• Where is the virus in the brain?

• What happens to the viral reservoir with prolonged antiretroviral therapy?

• Can the reservoir be silenced?

• Can the reservoir be eliminated?
Productive Infection in perivascular macrophages

Jones et al., 2000;
Kruman et al., 1998

Restricted Infection in astrocytes

Ranki et al., 1995
Tat in microglial nodules and macrophages in HIV encephalitis

Aggregates of Tat in microglial nodules

Texas A03

Kruman et al., 1998
• Where is the virus in the brain?

• What happens to the viral reservoir with prolonged antiretroviral therapy?

• Can the reservoir be silenced?

• Can the reservoir be eliminated?
PET scan with monoclonal antibody to SIV for detection of viral reservoirs

Santagelo et al., Nat Methods 2015
• Where is the virus in the brain?

• What happens to the viral reservoir with prolonged antiretroviral therapy?

• **Can the reservoir be silenced?**

• Can the reservoir be eliminated?
Antisense design and mechanism of action (Shock and Block)

A) ASO proposed mechanism(s). Single-stranded ASO associate with a complementary mRNA sequence to form an RNA-DNA heteroduplex. Binding inhibits expression by a) cleavage of the mRNA by RNase H; or b) blocking splicing and/or translation by steric hindrance.

Lisa Henderson et al., unpublished
• Where is the virus in the brain?

• What happens to the viral reservoir with prolonged antiretroviral therapy?

• Can the reservoir be silenced?

• **Can the reservoir be eliminated?**
Immune therapies/ viral activation (Kick and Kill)

- Latency Reversal Agents (kick the virus)
- Therapeutic vaccines (kick the immune system)
- Checkpoint inhibitors (kick the immune system)
- Broadly neutralizing antibodies
Immune therapies/ viral activation (Kick and Kill)

- Latency Reversal Agents: Immune activation in CNS
- Therapeutic vaccines: Immune activation in CNS
- Broadly neutralizing antibodies: Do not enter CNS
- Checkpoint inhibitors
Reversal of immune exhaustion

- APC/HIV infected cell
  - HIV virion
    - HIV Antigen
  - MHC (I/II)
    - TCR
  - Initial antigen signal
- HIV provirus
  - HIV genome
    - 5'LTR
    - 3'LTR
  - HIV mRNA
    - Antiretroviral therapy
  - Tat protein
    - Upregulates PD-L1
- T-cell
  - T-cell Antigen Targeting:
    - Effector response and cytokine upregulation
  - T-cell Anergy:
    - No effector response or cytokine upregulation
<table>
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• Immune therapies/ viral activation
  – Latency Reversal Agents
  – Therapeutic vaccines
  – Broadly neutralizing antibodies
  – Checkpoint inhibitors

• Gene therapies
  – Genetic scissors
    • HIV receptor (CCR5 and CXCR4)
    • HIV proviral DNA
Genetic Scissors

HIV receptors: CCR5, CXCR4

HIV genome

https://www.biznews.com/health/2015
Gene therapy

HIV-infected Animal Models

Excision of HIV proviral DNA

Suppressing HIV transcription

Deleting HIV structural/functional genes to abolish HIV replication

Yin et al., Mol Therapy 2017
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