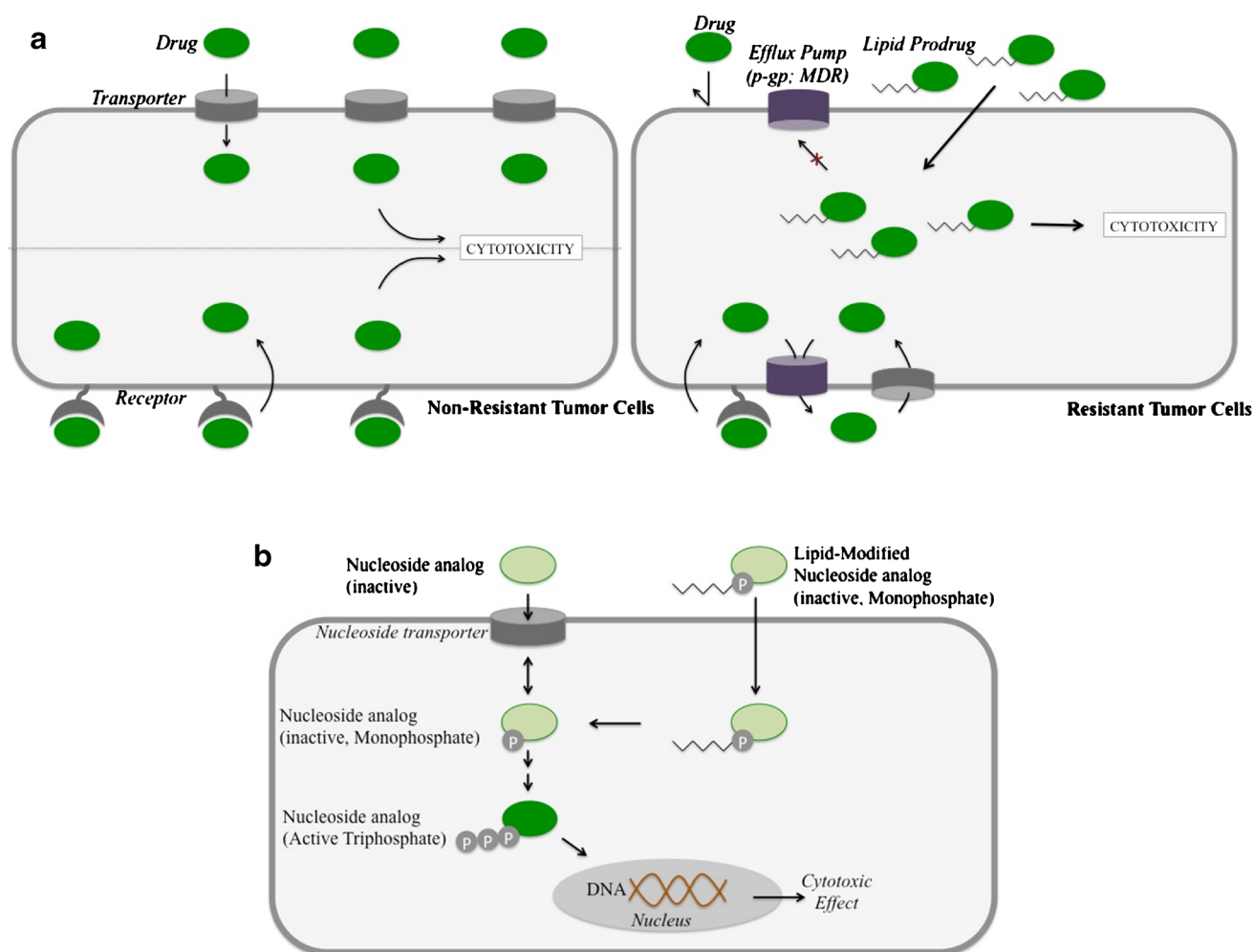


**Fig. 1.** Types of lipids and conjugation sites used in prodrug delivery. **a** Fatty acid conjugates are linked to prodrugs via the carboxylate or the  $\omega$ -carbon of the lipid chain (preferred). **b** Glyceride conjugates are typically modified in the 2-position. **c** Phospholipid conjugates are linked via the phosphate group or in the 2-position of the glycerol backbone

