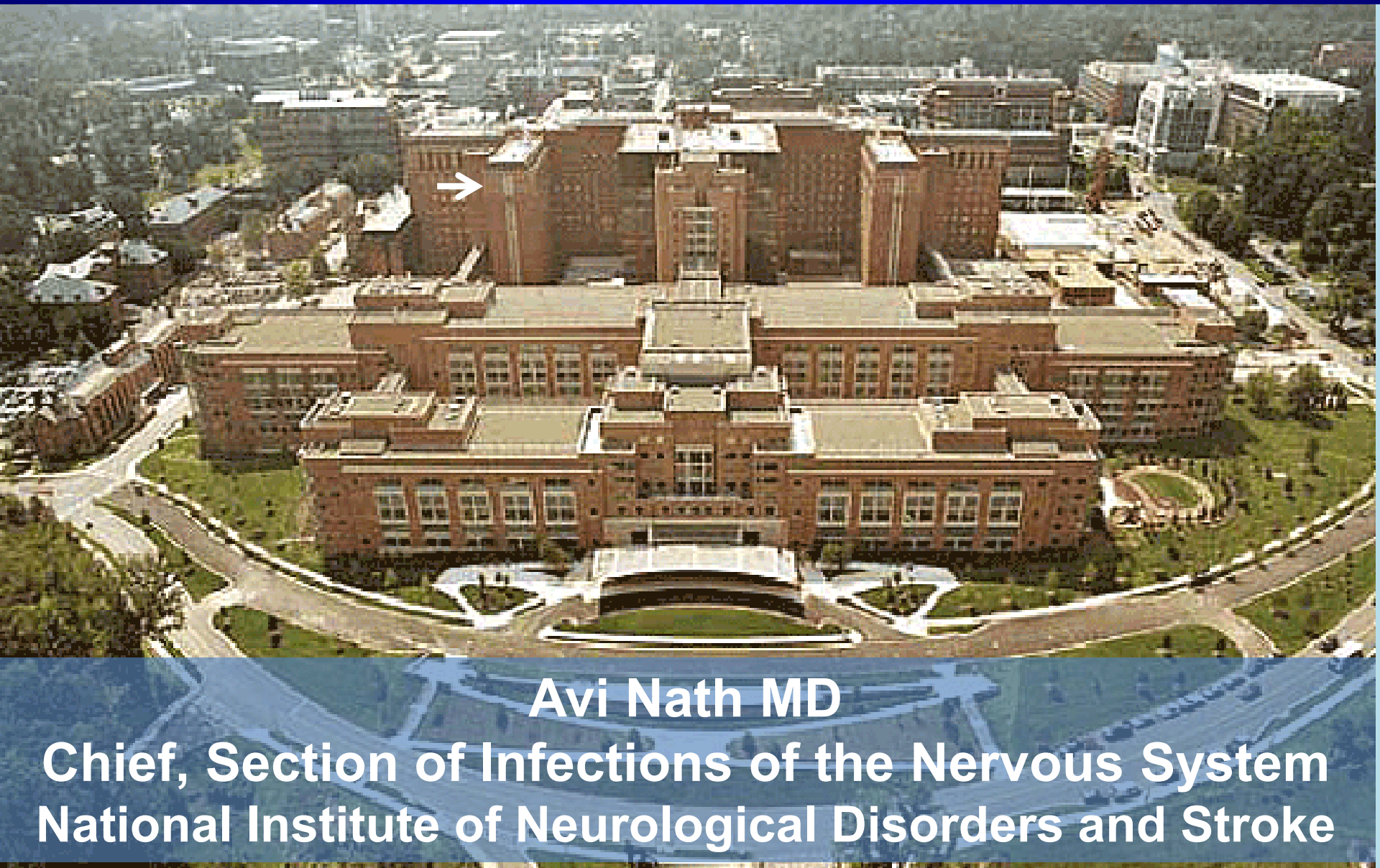
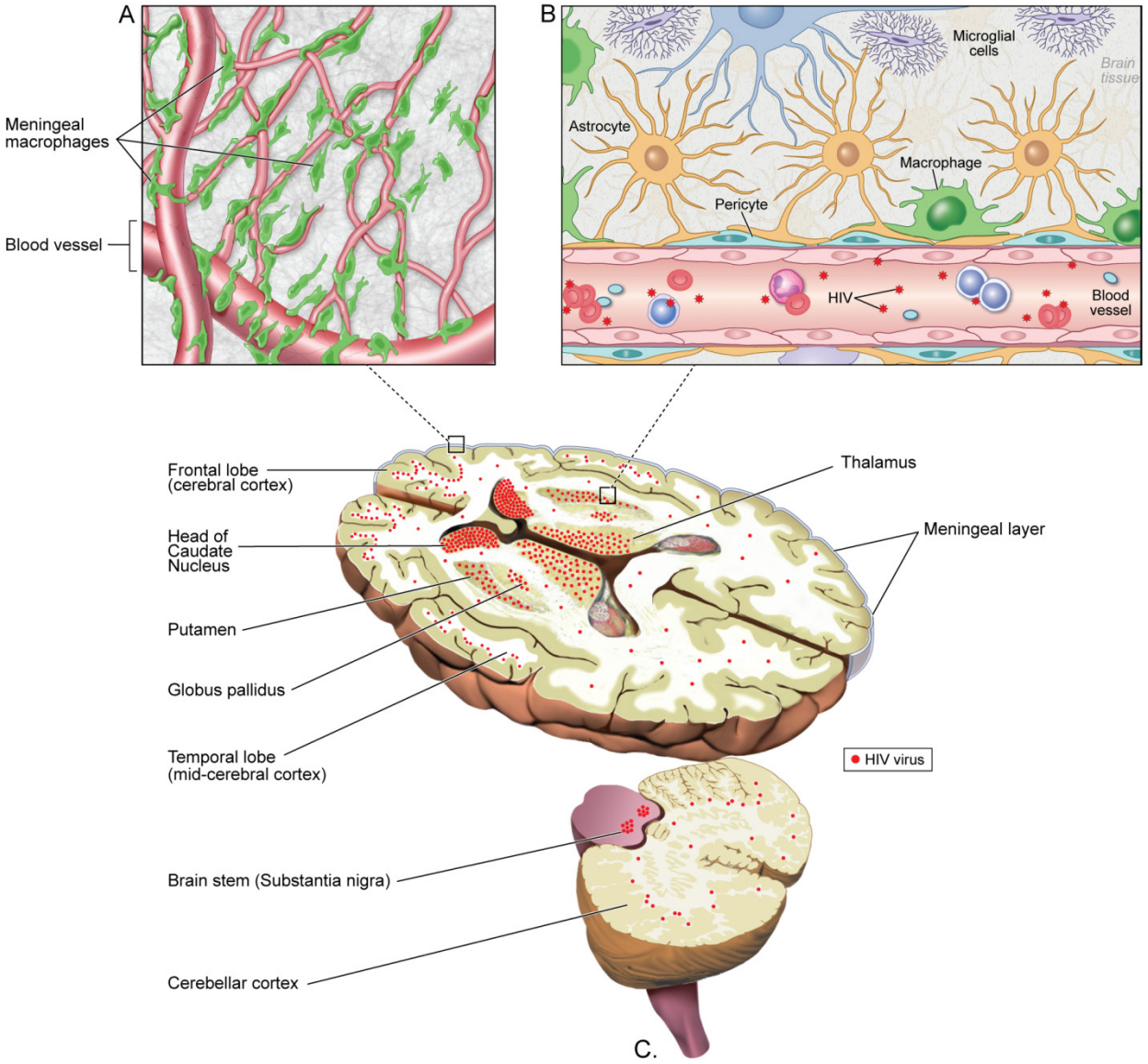
HIV reservoirs in brain: Advances in detection and elimination



