HIV-Eradication - should we be optimistic ?

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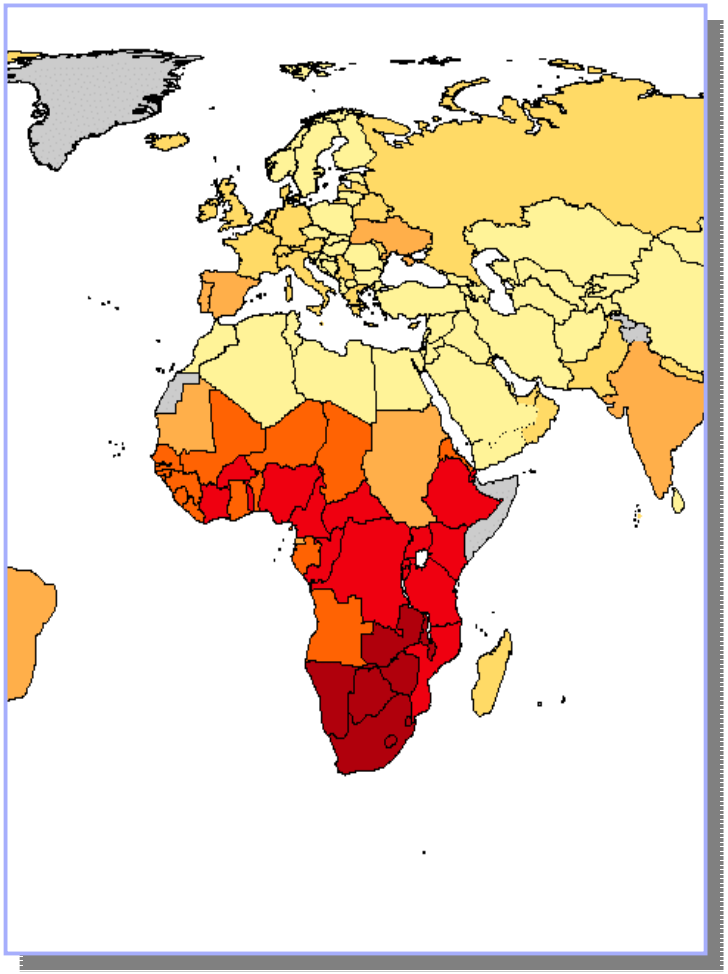
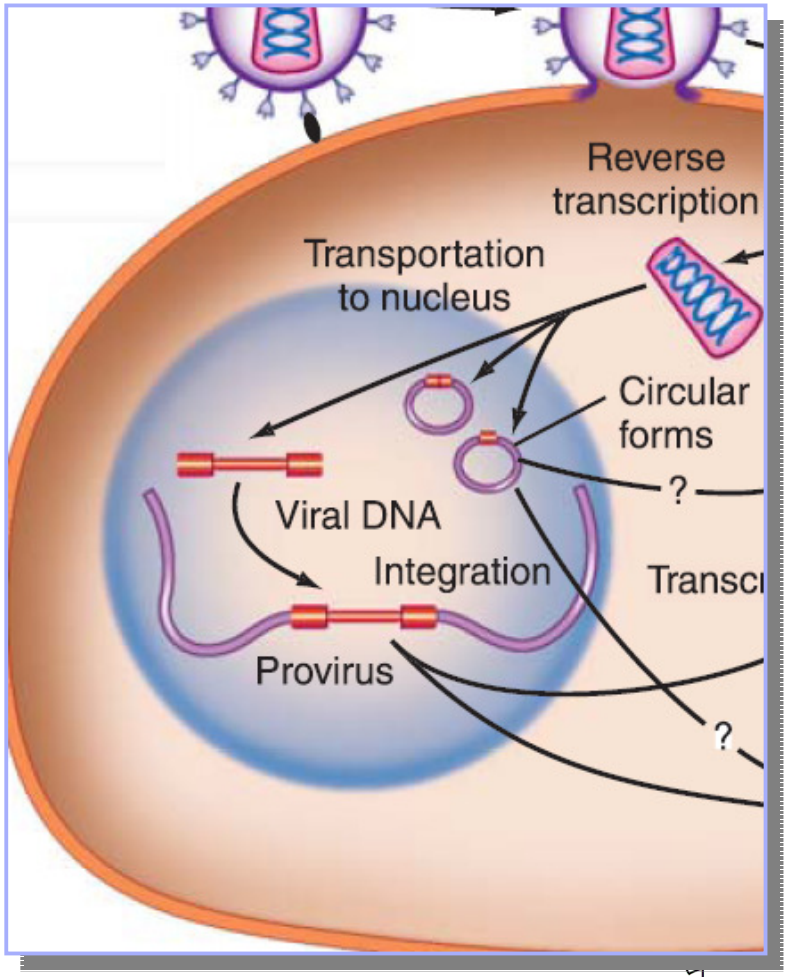
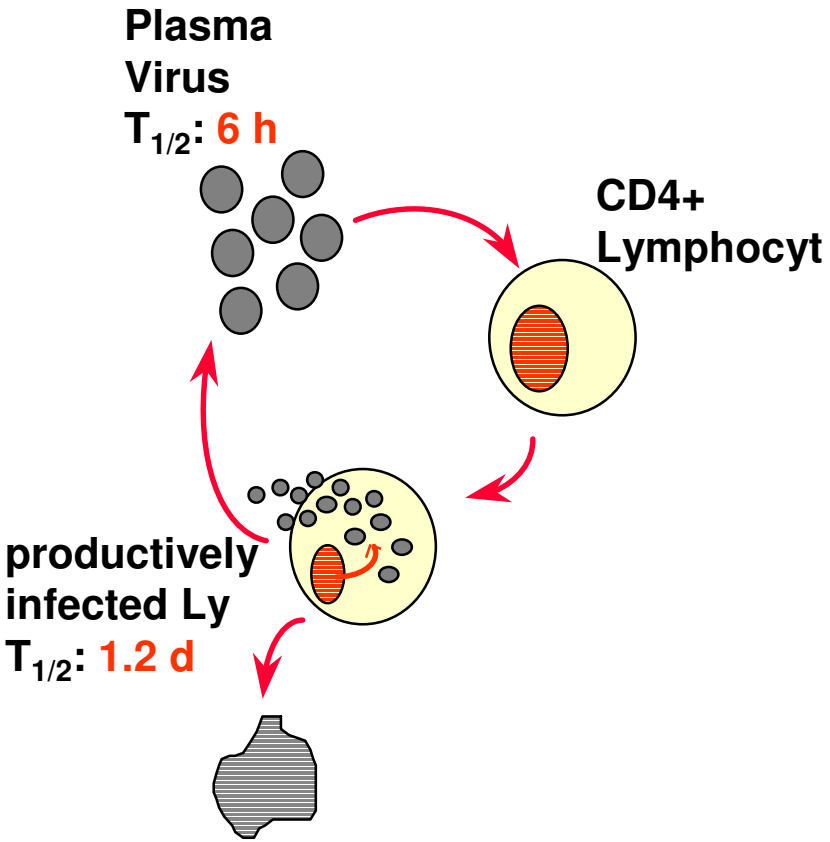
Eradication ?

