Protein Phosphatase-1 Inhibitors (PP1) which can be used for the Ebola Virus and HIV-1 Virus

Howard University researchers have identified a family of small molecule inhibitors which inhibit PP1 preventing Ebola Virus replication and HIV-1 replication in the host cell.

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Inventors
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Potential Commercial Applications
-New class of Ebola and HIV-1 therapeutics
-Potentially useful when administered alone or in combination with existing therapeutics
-Potentially useful against strains resistant to other therapies

Stage of Development
-*In vitro* toxicity testing for Ebola Virus inhibition
-*In vitro/In vivo* toxicity testing for HIV transcription.

Status
Seeking development & licensing partners

Background
Ebola virus infections are mainly found in Central Africa on a regular basis. The virus has the potential to cause hemorrhagic fever in humans killing 90% of the infected. There is a broad distribution and significant diversity of the Ebola Virus due to genetic recombination events thus causing the urgent need for the development of treatment.

HIV-1 replication is dependent on numerous steps including entry of the virus into cells, crossing into the nucleus, transcription of HIV DNA, and budding of new viral particles. These steps are regulated by several HIV-specific proteins which present targets for therapeutic inhibition. HIV protease, integrase, reverse transcriptase, and host cell CCR5 have all been targeted with pharmaceuticals. Unfortunately, existing therapies lose efficacy as HIV becomes resistant, and new targets for pharmaceutical inhibition are desirable.

Description of Technology
Dr. Nekhai has identified a family of small molecules that can be used to treat and/or prevent Ebola Virus Infection along with decreasing HIV1 replication. These small molecules are host cell protein phosphatase-1 (PP1) inhibitors. PP1 is needed for the dephosphorylation of VP30, a viral protein needed for Ebola Virus replication. The phosphorylated form of VP30 is transcriptionally inactive. These PP1 inhibitors prevent Ebola virus replication without exhibiting any cellular toxicity. Multiple different routes of administration have also been described along with combination therapy with current therapeutic regimens.

These molecules also inhibit HIV1 replication by interfering with its interaction with host cell PP1. Normally, HIV1 Tat binds to the host cell PP1 which causes HIV1 transcription. These inhibitors have been shown to prevent Tat induced HIV1 transcription. The binding of HIV1 Tat to host cell PP1 causes the translocation of PP1 to the nucleus of infected cells which is crucial for HIV1 transcription. There is a step in HIV1 replications which includes the dephosphorylation of CDK9 Thr 186 and the dephosphorylation of CDK9 Ser 175 by PP1, which, if inhibited, halts HIV1 replication.

These inhibitors have been selected from a library, which in general, possesses good ADME properties and drug-like characteristics. Several in the family have been tested and show inhibition of Tat transcription *in vitro* between 2 and 10µM concentration, without toxicity to 293T or reporter CEM GFP cells. These inhibitors have undergone limited testing in a mouse model but full toxicity studies remain to be performed. The Tat transcription inhibitors of the current invention could be administered alone or in combination with existing therapies.

Opportunity
Howard University is seeking development partners to further characterize the compound family, to complete toxicity testing and to explore novel drug delivery systems. Dr. Nekhai is available to talk about the invention under a NDA.