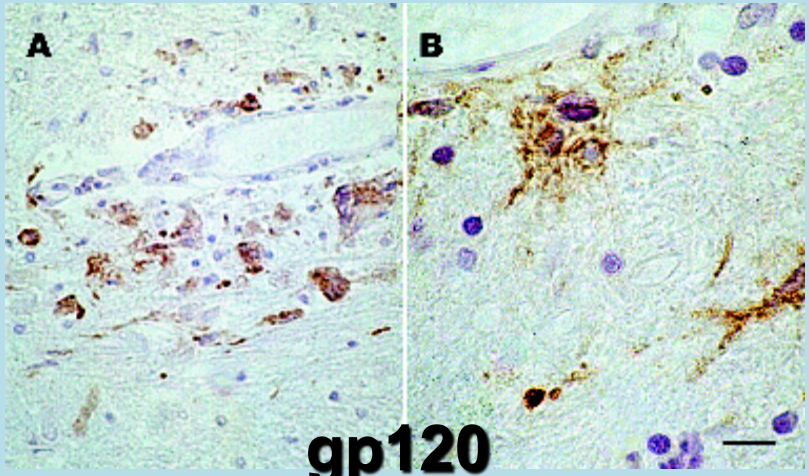
Avi Nath MD
Chief, Section of Infections of the Nervous System
National Institute of Neurological Disorders and Stroke

- 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?



Nath A. J Neurovirol 2015

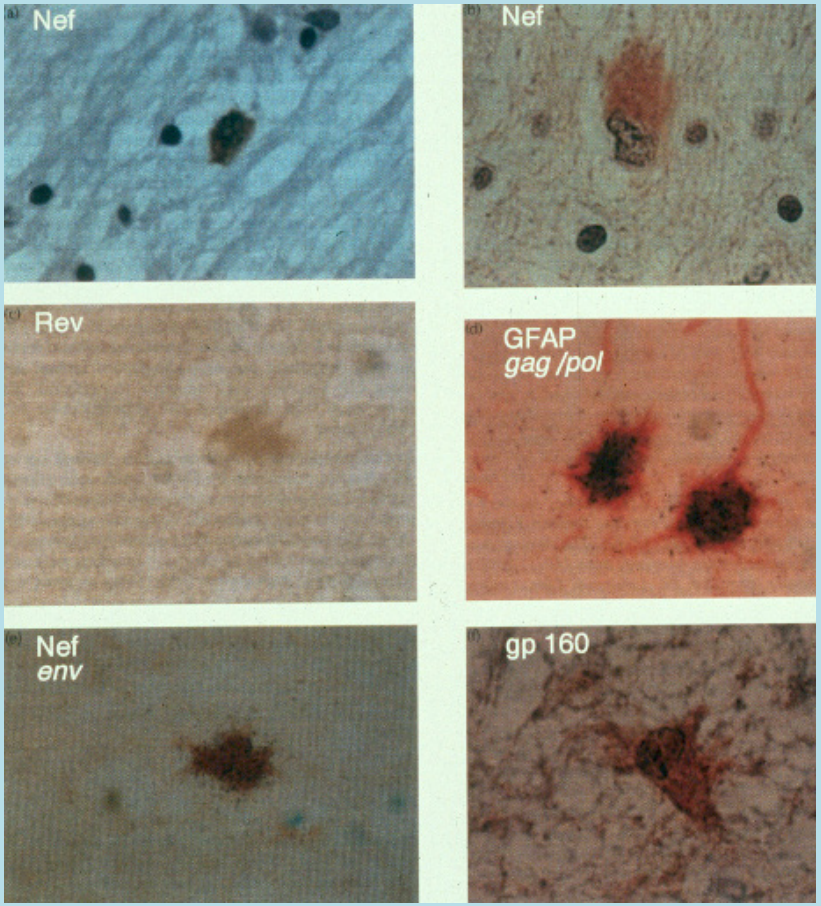
Productive Infection in perivascular macrophages



Jones et al., 2000;

