Eradication and Cure

Ronald J Ellis, MD, PhD

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Cockerham and Deeks, 2014
HIV Reservoir Sites

- Brain: macrophages and glial cells
- Blood, semen, vaginal fluids: macrophages
- Bone marrow: Lymphocytes
- Skin: Langerhans cells
- Lymph nodes and thymus: Lymphocytes and dendritic cells
- Lung: Alveolar macrophages
- Colon, duodenum, rectum: Chromaffin cells
Cure strategies

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Unanswered questions

- What is the size of HIV DNA populations in the brain and where are they distributed?
  - How much HIV DNA remains in patients with virologic suppression on ART?
- Do HIV DNA populations in the brain uniquely contribute to viral rebound following antiretroviral treatment interruption?
- Can HIV DNA in the brain be reached using “kick and kill” interventions? Will this be safe?
- Are HIV DNA populations in brain replication competent?
- Can early ART initiation and behavioral adherence interventions minimize the size of the brain HIV DNA reservoir?
What the HNRC can do to help tackle unanswered questions

- Evaluate archived CSF and blood samples from pts who underwent treatment interruption to assess whether CNS HIV DNA contributes to viral rebound
- Evaluate HIV DNA in autopsy tissue from brain bank donors who were virologically suppressed prior to death
- Characterize HIV transmission networks
- Devise and test behavioral interventions (adherence, early treatment initiation, TAP) to minimize the size of HIV DNA reservoirs at both individual and community levels
Example of Viral Rebound Dynamics

P4 viral dynamics

Days

HIV RNA (Log10)

HIV RNA Blood

HIV RNA CSF

14 days
Approach

- 14 subjects interrupting ART
- Sequencing: HIV-1 env (C2-V3), gag (p24), and pol (partial RT) amplified from cell-free HIV RNA (blood and CSF).
  - Roche 454 FLX Titanium platform.
- Significance of compartmentalization: $F_{ST}$
Pairwise distances and phylogenetic relationships

Mixed populations: $F_{ST} = 0.12$, $p = 0.22$

Compartmentalized populations: $F_{ST} = 0.53$, $p < 0.001$

*Inter-compartment distances*
Summary

- Viral populations compartmentalized between blood and CSF in 10/14 pts at 1st time point assessed post-rebound
  - Of those sampled within 2 weeks, 4/4 compartmentalized
- Longitudinal change: evolution of both compartmentalization and intermixing observed.
  - Only one pt maintained genetically mixed populations for the entire study follow-up
Detecting brain HIV DNA in suppressed individuals

Antemortem
Plasma and
CSF HIV RNA

Postmortem
Brain
HIV DNA

Brain tissue samples
N=15

Detectable N=11
Detectable 10/11

Undetectable N=4
Detectable 3/4
Replication Competence in Brain Tissue

- Select cases >2y plasma HIV RNA suppression
- Extract Brain HIV DNA; amplify and dilute
- Barcode and screen for full-length (FL) sequences
- Ligate FL (N=~30/sample) HIV DNA into SMRTbell (™) library complexes
- Consensus sequence FL HIV DNA
- Eliminate APOBEC hypermutation and large-scale deleted sequences
- Clone remaining intact FL HIV DNA into expression vectors
- Demonstrate infection of CD4+ T-cells and evaluate replication kinetics
Implications of this line of research

- Major point of significance is whether there is a reservoir of replication competent HIV DNA in the brain of virally suppressed individuals that needs to be specifically targeted.
- Evaluate the importance of targeting brain HIV DNA
- Behavior is central to HIV transmission and will need to be considered in devising eradication interventions
Feedback Requested

- Are there additional areas relevant to the Cure agenda to which you think the HNRC might contribute?
Thank you for your attention

Ronald J Ellis

Neuromedical Core Director
University of California, San Diego
Backup slides
## Compartmentalization Results (TP1)

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* Time from viral rebound to sampling