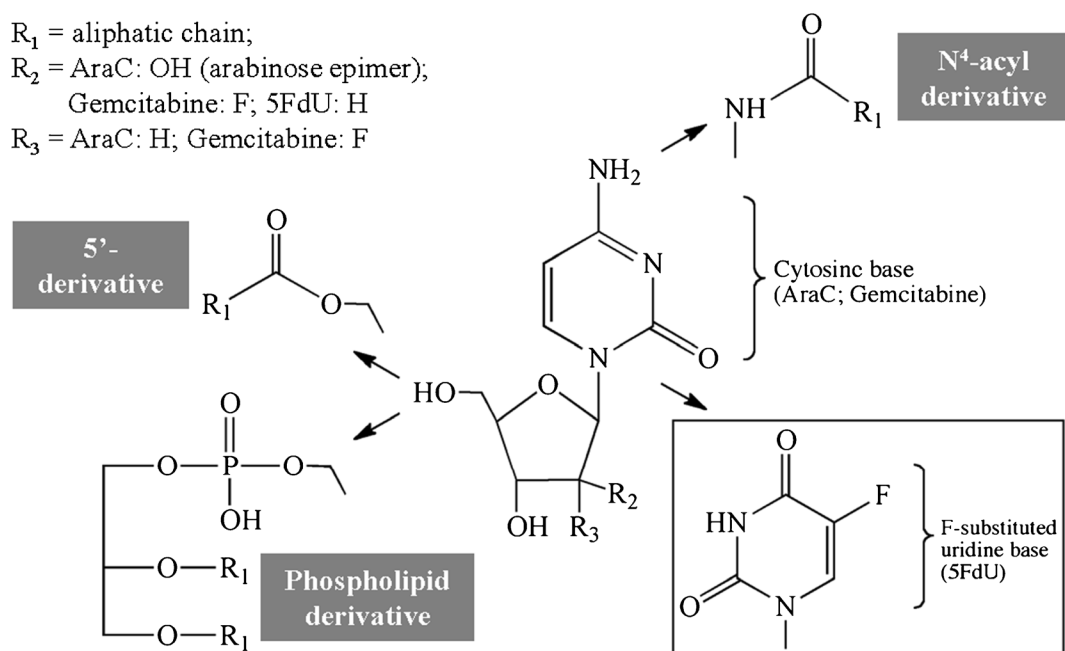
accumulation compared to free drug (23–25). Therefore, increased antitumor efficacy can be achieved using lipid conjugation strategies by increasing cell permeability and retention of anticancer agents (Fig. 2a).

Nucleoside analogs are one of the most common classes of anticancer drugs combined with lipids to enhance their therapeutic effect. AraC, for example, is internalized into cells via the nucleoside transporter where it is converted via three different kinases into mono-, di-, and triphosphate forms. Cytosine arabinoside triphosphate, the active form, damages the DNA of rapidly dividing cells and inhibits DNA and RNA polymerases and nucleotide reductase enzymes important for DNA synthesis. The drug has a limited activity against solid tumors due to the inactivation by cytidine deaminase, exonuclease degradation of the monophosphate form as well as the low retention and rapid elimination of the

active triphosphate form (26–28). AraC lipid conjugates include N<sup>4</sup>-acyl derivatives, 5'-esters, and phospholipid conjugates (Fig. 3). The N<sup>4</sup>-acyl derivatives of AraC, with C<sub>15</sub>–C<sub>22</sub> chain lengths, have shown improved antitumor activity attributed to the increased cell internalization that is independent of the nucleoside transporter and to the decreased deactivation by the deaminase enzyme. The conjugation of lipids (C<sub>16</sub>–C<sub>20</sub>) to the 5'-position of the sugar moiety was also developed in order to prolong the retention of the prodrug inside the cell. In order to be activated via phosphorylation, these derivatives need to be converted back to AraC inside the cells. In structure-activity studies comparing carbon chain lengths from C<sub>16</sub> to C<sub>22</sub>, it was found that the prodrug conjugates with the shorter, unsaturated chains tested were more efficacious due to lower intracellular hydrolysis rates, leading to longer intracellular



