Submitter Name: Hemayet Ullah
Submitted email: hullah@howard.edu

Host Targeted Antivirals Inhibit RACK1 mediated IRES Activities in HIV-1

Israa Malli,[1,2] Namita Kumari,[3,4] Larisa Dubrovsky,[5] Andrey Ivanov,[3] Michael Bukrinsky,[5] Sergei Nekhai,[1,3,4] Sivanesan Dakshanamurthy, [6]* and Hemayet Ullah,[2]*

[1] Department of Microbiology, School of Medicine, Howard University, Washington DC, USA;
[2] Department of Biology, College of Art and Science, Howard University, Washington DC, USA;
[3] Center for Sickle Cell Disease, Howard University, Washington DC, USA;
[4] Department of Medicine, School of Medicine, Howard University, Washington DC, USA;
[5] Department of Microbiology and Tropical Medicine, School of Medicine, the George Washington University,
[6] Department of Oncology, and Clinical & Experimental Therapeutics Program, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington DC, USA.

* Corresponding Authors: Sivanesan Dakshanamurthy (sd233@georgetown.edu) and Hemayet Ullah (hullah@howard.edu)

Host ribosome associated scaffold protein Receptor for Activated C Kinase 1 (RACK1) is utilized by a diverse group of human viruses for Internal Ribosomal Entry Sites (IRES) – mediated translation of viral mRNAs. We recently reported inhibition of herpes virus by small molecules targeting the RACK1 functional site. Here, we tested these molecules against HIV-1 and HCV, as HIV-1 contains two potential IRES sites and HCV translation occurs exclusively through IRES. The compounds were tested for the inhibitory activity against dicistronic reporter constructs. Compounds significantly downregulated activities of HIV-1 and HCV-related dicistronic constructs in transfected HEK293T cells. The compounds also strongly downregulated production of the HIV-1 capsid protein p24 in HIV-infected cells. In addition, production of HIV-1 Gag precursor p55 and p55-derived proteins p24 and p17 was significantly suppressed in the compound treated cells infected with the VSV-G-pseudotyped HIV-1 virus. Hepatitis C virus (HCV), tested as a positive control for IRES activities, was also significantly inhibited by RACK1 functional inhibitor compounds. As HCV replicates exclusively through IRES, this inhibition heralds a new avenue in its therapeutic application as an anti-HCV treatment. Since a number of human and plant pathogenic viruses are reported to use IRES, our RACK1 compounds can be established as broad host-targeted antivirals.
Keywords: RACK1, HIV-1, Hepatitis C, HCV, Internal Ribosomal Entry Site, IRES, Translation, HEK293T, AZT, SD29, Arabidopsis, Host Targeted Antiviral (HTA).