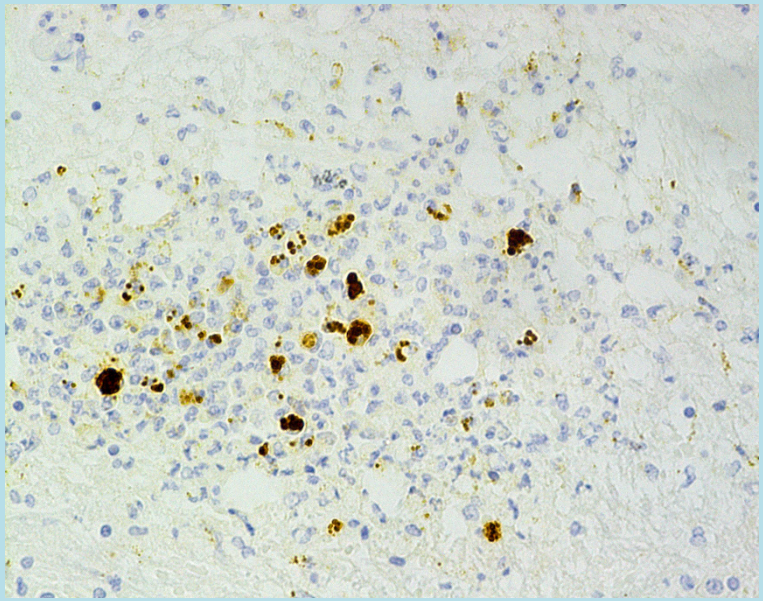
Kruman et al., 1998

Restricted Infection in astrocytes



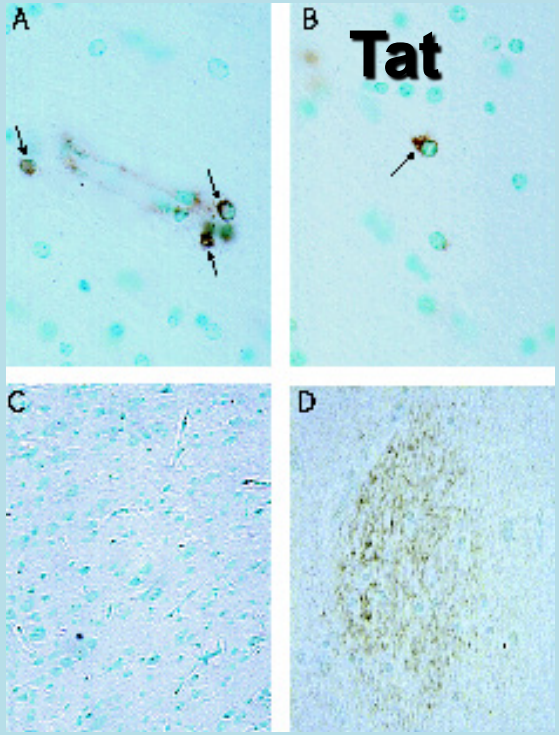
Ranki et al., 1995

Tat in microglial nodules and macrophages in HIV encephalitis

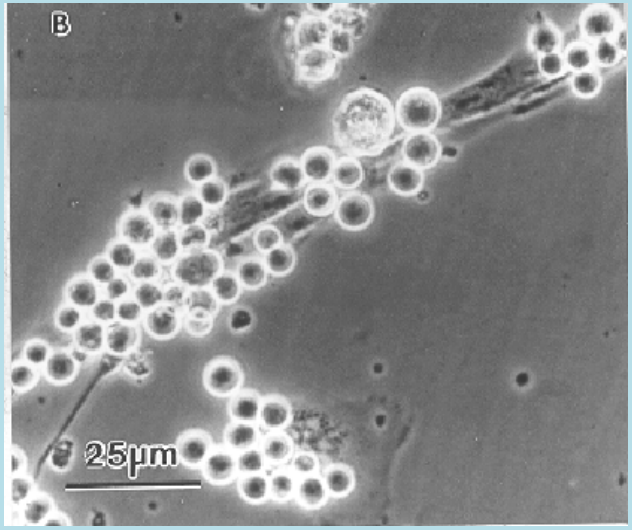


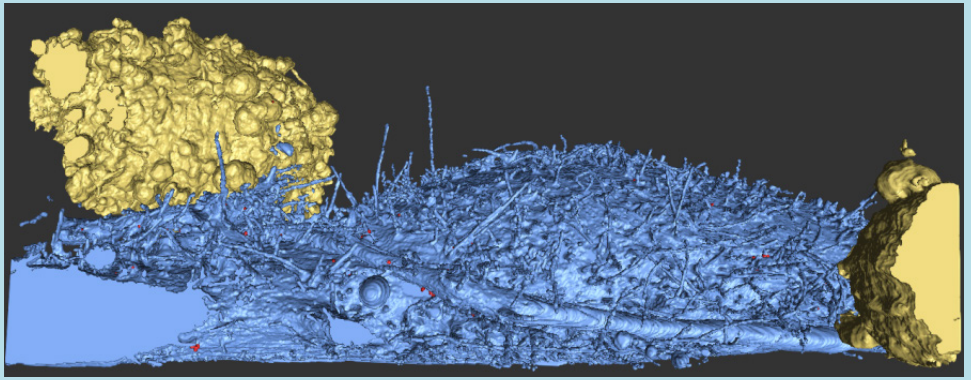