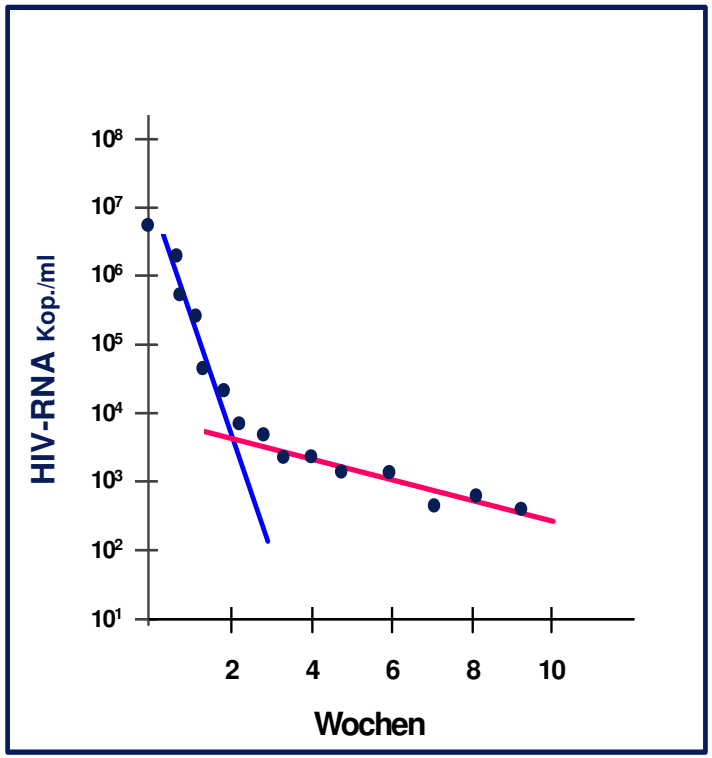




Success of HAART

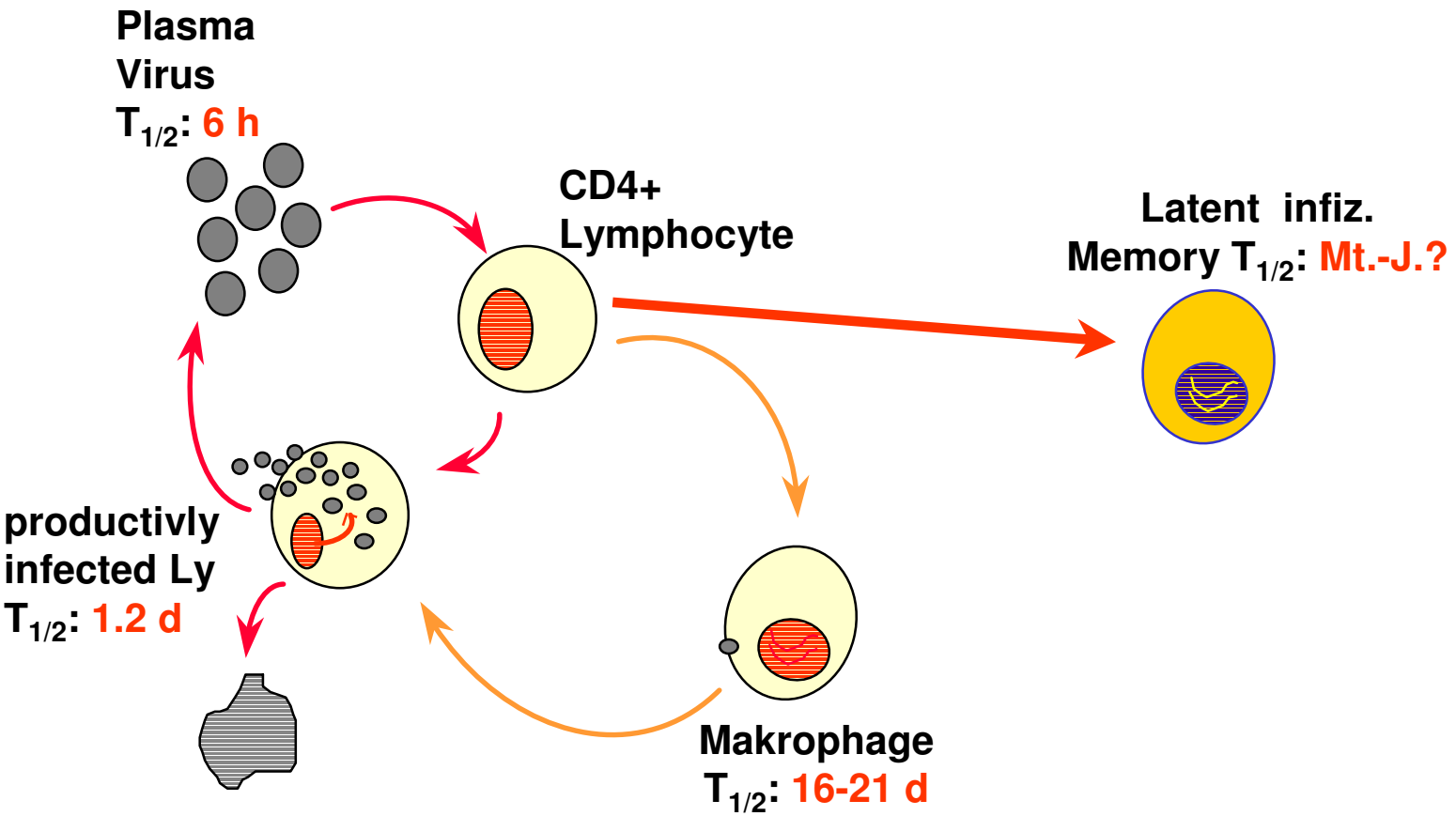
