



# Novel Inhibitors Targeting HIV Vif Protein

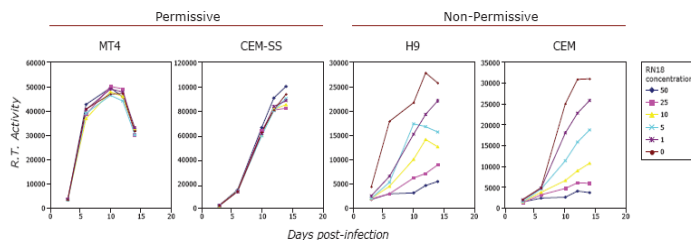
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## Background

According to WHO estimates, as of January 2006, AIDS has killed 25 million people since its discovery in 1981. Viral protease & reverse transcriptase inhibitors dominate the regimen for treating HIV infection. These drugs have contributed greatly to slow the number of new infections. However, swift evolution of resistance to these drug classes has fueled the search for agents targeting other HIV proteins. Further, the HIV drugs currently available can have severe side effects because of their structural & functional similarities to vital human proteins. Hence, there is an urgent need for development of new therapeutic entities that can potently & specifically inhibit the activity of other HIV proteins.

## Technology

UMass Medical School investigator Dr. Tariq Rana & colleagues have identified novel therapeutic candidates for treating HIV infections. These small molecules specifically inhibit the activity of the HIV-1 protein, **Virion infectivity factor (Vif)**. Vif facilitates HIV-1 replication *in vivo* by binding human antiviral factor APOBEC 3G (A3G) & targeting it to proteosomes for degradation. To identify small molecules inhibitors of Vif function the investigators developed a HTS assay based on Vif mediated down regulation of a fluorescently labeled A3G. Several compounds were identified that inhibited the Vif-A3G interaction. Because of its potency, RN18 was subjected to detailed biochemical analysis. The efficacy and specificity of RN-18 was ascertained and validated by monitoring viral replication, the expression level of A3G protein, and Vif and A3G protein stability in permissive and non-permissive cells.



RN-18, specifically inhibits HIV-1<sub>LA1</sub> replication in non permissive cells but not in permissive CD4+T cells

## Applications

HIV/AIDS therapy

## Salient Features and Competitive Advantages

- **Novel Target:** Validates Vif-A3G interaction as a novel target for developing HIV inhibitors.
- **Reduced HIV Replication:** RN-18 reduced reverse transcriptase activity in HIV-1 infected H9 cells in a dose dependent manner with an IC50 of about 3µM.
- **Selective Inhibition & Reduced Vif Protein Stability:** RN-18 caused a dose dependent decrease in Vif protein level exclusively in non-permissive (A3G expressing) H9 cells. Also, RN-18, reduced Vif half-life from 57.6 minutes to 31 minutes in A3G expressing cells.
- **Enhanced Cellular APOBEC expression:** RN-18 significantly increased expression of APOBEC family members A3G, A3F and A3C in HIV infected cells, thereby, boosting host antiviral defense.
- **Boost Viral APOBEC levels:** RN-18 enhanced viral A3G levels, thereby ensuring defective HIV replication in new hosts.
- **Potentially Low Toxicity:** RN-18 specifically targets HIV-1 Vif with no effect on general proteosome-mediated protein degradation pathways of host cells. Consequently, RN-18 may have lower side effects.
- **Combination Therapy:** Vif inhibitors would be ideally suited for treating HIV infection in combination with inhibitors targeting other HIV proteins.
- **Unmet Market Need:** Vif inhibitors represent a new class of HIV treatments desirable to overcome drug resistance problems associated with existing drugs.

## Business Opportunity

UMass OTM is seeking statements of interest from parties interested in licensing and/ or sponsoring collaborative research to commercialize this technology.

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