Aggregates of Tat in microglial nodules

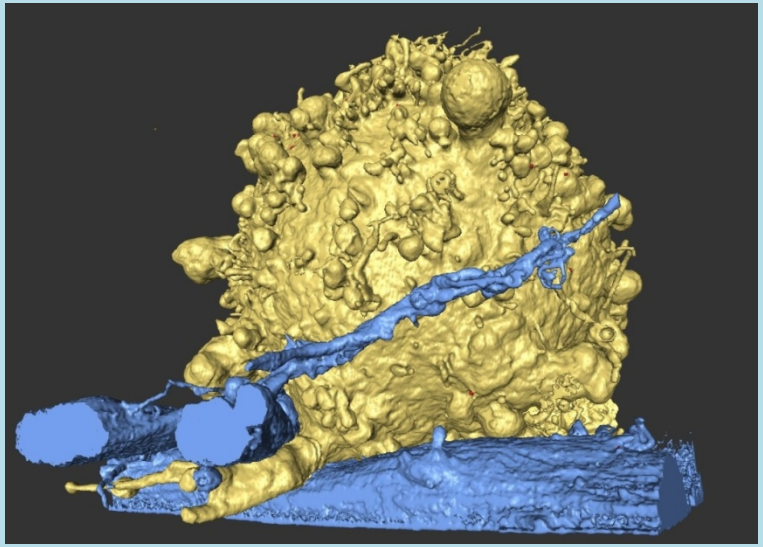
Texas A03

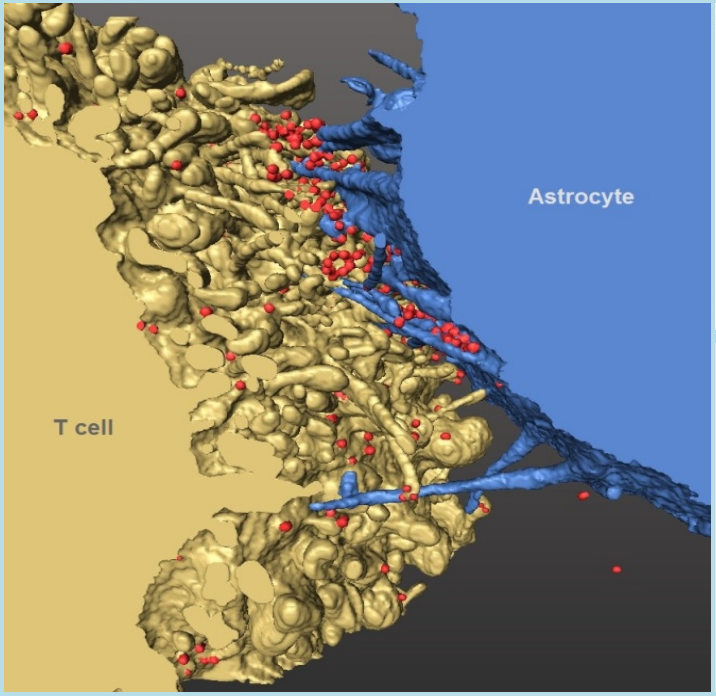


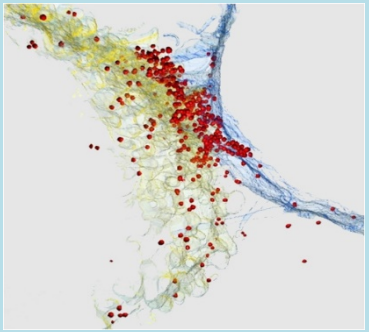
Kruman et al., 1998

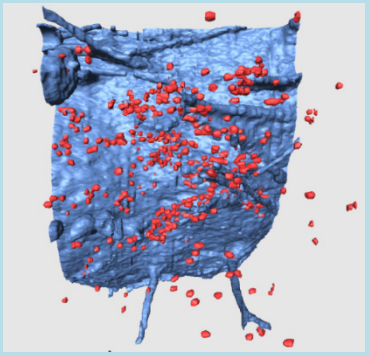






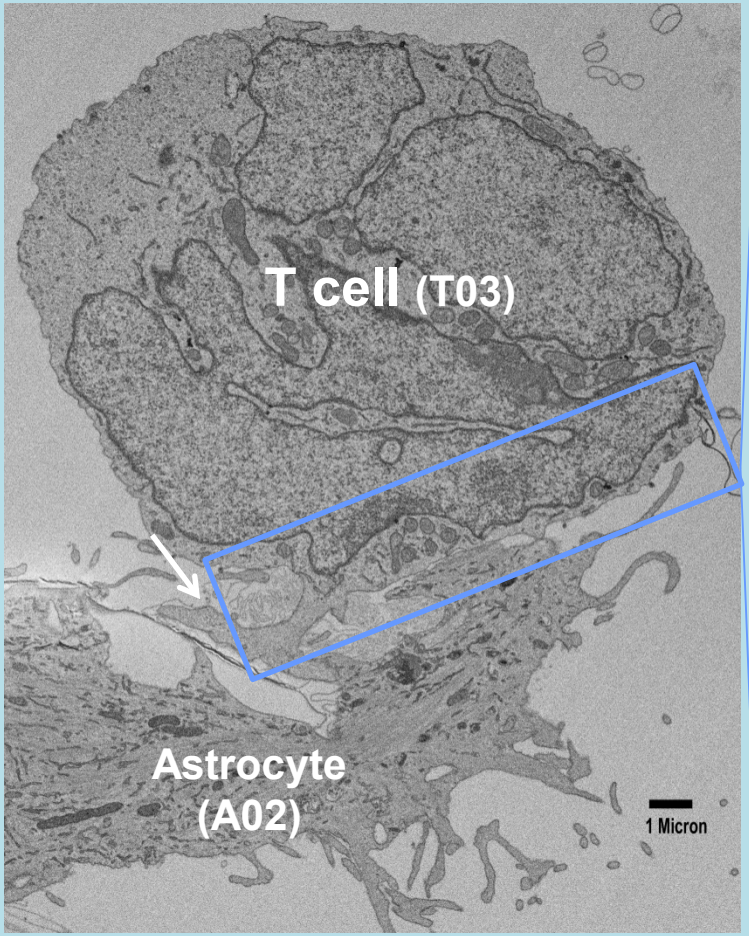






Do and Subramanium J Virol 2014