Hopes in 1996





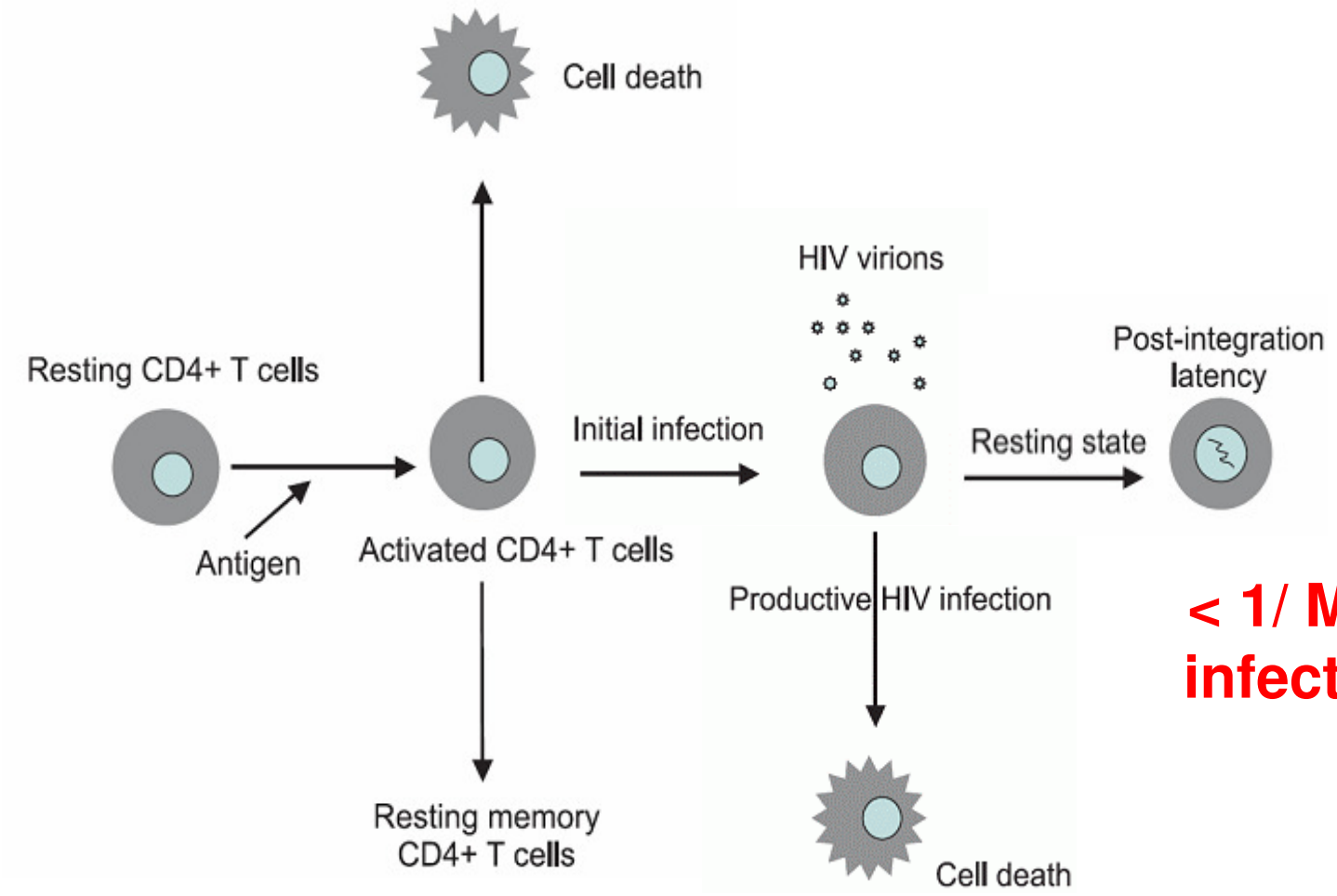
But....

