bioavailability. The compound must be administered by intravenous injection and is associated with toxicity related to concentration in the kidney proximal tubule.[77] Its clinical utility is further limited by the requirement for co-administration with probenecid and hydration therapy to minimize kidney toxicity. To improve the oral pharmacokinetic properties and antiviral activity of CDV, a prodrug strategy was devised to camouflage the acyclic nucleoside phosphonate with a partially metabolized phospholipid moiety.[78] The resulting alkoxyalkyl analogs of CDV had greatly improved antiviral properties, oral bioavailability and decreased accumulation in the kidney.[75,79,80]

Phospholipid prodrugs of acyclic nucleoside phosphonates mimic the metabolism of lysophosphatidylcholine (LPC) in animals to increase absorption (Figure 4.3).[76] Once absorbed, the LPC is reacylated to phosphatidylcholine in enterocytes and incorporated into chylomicrons. Chylomicrons are secreted into intestinal lymphatics, where they enter the circulation through the thoracic duct. Three lipid moieties were evaluated as produgs of CDV, hexadecyloxypropyl (HDP), octadecyloxyethyl (ODE) and oleyloxypropyl (OLP), all of which were shown to improve the antiviral activity relative to CDV.[75,79] Replacing the acyl ester bond at the sn-1 position of LPC with an ether linkage prevents hydrolysis of the acyl group by lysophospholipase during absorption (Figure 4.3).[76] The hydroxyl at the sn-2 position of glycerol in LPC was replaced with a hydrogen atom, which prevented reacylation by lysophosphatidylcholine acyltransferases present in small intestinal enterocytes and other tissues.[76] Finally, it should be noted that compounds such as CDV have a phosphonate (–P–CH_2–) linkage to the acyclic nucleoside base that is not subject to cleavage by phospholipase D or phosphodiesterase. Therefore, metabolic cleavage is catalyzed by phospholipase C, which is not present in plasma or pancreatic secretions, providing stability for the lipid prodrug and other compounds of this type during oral absorption and transport in plasma to tissues.

CMX001 is designed to be actively taken up by cells by phospholipid transport pathways and passive diffusion. Indeed, the rate of radiolabeled CMX001 uptake into MRC-5 human lung epithelial cells is ~23-fold greater than CDV, which is taken up by cells *via* fluid-phase endocytosis.[81,82] The enhanced intracellular uptake leads to a significant increase in antiviral potency.[75,81] Plaque reduction assays comparing CDV and cCDV in human foreskin fibroblast cells infected with vaccinia virus or cowpox virus showed that HDP-CDV was 57- and 13-fold more potent than CDV and cCDV, respectively.[75] Although these compounds were more toxic than the parent nucleotide analogs, the selectivity index was increased by 4–13-fold.

Mice administered [^{14}C]CMX001 orally at 5 mg kg^{-1} showed drug-associated radioactivity absorbed from the gastrointestinal tract and wide distribution to tissues by 2 h post-dosing. The highest levels of drug were detected in the small intestine and levels in the lung, liver, kidney and spleen ranged from 0.1 to 10 μg-equivalents per gram of tissue through 24 h post-dosing. Moderate to low levels of drug were detected in remaining tissues and those in which levels were below the limits of quantification included the brain and spinal cord.[83] Thus, CMX001 is readily absorbed following oral administration and widely distributed into tissues.