Evaluating the impact of an adjunctive therapy on viral reservoir size and predicting time to viral rebound using mathematical modeling.

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Each year ~160,000 infants get infected with HIV, >50% during breastfeeding. While lifelong anti-retroviral therapy (ART) results in effective viral suppression, these infected infants are predisposed to long-term drug-associated complications and development of drug resistance. Therefore, to achieve sustained viral remission in these infants, novel intervention strategies that do not rely on daily ART will be required. Our recent \textit{ex vivo} findings indicate that inhibition of cellular heat shock protein 90 (Hsp90) along with ART can effectively reduce proportion of HIV infected cells by targeting antiviral and T-cell activation pathways. Based on these results, we propose to evaluate a novel \textbf{multifunctional viral inhibition} strategy, where we hypothesize that incorporating SNX-5422, an orally bioavailable Hsp90 inhibitor that has excellent safety record in phase I/II clinical trials for cancer therapy, in the ART regimen, will rapidly contain HIV replication by targeting immune activation-mediated cell-to-cell viral transfer and will limit further establishment of viral reservoir by reducing cell-associated viral loads, thereby achieving long-term HIV remission in postnatally infected infants.

In this project, our overall goal is to evaluate the impact of ART and the combination therapy (SNX-5422+ART) on HIV replication and viral reservoir size, and mathematically predict viral rebound time from the size of the viral reservoir. We will have longitudinal viral load and viral reservoir data from infant rhesus macaques during SHIV infection and therapy. The intern will

1. Perform statistical tests on viral load, viral reservoir size and immune activation status of the macaques on ART vs combination therapy.
2. Develop a mathematical model that can predict time to viral rebound post ART-interruption from viral reservoir size.
3. Use the developed model to predict viral rebound times in infant RMs treated with combination therapy.

**Expectations**

- Familiarity with nonlinear ordinary differential equation models
- Able to code numerical simulations in Python and/or R
- Understanding of statistics for model evaluation and selection

**Timeline**

- Weeks 1–2: Review and summarize literature on mathematical models for HIV reservoir and viral rebound.
- Weeks 3–4: Fit mathematical models to longitudinal data and develop a model that can predict viral rebound time from viral reservoir size.
- Weeks 5–8: Apply the developed mathematical model to validation cohort data and combination therapy data.
- Weeks 9–10: Write down relevant findings and poster preparation

**Special Features**

- The intern will interact with a group of immunologists, mathematicians and statisticians who meet weekly to discuss the modeling of viral dynamics.