Jacob Jackson, Biological Sciences

University: University of Missouri
Year in School: Senior
Hometown: Kirksville, Missouri
Faculty Mentor: Dr. Stefan Sarafianos, Molecular Microbiology & Immunology
Funding Source: Life Sciences Undergraduate Research Opportunity Program

HIV versus the Terminator: Drug resistance of HIV reverse transcriptase with mutations at the connection subdomain

Jacob C. Jackson, Matthew M. Schuckmann, and Stefan G. Sarafianos

Antiretroviral drug therapy can prolong the life of an HIV-infected individual, but this treatment also promotes drug-resistance mutations. The replicative enzyme of HIV, reverse transcriptase (RT), is a primary target for anti-HIV drug therapy because it is responsible for converting the single stranded RNA genome of HIV into double stranded DNA for integration into the host genome. Many current anti-HIV drugs belong to two classes of inhibitors that target RT: nucleoside reverse transcriptase inhibitors (NRTIs) incorporate into and chain-terminate nascent transcription products of RT, whereas non-nucleoside reverse transcriptase inhibitors (NNRTIs) alter enzyme-nucleic acid interactions, thereby affecting the efficiency of DNA polymerization. Here, we focus on NRTI resistance mutations that are located at the connection subdomain of the enzyme in the presence and absence of thymidine analog associated mutations (TAMs). TAMs cause resistance to the commonly prescribed chain terminator 3'-azido-3'-deoxythymidine (AZT) through excision of the incorporated AZT-monophosphate. Mutations in the connection domain, such as N348I, confer resistance to NRTIs and NNRTIs and augment AZT resistance when present in combination with TAMs. Although the underlying mechanism of N348I resistance remains elusive, it has been suggested that the mutation compromises ribonuclease (RNase) H activity, which is responsible for cleaving the viral genomic RNA of the RNA/DNA heterodimeric intermediate. Changes in RNase H cleavage affect the availability of AZT-terminated primers to be excised, thereby increasing the unblocking of template/primer and NRTI resistance. Our investigation attempts to determine if AZT-resistance mutations affect resistance to other commonly prescribed NRTIs, as well as to competitive substrate inhibitors currently in development, through changes in template/primer processing. In addition, we are examining the effects of NRTI and NNRTI cocktails on the RNase H activity of RT possessing connection domain mutations. Our findings should provide insight for screening novel inhibitors for their efficacy against emergent strains of drug-resistant HIV.