Optimizing the Oral Bioavailability and Activity of Antiviral Drugs

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Lack of sufficient oral bioavailability is a recurring problem in the design and development of drugs. With NIH support over the past 15 years, we developed a medicinal chemistry strategy for modifying drugs to enhance oral bioavailability. Several years ago, our laboratory was asked by the NIH and the US Army to convert a smallpox lead compound, cidofovir (CDV) with oral bioavailability less than 6%, to an orally active drug. CDV is an acyclic nucleoside phosphonate with two negative charges which impair its absorption and its cell penetration. When disguised as a phospholipid metabolite, the new analog is highly bioavailable, enters target cells more readily and is orally active in four models of lethal poxvirus disease. This strategy is generally applicable to antiviral nucleosides and other drugs having suitable linking functionalities. The hexadecyloxypropyl ester of CDV is currently in Phase I clinical trials in normal human volunteers.