**Fig. 2.** Improved tumor targeting. **a** Enhanced penetration and reduced efflux. Lipid prodrugs can improve drug targeting by overcoming resistance mechanisms, including receptor downregulation, and drug efflux. Small-molecule antitumor drugs generally depend on surface transporters or receptors for internalization. However, tumor resistance involves downregulation of these surface molecules, and therefore, the drug can no longer accumulate inside tumor cells to exert cytotoxicity. Since lipid prodrugs can be internalized via passive absorption, this issue can be overcome. Another tumor resistance mechanism is the expression of drug efflux transporters, including p-gp and MDR. Lipid prodrugs may have reduced substrate recognition by these transporters, leading to increased accumulation compared to the free drug. **b** Enhanced activity of nucleoside monophosphate conjugates. Nucleoside analogs are typically internalized via the nucleoside transporter and subsequently activated through a series of steps to the mono-, di-, and triphosphate forms. The active triphosphate form interacts with DNA in the nucleus to exert its cytotoxic effect. Lipid monophosphate nucleoside conjugates can improve efficacy by (1) enhancing passive internalization, independent of the nucleoside transporter, and (2) bypassing the first and rate-limiting monophosphorylation step in the activation process.



**Fig. 3.** Nucleoside analog conjugates. Nucleoside analogs are modified with lipids via their N<sup>4</sup>-acyl site or via the 5'-hydroxyl group

retention (29,30). One C<sub>18</sub>-AraC 5'-modified analog, CP-4055, showed success *in vivo* and was tested in clinical trials (31). Finally, phospholipid-linked AraC conjugates were also developed. Following enzymolysis, these prodrugs release the monophosphate form of AraC (32–34). Although the mechanism of increased efficacy is still unknown, it has been shown that they lead to a more prolonged intracellular retention of the triphosphate (active) form than the parent AraC drug.

Other nucleoside analog conjugates have also been made, including 5-fluoro-2'-deoxyuridine (5FdU, Fig. 3) (35,36), gemcitabine (CP-4126, Fig. 3) (37–40), and troxacitabine-lipid conjugates (41). Similar to studies on AraC, results of these lipid prodrugs showed increased efficacy in various types of *in vitro* and *in vivo* tumor models. In these cases, the increased efficacy was attributed to the increased passive diffusion through cell membranes.

Other than nucleoside analogs, lipid conjugation strategies have also been applied to several other types of anticancer agents. Antibiotic derivatives, including mitomycin C (MMC) and doxorubicin (docosahexaenoic acid-DOX conjugates), have been linked to lipids via thiol (dithiobenzyl linker) (42) or pH-sensitive (hydrazine) linkers, respectively (43). A variety of taxane-lipid conjugates, involving modification at 2' or 7-OH positions of a series of second-generation taxoids (paclitaxel, docetaxel, SB-T-1103, SB-T-1104, SB-T-1213, SB-T-1214, SB-T-1216, and SB-T-1217), have also been tested (44).

### Liver Targeting

One approach in liver targeting is to exploit the physiological fate of lipids, which naturally accumulate in this organ. This approach is used in designing lipid prodrugs for treatment of chronic liver diseases such as viral hepatitis, cancer, and steatohepatitis. A majority of liver-targeted lipid

prodrugs focus on nucleoside analogs to treat viral hepatitis, the most common chronic liver disease. Nucleoside analogs are known to exhibit not only high antiviral activity but also show many extrahepatic side effects. Thus, there is a strong rationale to improve their targeting to the liver. One of the first examples of lipid prodrugs for liver targeting was reported for the antiviral drug, acyclovir. The bioactive form of acyclovir, and of most nucleoside drugs, is the triphosphate form. However, the conversion of acyclovir to the nucleoside triphosphate (NTP) involves a series of phosphorylation steps and is relatively inefficient. In order to overcome this issue, a series of phospholipid prodrugs were tested. The acylated prodrug, modified at the 5'-phospho AZT position, is deacetylated by phospholipases and phosphodiesterases to form the monophosphate form of AZT, thus bypassing the first step in activation of AZT. The monophosphate form is then converted into the active NTP (Fig. 2b) (45). Another example of a nucleoside lipid prodrug is YNK-01, an AraC analog (46). Although there are examples of their success, results from studies utilizing lipid modification in liver targeting tend to show extrahepatic activity. These types of prodrugs are not only effective in treating hepatic viral diseases but also non-hepatic viral targets, indicating that the drugs are cleaved at other sites. This outcome is not surprising since most of the enzymes (primarily esterases) involved in prodrug conversion are also present in the blood, kidney, and other tissues. Therefore, the success of these types of prodrugs relies more on the high liver accumulation than the specific activation in this organ.

