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Drug Leads that Inhibit Vif and Enable APOBEC3G are Broadly Neutralizing of HIV1 Clades and Drug-resistant Strains

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HIV Viral infectivity factor (Vif) evokes the destruction of the host restriction factor known as APOBEC3G (A3G).Vif dimerization has been shown to be essential for Vif binding to A3G and A3G degradation. Experimental data show that in the absence of Vif, virion-assembled A3G will hypermutateproviral DNA during reverse transcription. The open questions are: can Vif be successfully drugged and by sparing A3G, will hypermutation activity be sufficient to inhibit viral replication? High throughput screening (HTS) assays were developed using FRET for Vif dimerization. The screens were used to select compounds with dose-dependent signals by preventing Vif FRET. A secondary assay for Vif-dependent A3G degradation was used to identify compoundsthat preserved A3G. These were triaged for the ability to inhibit pseudotyped HIV replication and to have low cytoxicity. Ion torrent sequencing of integrated viral genomes revealed extensive hypermutation characteristic of A3G preferences. Following medicinal chemistry, a lead was tested in a seven day spreading infection in PBMC. TheVif dimerization FRET assay provided a robust HTS method applicable to a large library of drug-like molecules. Quantitative HTS followed by orthogonal secondary screen and cytotox counter screening enabled selection of limited number of chemistries for pseudo typed viral testing. A lead (SMVDA) was selected with nanomolar IC50. By impairing Vif dimerization, A3G degradation was reduced and viral particle incorporation of A3G was enhanced. Proviral DNA isolated form target cells showed numerous tracts of dG to dA hypermutation that corresponded to multiple nonsense codon and sense changes. 17 different clades and 8 drug resistant strains of HIV infecting PBMC were sterilized by seven days following a single dose of SMVDA.

Conclusions: Drugging Vif led to massivedG to dAhypermutation of HIV proviral DNA, such that the protein coding capacity of the virus would be severely compromised. Inhibitors of Vifare broadly neutralizing and inhibited all drug resistant strains of HIV tested. DruggingVif therefore is achievable and the data suggest that this will serve as a firewall for viremia induced by activating reservoirs as well as a solution for rescue and salvage therapies.

Biography

Harold Smith is a tenured professor of biochemistry and biophysics at theUniversity of Rochester, School of Medicine and Dentistry. Dr. Smith¹sprimary function at the University is basic research and in this contexthe is fully engaged in biomedical laboratory research as well as trainingpostdocs, graduate and undergraduate students. The Smith lab¹s primaryinterest is understanding the composition, regulation and structure ofmacromolecular complexes involved in regulating gene expression at thelevel of messenger RNA expression and processing. Our focus is on aplatform of enzymes that change the genetic code at the DNA or RNA levelby deaminating cytidine to form uridine. Current data suggest that thisfamily of cytidine deaminase function with other proteins (auxiliaryproteins) as holoenzymes complexes which we refer to as editosomes (forRNA) or mutasomes (for DNA). RNA editing or DNA mutational activity bythese enzymes affect the protein coding capacity of mRNAs and thereby candiversify the proteins that are expressed by cells (the proteome). In 2003he founded OyaGen, Inc as a drug discovery and drug development biotechfocused on anti retroviral therapeutics.

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