Title: The Discovery of the HIV-1 Attachment Inhibitor Fostemsavir

Human immunodeficiency virus-1 (HIV-1) infection currently requires lifelong therapy with drugs that are used in combination to control viremia. An unsubstituted indole-3-glyoxamide was discovered as an inhibitor of HIV-1 infectivity using a phenotypic screen and derivatives of this compound were found to interfere with the virus entry process by stabilizing a conformation of the coat gp120 protein not recognized by the host cell CD4 receptor. An extensive optimization program led to the identification of temsavir which successfully advanced through Phase 3 clinical trials as its phosphonooxymethyl derivative fostemsavir, a prodrug designed to address dissolution- and solubility-limited absorption issues. In this presentation, the studies leading to the discovery and development of fostemsavir, which was approved by the FDA on July 1st, 2020, will be summarized.