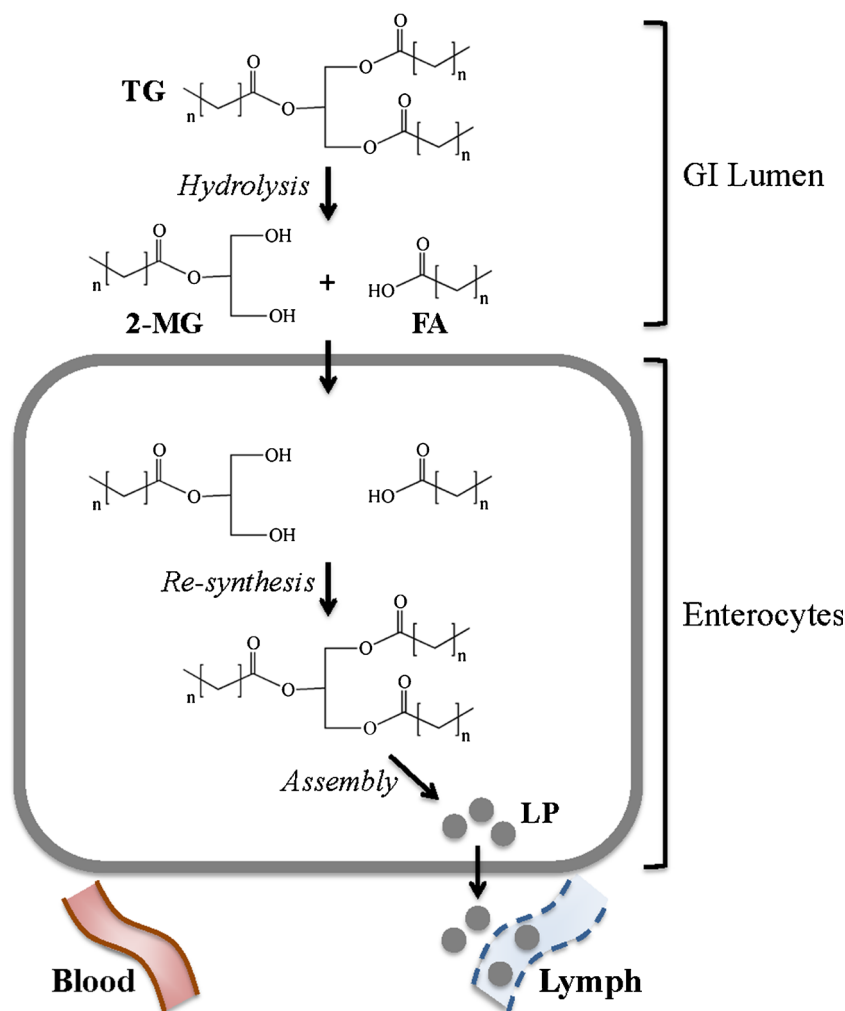
### Lymphatic Targeting

Access to systemic circulation through the gastrointestinal (GI) epithelium can occur by absorption into portal blood

or through the intestinal lymphatic system. The predominant pathway following oral drug administration is into the portal blood, mainly due to the high amount of blood flow in comparison to intestinal lymph flow. On the other hand, the lymphatic system is the main route of transport for dietary lipids, including triglycerides and lipid-soluble vitamins. These analytes are hydrolyzed in the GI lumen to their corresponding monoglycerides and fatty acids, and then resynthesized into triglycerides and assembled into lipoproteins in enterocytes. The resultant lipoproteins are then preferentially taken up into the lymphatic system (Fig. 4). Utilizing this natural pathway, hydrophobic lipid-modified drugs are also preferentially absorbed by the lymphatic system. This process can be advantageous from a PK perspective, since absorption into the lymph system rather than portal blood bypasses the liver and avoids first-pass metabolism (22). This benefit is exploited for several drugs, such as orally administered testosterone (testosterone undecanoate prodrug) (47–49), that are ineffective due to their extensive first-pass metabolism. Alternatively, from a

drug targeting perspective, preferential absorption into the lymphatic system can be used to target drugs to treat lymphatic cancers (50,51) and is also important for antiviral medication for protection of B and T lymphocytes (52–54).

