June 17, 2009

Chemicals Targeting an HIV-1 Nef/Host Cell Kinase Complex as Novel Anti-Retroviral Compounds

Damilola A. Adepegba, Department of Natural Sciences, University of Maryland Eastern Shore

Billy W. Day, Mentor, Departments of Pharmaceutical Sciences and of Chemistry, University of Pittsburgh

Introduction

Human immunodeficiency virus (HIV) can be acquired through different mechanism such as breast feeding, sexual intercourse, needles, blood to blood contact with open wounds, or in utero. The HIV virus attacks and conquers the immune system, subsequently resulting in AIDS. The epidemic of AIDS has resulted in many anti-retroviral drugs to manage the deadly disease. HIV-1 encompass accessory proteins that are essential participants in the progression of AIDS. Nef has been identified as one of the essential proteins and therefore has become a target (1,2). Nef (Figure 2) forms a complex with its host cell binding partner, the Src family kinase Hck. Nef activates Hck through a mechanism that involves displacement of the SH3 domain from a negative regulatory interaction with the catalytic domain (9,10). Although the actual pathway function has not been totally elucidated for Nef, it is known to influence several classes of signaling molecules, including immune receptors, trafficking proteins, guanine nucleotide exchange factors, and protein kinases (3-5). These characteristics that Nef acquire enhance the viral replication and contribute to immune evasion as well as survival of infected cells (6-8). A high-throughput screening assay identified two classes of inhibitors of this protein-

protein interaction. One class of inhibitors of HIV activity and Nef:Hck interaction was diphenylfuropyrimidines, the other 2-arylsulfonamido-3-arylaminequinoxalines. Remarkably, these agents block Nef-dependent HIV replication and show no apparent cytotoxic effects. These studies show a new and valid approach in the development of anti-HIV agents. More recent anti-retroviral drugs target enzymes such as integrase, protease, and reverse transcriptase; however, the HIV mutates and many different strains exist. This new approach of inhibiting the protein-protein interaction appears to be effective and may accelerate the discovery of new anti-HIV agents. Structurally similar analogs illustrate similar actions of inhibiting the replication of Nef-dependent anti-retroviral activities, therefore showing that the two scaffolds may be valuable in the investigation of HIV Nef function.