Not as simple as that



The next problem to solve

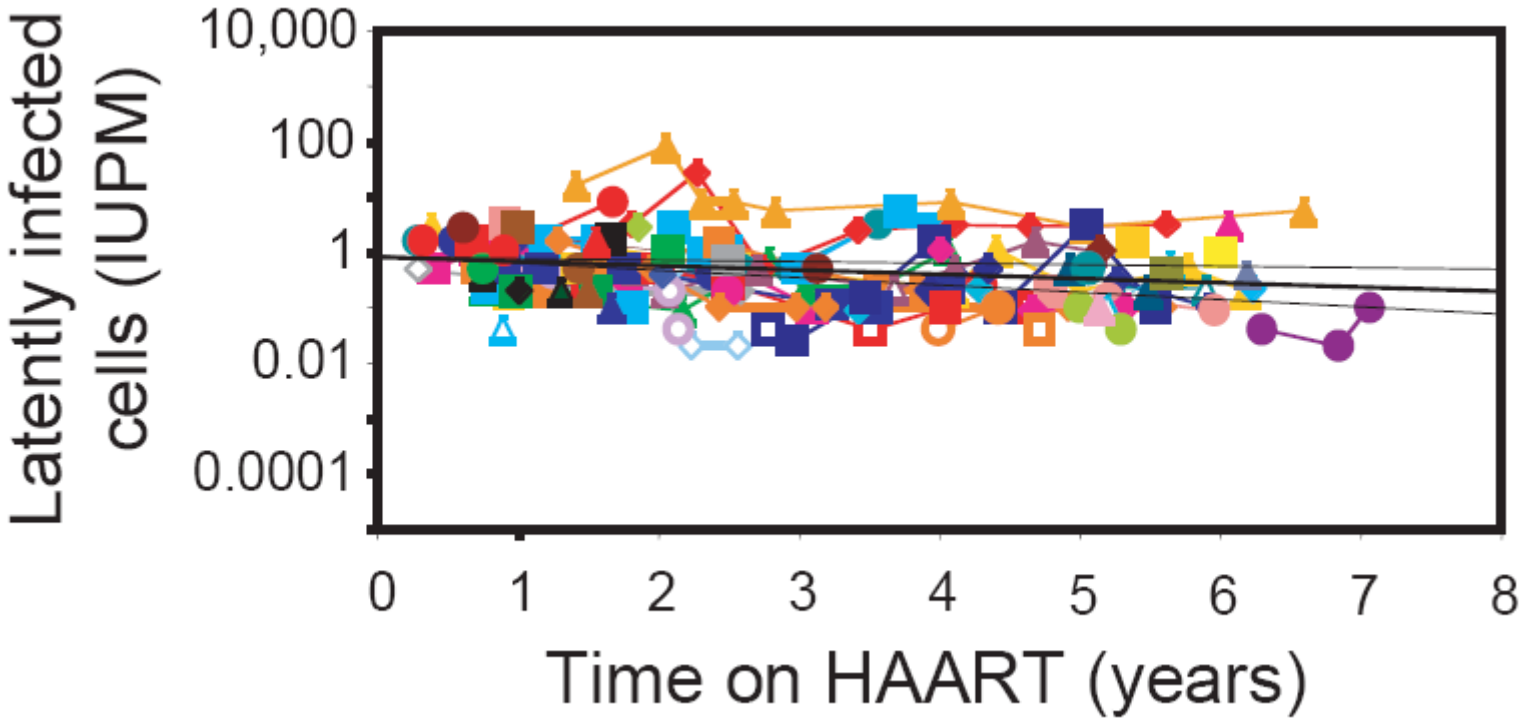
Long lived Memory T-Cells



< 1/ Mio infected

The end of the dream

Slow decay of latently infected pool



Here we show that even in treated patients who have had no detectable viremia for as long as 7 years, the reservoir decays so slowly ($t_{1/2}$ = 44 months) that eradication is unlikely.