There are many examples of using lipid modification, in the form of lipophilic esters or ethers, glycerides, and phospholipids, to target the lymphatic system following oral delivery (Table I). The simplest form of the three, lipophilic esters/ethers, also has the most limited success. The results often show that the extensive pre-absorptive hydrolysis circumvents lymphatic transport; however, some success has been noted for delivery of highly potent hormone drugs such as testosterone (48,49,55). In strategies utilizing glycerides to enhance lymphatic transport, the site of drug attachment to the glyceride is an important consideration. In the natural lipid biosynthetic pathway, triglycerides are hydrolyzed to produce fatty acids along with sn-2 monoglycerides (Fig. 1). Both of these components are internalized into enterocytes in the GI tract, re-acylated, and incorporated into lymph lipoproteins (Fig. 4). Since the sn-2 monoglycerides remain



**Fig. 4.** Targeting the lymph system by fatty acid modification. Triglycerides (TG) are hydrolyzed in the lumen of the GI tract to form the respective 2-monoglyceride (2-MG) and fatty acid (FA). Following internalization of 2-MG and FA into enterocytes, they are resynthesized into TG, which are subsequently packaged into lipoproteins (LP). LPs have preferential access to the lymph, where they avoid first-pass metabolism and have access to lymphocytes



**Table I.** Lipid Prodrugs for Targeting the Lymphatic System

Parent drug	Lipid	Lipid modification site	Linkage	Reference(s)
AZT	Fatty acid (butyrate, C <sub>4</sub> ; laurate, C <sub>12</sub> ; oleate, C <sub>18</sub> )	Carboxylate group	Ester	(78)
Retinol	Fatty acid (palmitate, C <sub>16</sub> )	Carboxylate group	Ester	(79)
Testosterone	Fatty acid (undecylate, C <sub>10</sub> )	Carboxylate group	Ester	(48,49,55,80)
L-dopa	1,3-Dihexadecanoylpropane-1,2,3-triol glyceride	sn-2	Ether	(19)
Melphalan	1,3-Dipalmitoyl glyceride	sn-2	Ether	(81,82)
Chlorambucil	1,3-Dipalmitoyl glyceride	sn-2	Ether	(18)
Aspirin	1,3-Bis(alkanoyl)-2-( <i>O</i> -acetylsalicyloyl)glyceride	sn-1	Ether	(13,83)
Fluorouridine	Dipalmitoylphosphate	sn-3	Phosphodiester	(84)

AZT Azidothymidine

intact, the majority of studies utilize this site of attachment for prodrug design. Similarly, for phospholipid-modified prodrugs, the most common drug attachment site is the phosphate group of the phospholipid backbone. This design allows for the absorption of the drug-lysophospholipid analog through the natural phospholipid processing pathway (Fig. 4).

### LIPID-BASED CARRIERS TO IMPROVE PRODRUG TARGETING

Lipid carriers are an important technology in drug delivery. These types of carriers can be utilized to overcome inadequacies in drug absorption or targeting, to enhance stability, or to improve poor aqueous solubility. Prodrugs, in particular, can benefit from lipid carriers in cases where the bond between the drug and moiety are too unstable under storage conditions or *in vivo*. Further, the lipid prodrugs described in “**LIPID MOIETIES IN TARGETED PRODRUG DESIGN**” suffer poor aqueous solubility and cannot be formulated at high enough concentrations for clinical application. Finally, lipid-based drug carriers can be combined with prodrugs to develop a “double prodrug” approach, where the carrier can aid in the targeting or delivery of a prodrug to its active site via either increased stability and/or retention or the combination of active targeting approaches. In this section, these advantages will be explored using two common lipid-based carriers: liposomes and lipoproteins.