G



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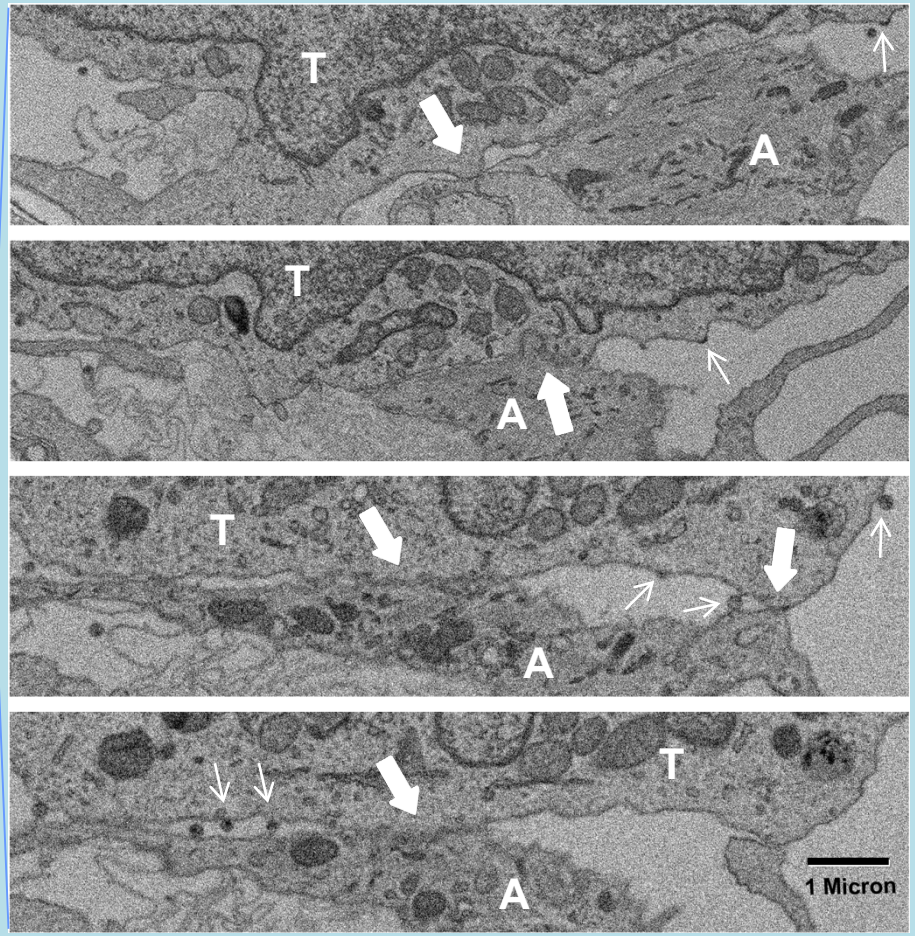

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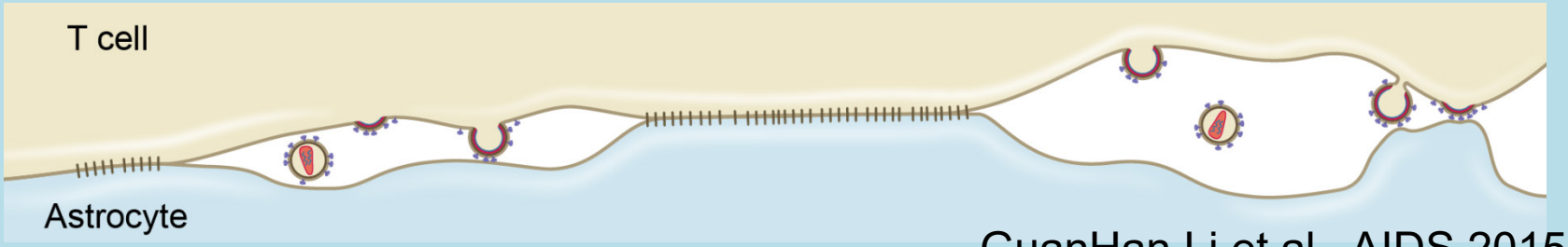


GuanHan Li et al., AIDS 2015

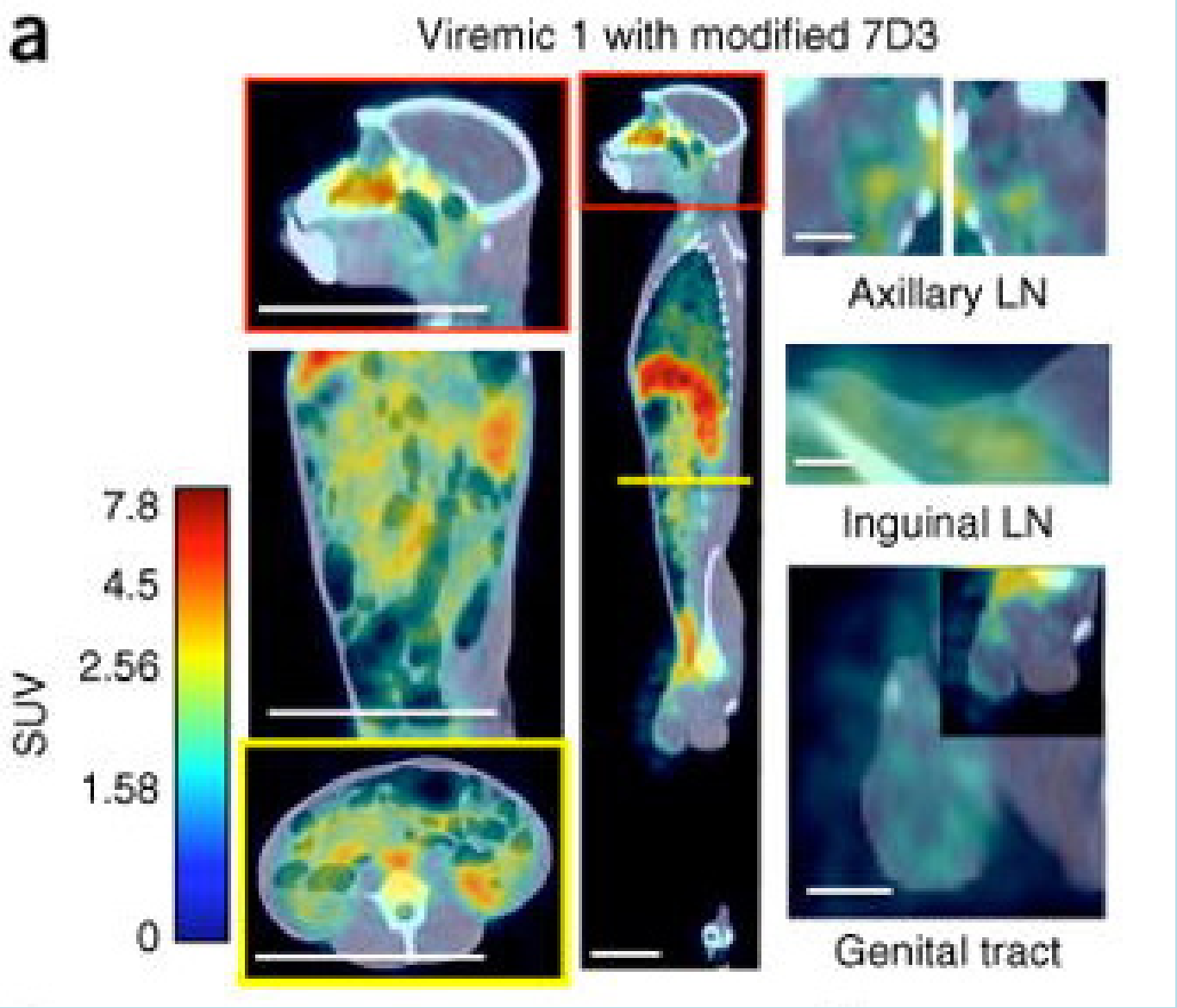
- Where is the virus in the brain?

