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**Making Nucleoside Phosphonates Orally Active: Compounds for Oral Treatment
of Smallpox and Other Viral Diseases**

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Alkoxyalkyl nucleoside phosphonates (ANP) are an important class of antiviral agents with activity against most DNA viruses and some retroviruses. However, ANP entry into cells is slow and oral bioavailability is limited. A novel prodrug approach will be described which enhances ANP cell entry, oral bioavailability and antiviral activity. The mechanism of enhanced antiviral activity will be discussed and data will be presented on the activity of oral cidofovir analogs in lethal models of viral diseases. The strategy can be applied to other ANPs and some data presented showing the activity of several other ANP analogs against poxviruses, herpesviruses, hepatitis B and C and HIV-1.