#### Liposomes

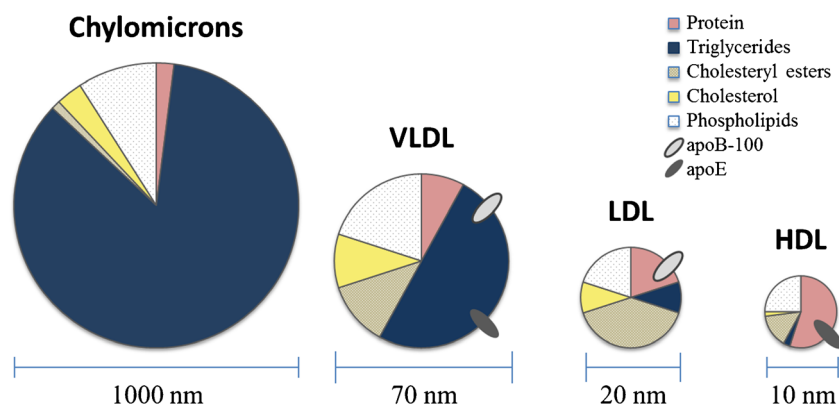
The application of liposomes in drug delivery is a well-established field, with several liposomal drug formulation approved in the clinic over the last 20 years. Hydrophobic drugs or lipid-modified drugs can be incorporated directly into the lipid membrane of a liposome, while hydrophilic prodrugs can be encapsulated within its aqueous core. Due to advancements in liposome technology, including stabilization of lipids and maintenance of a relatively small size (~100 nm), modern liposomes generally show long blood circulation times ( $t_{1/2} > 40$  h), with only 10–15% of the dose delivered to the liver (56,57).

In order to overcome formulation issues for hydrophobic prodrugs, particularly the lipid prodrugs described in “**LIPID MOIETIES IN TARGETED PRODRUG DESIGN**”, liposomes are commonly utilized. The advantage of combining lipid prodrugs with liposomes is twofold, where the

entrapment efficiency of the lipid prodrug is increased compared to the free drug and the prodrug is protected from hydrolysis and enzymatic cleavage while encapsulated in the carrier (58). Liposomes have been used to enhance the delivery of phospholipid prodrugs for antiviral agents (45,59), 6-mercaptopurine glycerol monostearate analogs (60), AraC analogs (61,62), and gemcitabine-acyl derivatives (38). Liposomes have also been applied for delivery of ocular prodrugs. Lipid prodrugs for ocular agents are challenging because the prodrug needs to be stable, particularly against hydrolysis, at the ocular surface, but must be rapidly converted once absorbed. For example, liposome carriers have been utilized for pilocarpine prodrugs to prevent against hydrolysis at the ocular surface. Due to its poor permeability across the corneal membrane, various mono- and di-ester prodrugs of pilocarpine have been generated. These prodrugs undergo rapid hydrolysis and therefore have instability issues in storage solution and at the ocular surface (63). As shown by Burke *et al.*, liposome formulations can protect against hydrolysis and enhance stability at the ocular surface (64).

As mentioned, the combination of prodrugs with liposomes can also enable a double prodrug approach for targeting applications (65). Lipid prodrugs generally provide no active antitumor targeting and enhance bioactivity via increased passive absorption. Therefore, several different strategies utilized to enable the targeting capabilities of liposomes, which were recently reviewed in detail (66), can also be applied to lipid prodrugs. The two main approaches are the addition of targeting ligands or antibodies on the liposome surface (i.e., active targeting methods) (67,68) or incorporation of a bio-responsive modality to specifically release the liposome contents at the target site (56,66,69). The ligands or antibodies utilized in active targeting methods target overexpressed or uniquely expressed antigens or receptors located in the target site. More traditionally, monoclonal antibodies were utilized as targeting molecules (i.e., “immunoliposomes”). However, several drawbacks in their application have been noted, such as triggering of immunogenic responses and reduced affinity of the antibody after incorporation into the liposome. Recent alternatives include the incorporation of smaller molecules, such as hormones, peptide aptamers, or small-molecule ligands.