Siliciano, Nat Med, 2003

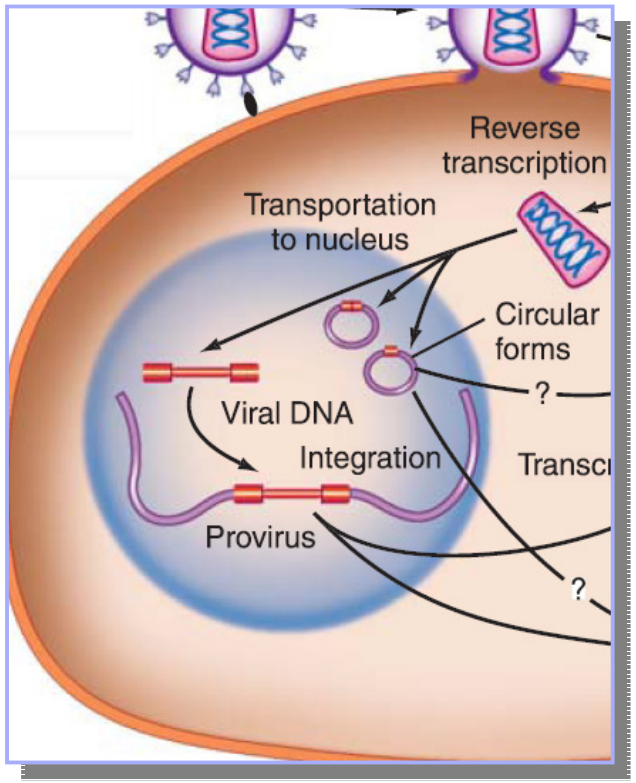
Latently infected resting T cells

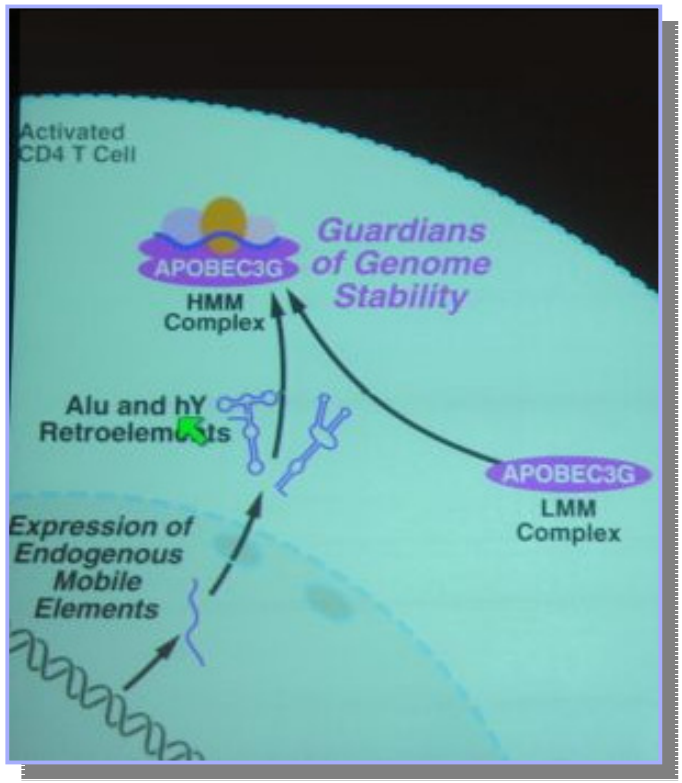
- Permit long term persistence
- HIV replication following Tx cessation
- Resistant to HAART
- Major obstacle to eradication

Provirus:

Let's get rid of the problem

Eradicate Provirus vs. Silencing Provirus





Strategies to attack latency

- **Activating latently infected cells + HAART**
  - Cytokines, LPS, Superantigens
  - Il-2 (Kulkosky, 2003)
  - Il-2 +OKT3 (Stelbrink 2002)
- **Cytotoxic targetting of latent cells**
  - Requires specific target on infected cells
  - Other infected cells or compartments might limit approach