- **What happens to the viral reservoir with prolonged antiretroviral therapy?**

- Can the reservoir be silenced?

- Can the reservoir be eliminated?

PET scan with monoclonal antibody to SIV for detection of viral reservoirs



Santagelo et al., Nat Methods 2015

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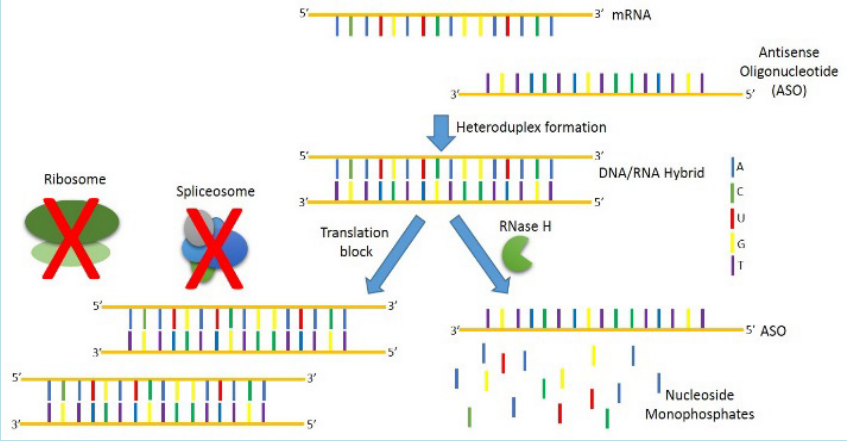
Antisense design and mechanism of action (Shock and Block)



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., unpiblished

- Where is the virus in the brain?
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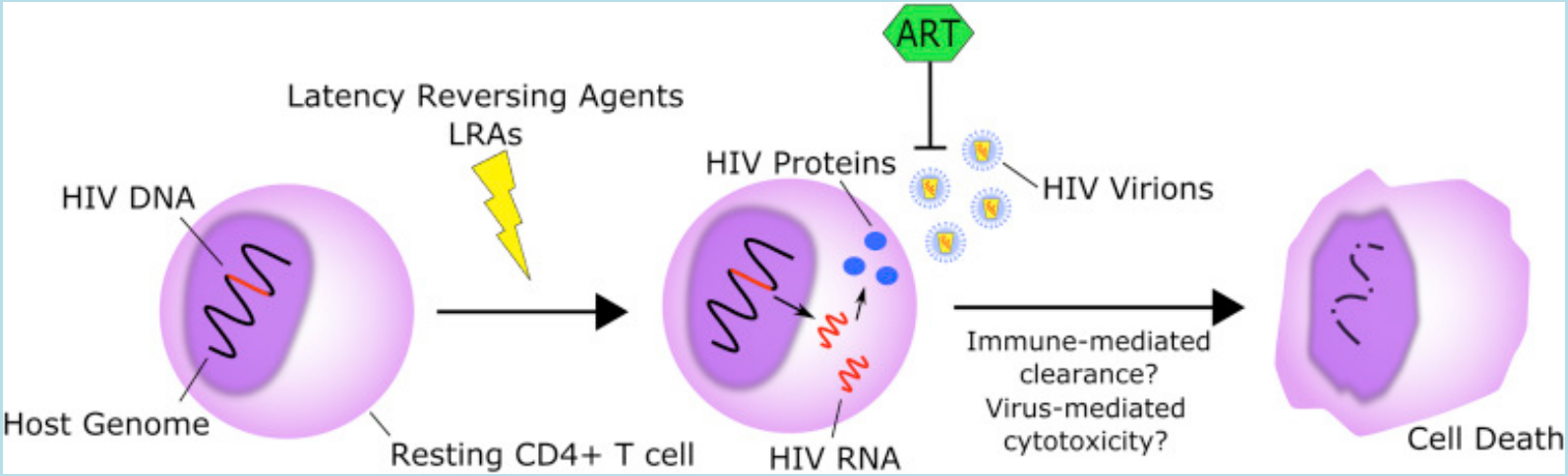
Immune therapies/ viral activation (Kick and Kill)

