



Abstract Title: Rational Design of Nucleoside Phosphonates for Intracellular Delivery Using Lipid Conjugation

Acyclic nucleoside phosphonates (ANPs) are highly effective antivirals, but are not readily taken up by cells. Chimerix has used lipid conjugation of ANPs to improve the absorption, distribution, metabolism and excretion (ADME) profiles of these agents. For example, CMX001 is an oral, lipid-ANP, which is converted inside cells to the active antiviral agent, cidofovir diphosphate (CDV-PP). CDV-PP acts as an alternative substrate inhibitor for the cytomegalovirus (CMV) viral DNA polymerase (UL54), the primary target for anti-CMV drugs. CMX001 is in Phase 3 development for prevention of CMV in the setting of stem cell transplantation. Learnings surrounding intracellular delivery of orally administered antivirals will be discussed, with specific review of lipid conjugation of ANPs and CMX001 as examples of successful approaches.