Too toxic, non specific

Activating NFkB

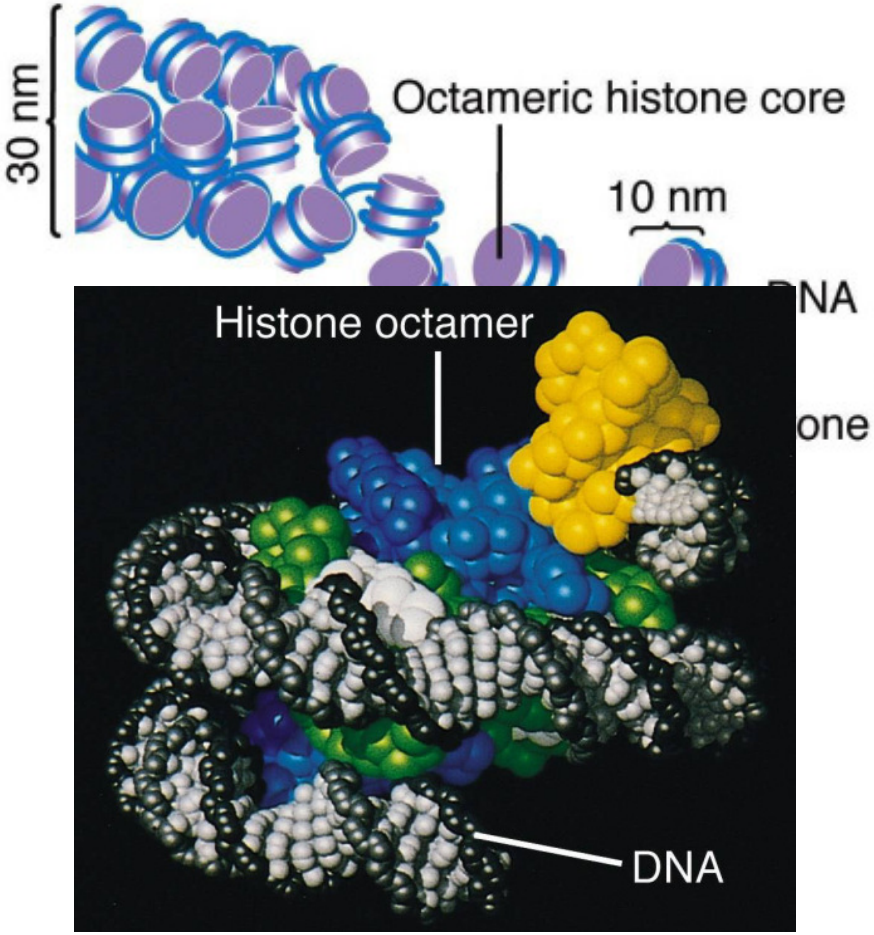
Prostratin – Homalanthus nutans

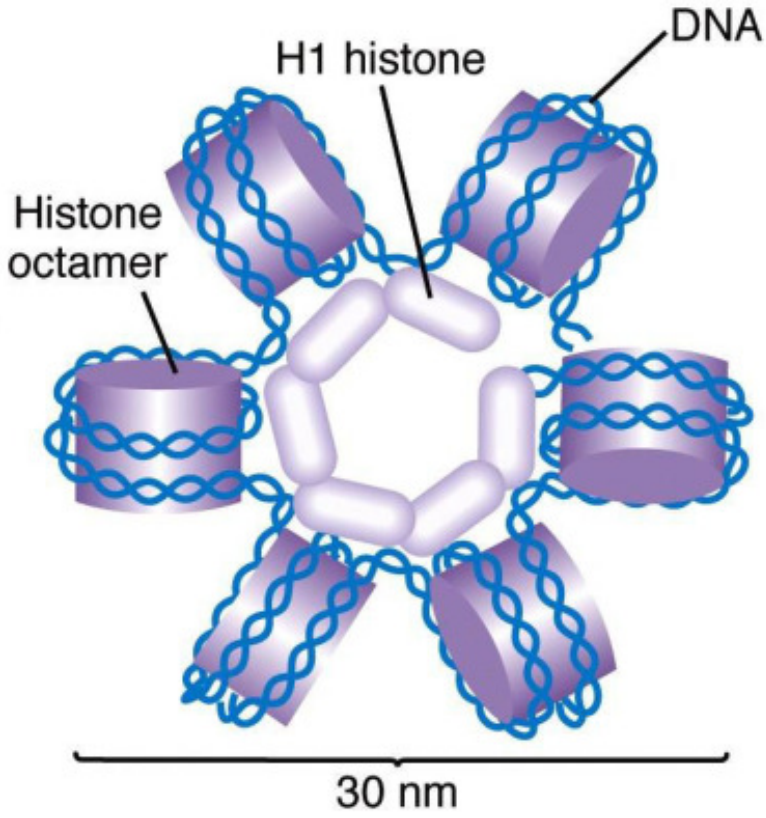
- (deoxy-)Phorbol Ester (PHA)
- Protein kinase C activator
- Does not induce tumor formation
- Activates NF-κB
- Activates transcription of HIV

Drug News Perspect 18(8), October 2005

Ok, replicating HIV is no problem, but..

What Determines Latency ?