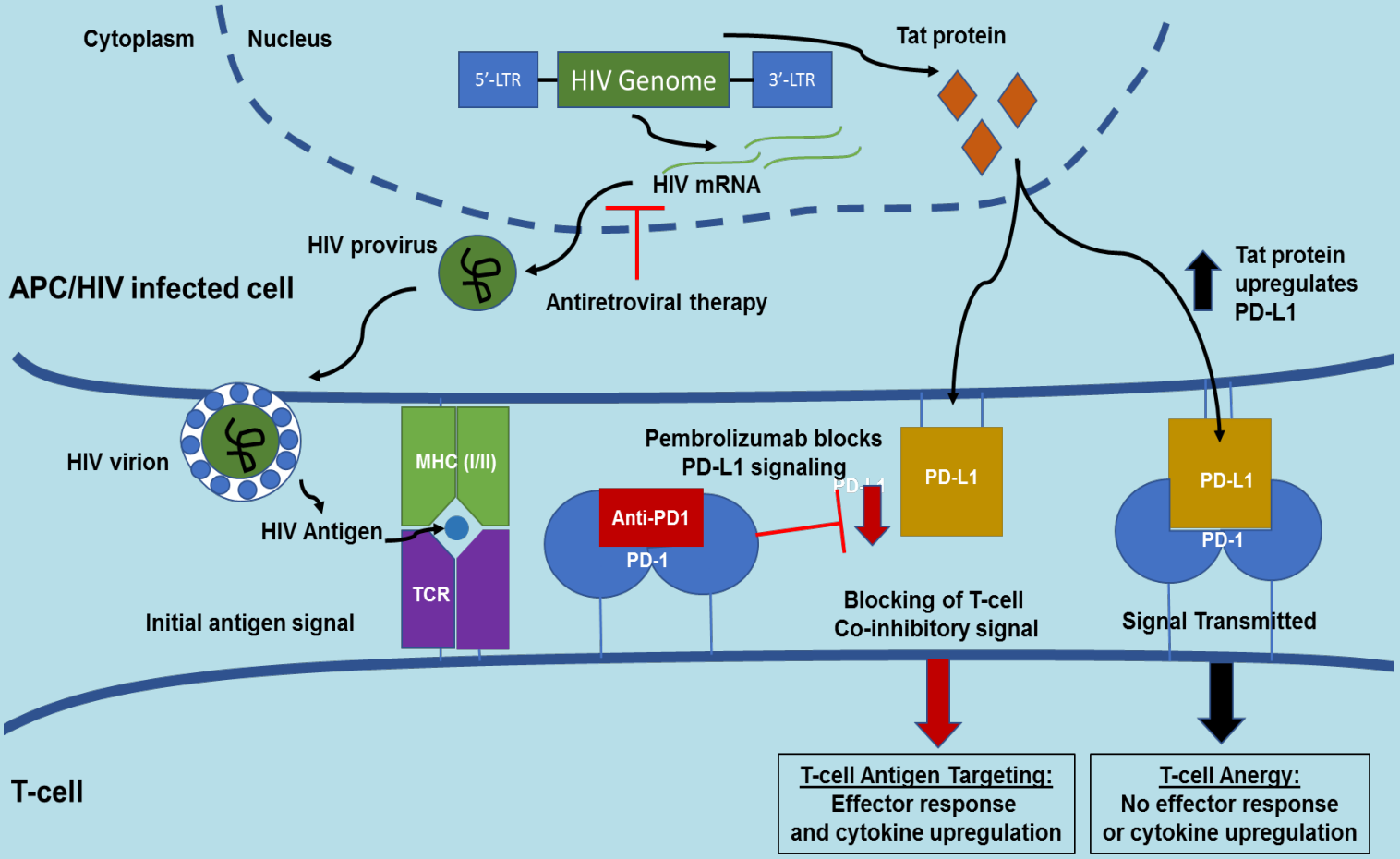
- Latency Reversal Agents (kick the virus)
- Therapeutic vaccines (kick the immune system)
- Checkpoint inhibitors (kick the immune system)
- Broadly neutralizing antibodies



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



Trial	Study Drug	Targets	Population	Phase
NCT03239899	Pembrolizumab	PD-1	CNS HIV-1 Reservoir	1
NCT03367754	Pembrolizumab	PD-1	HIV-1 with low CD4+	1
NCT02595866	Pembrolizumab	PD-1	HIV-1 + malignancies	1
NCT03304093	Nivolumab	PD-1	HIV-1 and NSCLC	2
NCT02408861	Nivolumab/Ipilimumab	PD-1/CTLA4	HIV-1 + malignancies	1
NCT03316274	Nivolumab	PD-1	HIV-1 and Kaposi's	1