Compared to actively targeted liposomes, bio-responsive liposomes represent a more recent targeting technology. These techniques can incorporate physical targeting methods, which use external stimuli to enhance targeting. For example,



**Fig. 5.** Size and composition of lipoproteins. Lipoproteins exhibit differences in their size; in their composition of proteins, triglycerides, cholesterol esters, cholesterol, and phospholipids; and in the types of surface protein molecules

thermosensitive liposomes use externally applied heat to release the liposome content near the target site. The thermoresponsiveness is imparted via either the use of lipid mixtures with a desirable lipid chain melting temperature ( $T_m$ ) which will destabilize the lipid membrane or the incorporation of thermosensitive polymers which undergo hydrophilic to hydrophobic transitions in response to temperature (70). Similarly, liposomes can be destabilized using light by photooxidation-induced phase transitions in the liposomal bilayer, by photodeprotection where photocleavable stabilizers are released, and by photoisomerization where light-induced isomerization interferes with bilayer packing (69). Alternatively, the contents of liposomes can be released following exposure to a specific microenvironment. For example, pH-responsive liposomes are designed to release their contents at a mildly acidic pH, which is encountered at the surface of tumors or in the endosome. The destabilization of pH-sensitive liposomes involves acid catalyzed hydrolysis of bilayer-stabilizing lipids (71).

### Lipoproteins

Lipoproteins are particles formed by the aggregation of lipids (i.e., triglycerides, phospholipids) and cholesterol of cholesteryl esters. The main advantages of lipoproteins as prodrug carriers are their lack of generating an immune response due to their endogenous nature, long circulation half-life, and relatively small particle size which aids in

increasing diffusion from vascular to extravascular sites (72). These particles are also quite versatile, where the lipid core incorporates hydrophobic drugs, and, depending on the subtype, can be internalized by receptors overexpressed on some types of cancer cells. The different types of lipoproteins are categorized based on their composition, size, and their assembly origin (Fig. 5). Each type has distinct advantages, and there are many examples of their applications in drug delivery (Table II).

Similar to liposome carriers, lipoproteins are also utilized to overcome formulation issues with lipid-based prodrugs. In general, low-density lipoprotein (LDL) nanoparticles are most commonly combined with anticancer prodrugs due to the added advantage of the upregulation of LDL receptors on the surface of tumors (73,74). Examples include paclitaxel oleate (75), N4-octadecyl-AraC (76), and doxorubicin-lipid conjugates (77). These studies show that the toxicity of the lipid prodrugs is improved after incorporation into LDLs and that the toxicity occurs in an LDL receptor-dependent mechanism.

### CONCLUSION

Lipid modification is a great asset in drug delivery applications. Commonly, lipid modification is utilized to enhance the pharmacokinetic properties of a drug, where the subsequent lipid conjugate exhibits a longer circulation half-life and increased serum protein binding. Other

**Table II.** Drug Delivery Using Lipoproteins

Lipoprotein	Advantage(s)	Example(s)
Chylomicrons	Routed via intestinal lymphatics (i.e., serve as natural carriers for transport through the lymph)	Gene delivery (85,86); iododeoxyuridine (87)
VLDL	Have ApoE (overexpressed on some types of cancer) as a protein ligand; high drug loading capacity due to low protein/high triglyceride composition	Boron neutron capture therapy (88); 5-FU, IUdR, doxorubicin, vindesine (89)
LDL	Internalized by LDL-R-mediated endocytosis; long serum half-life (2–4 days)	Doxorubicin (90); 5-FU, IUdR, vindesine (89); dexamethasone (91); fluorophore (diagnostics) (92); gene delivery (93,94)
HDL	Small size (5–25 nm); rapid internalization by cancer cells	Taxol (95); iododeoxyuridine (96)

VLDL very-low-density lipoprotein, LDL low-density lipoprotein, HDL high-density lipoprotein, 5-FU 5-fluorouracil, IUdR idoxuridine

advantages of lipid modification that are exploited when applied to prodrugs include enabling targeting tumor sites, the liver, or the lymphatic system. Many different types of lipid molecules are available, from simple fatty acid conjugation to complex lipoprotein particles, for use in drug delivery. Therefore, the numerous advantages and diverse forms of lipid modification and lipid carriers offer a significant benefit in improving prodrug delivery.

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