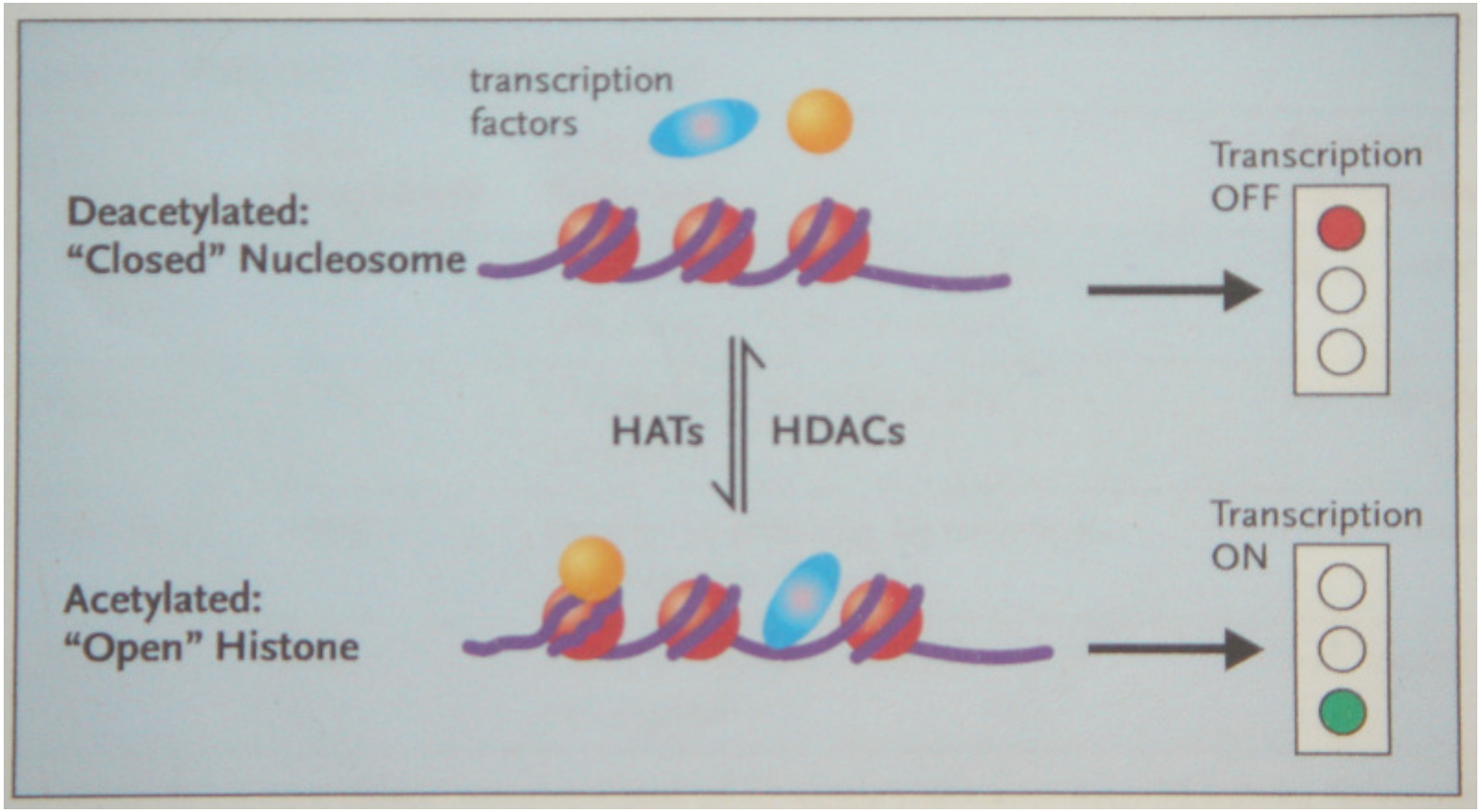




Griffiths et al, 2004

Accessing the target

Chromatin remodelling



Margolis, The PRN Notebook, December 2005

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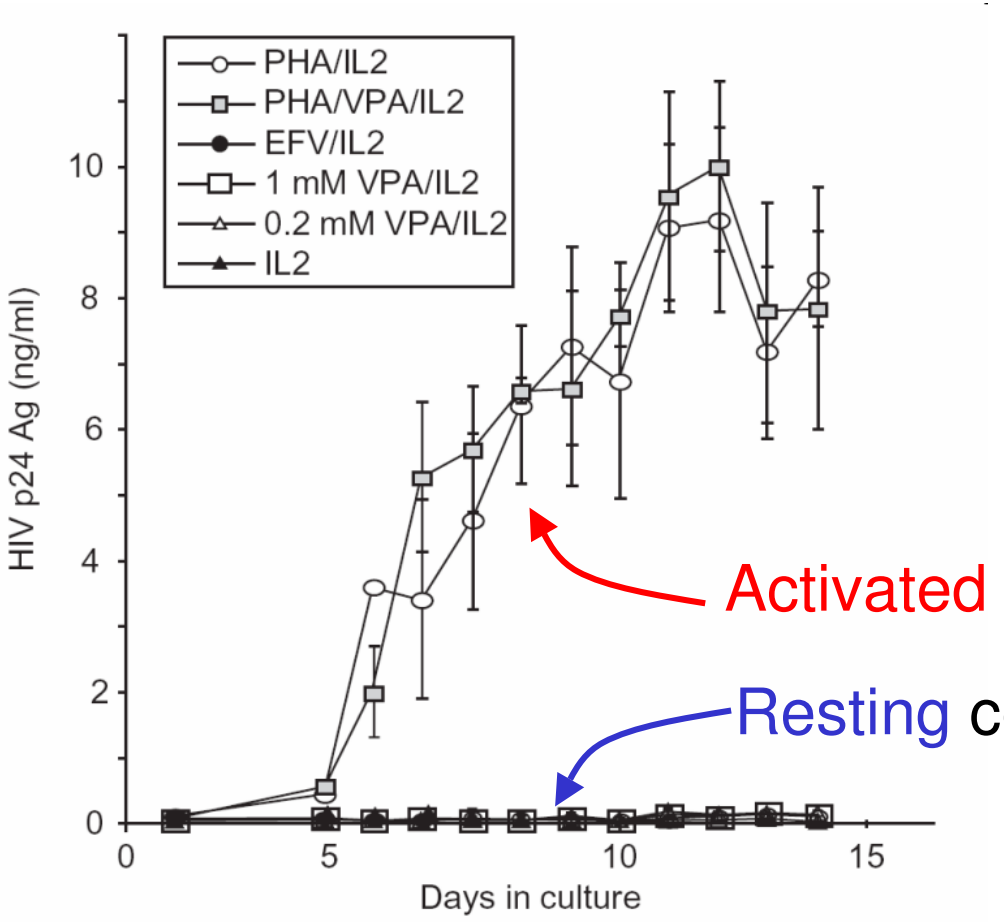
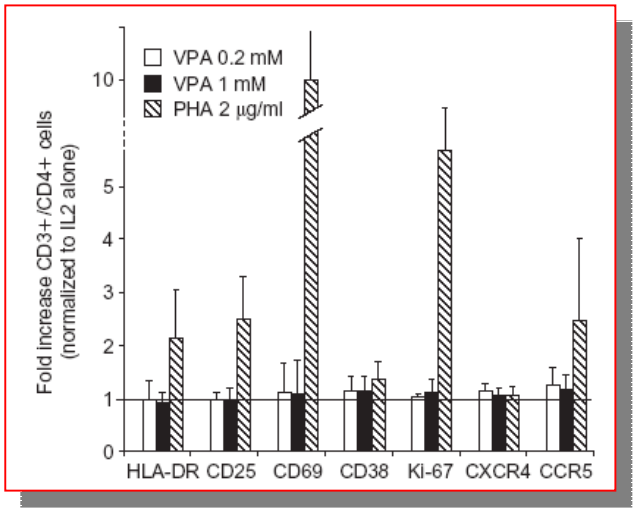
Valproate