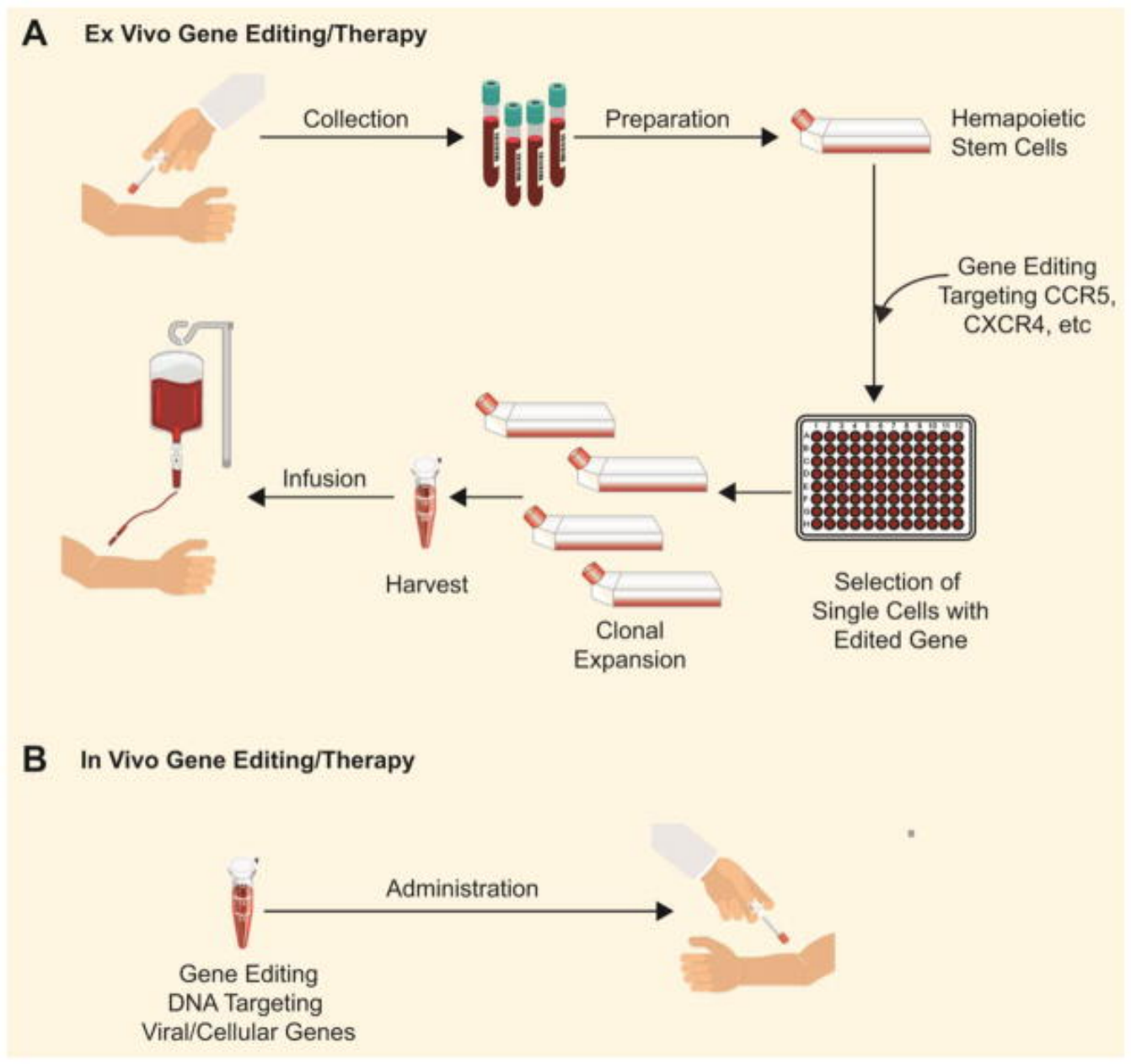
- Immune therapies/ viral activation
  - Latency Reversal Agents
  - Therapeutic vaccines
  - Broadly neutralizing antibodies
  - Checkpoint inhibitors
- Gene therapies
  - Genetic scissors
    - HIV receptor (CCR5 and CXCR4)
    - HIV proviral DNA

Genetic Scissors

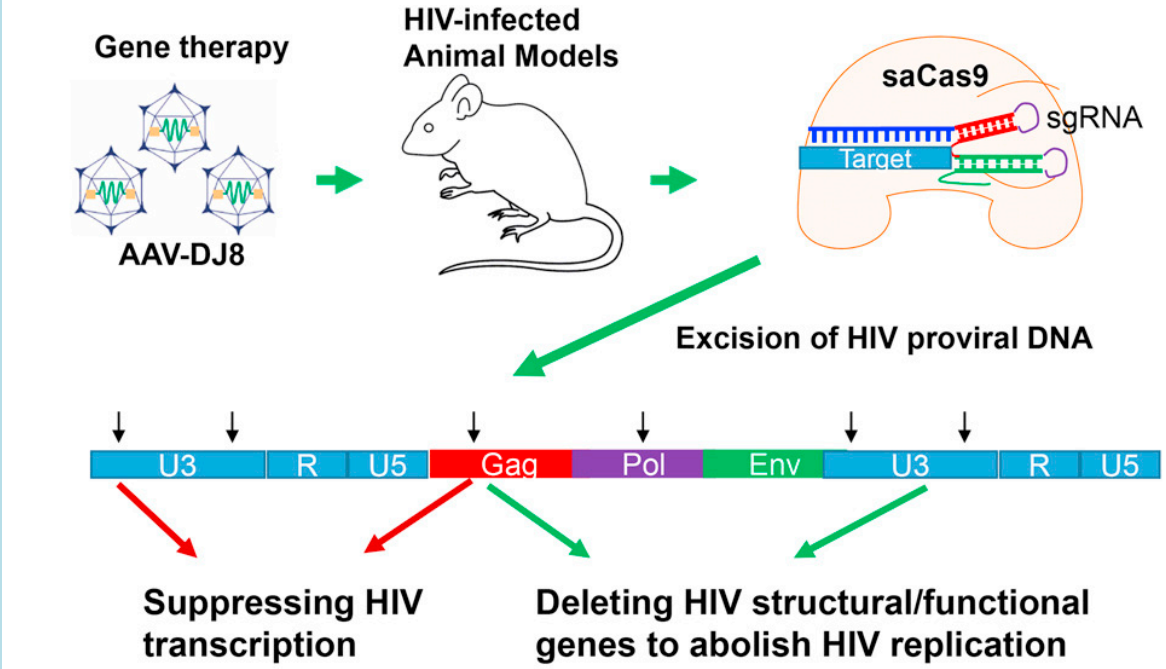
HIV receptors:
CCR5, CXCR4

HIV genome

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



Khalili et al., Cell Mol Life Sci. 2017



Yin et al., Mol Therapy 2017

Acknowledgements

Wenxue Li (Molecular biology)
Guanhan Li (Astrocyte infection)
Lisa Henderson (Antisense; Tat detection)
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Bryan Smith (HIV cohort)

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Fatah Kashanchi George Mason University (exosomes)
Sriram Subramanium NCI (scanning EM)