No Stimulation of HIV infection





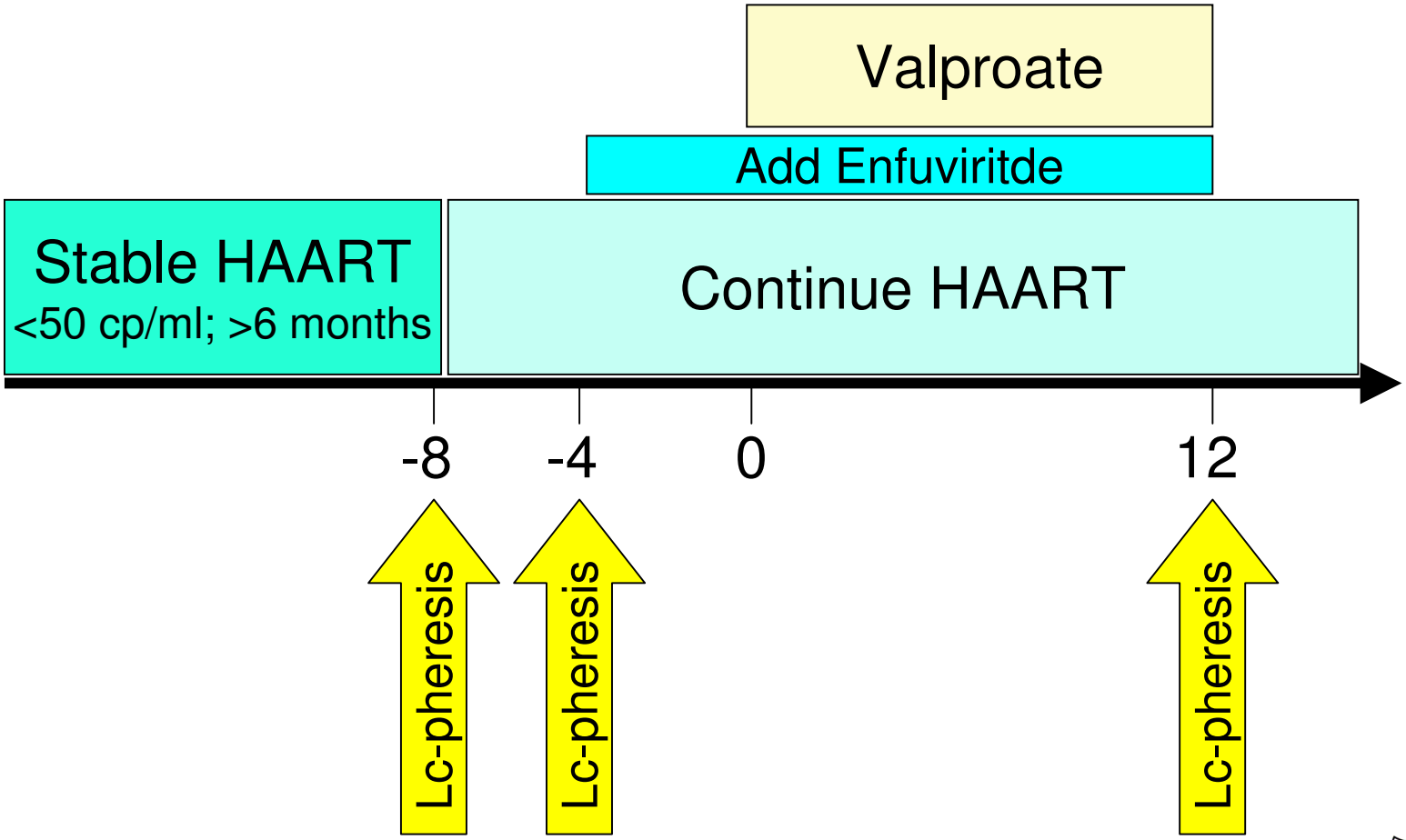
Activated cells (+/- VPA)

Resting cells (+/- VPA)

Ylisastigui et al, AIDS 2004

Proof of concept study

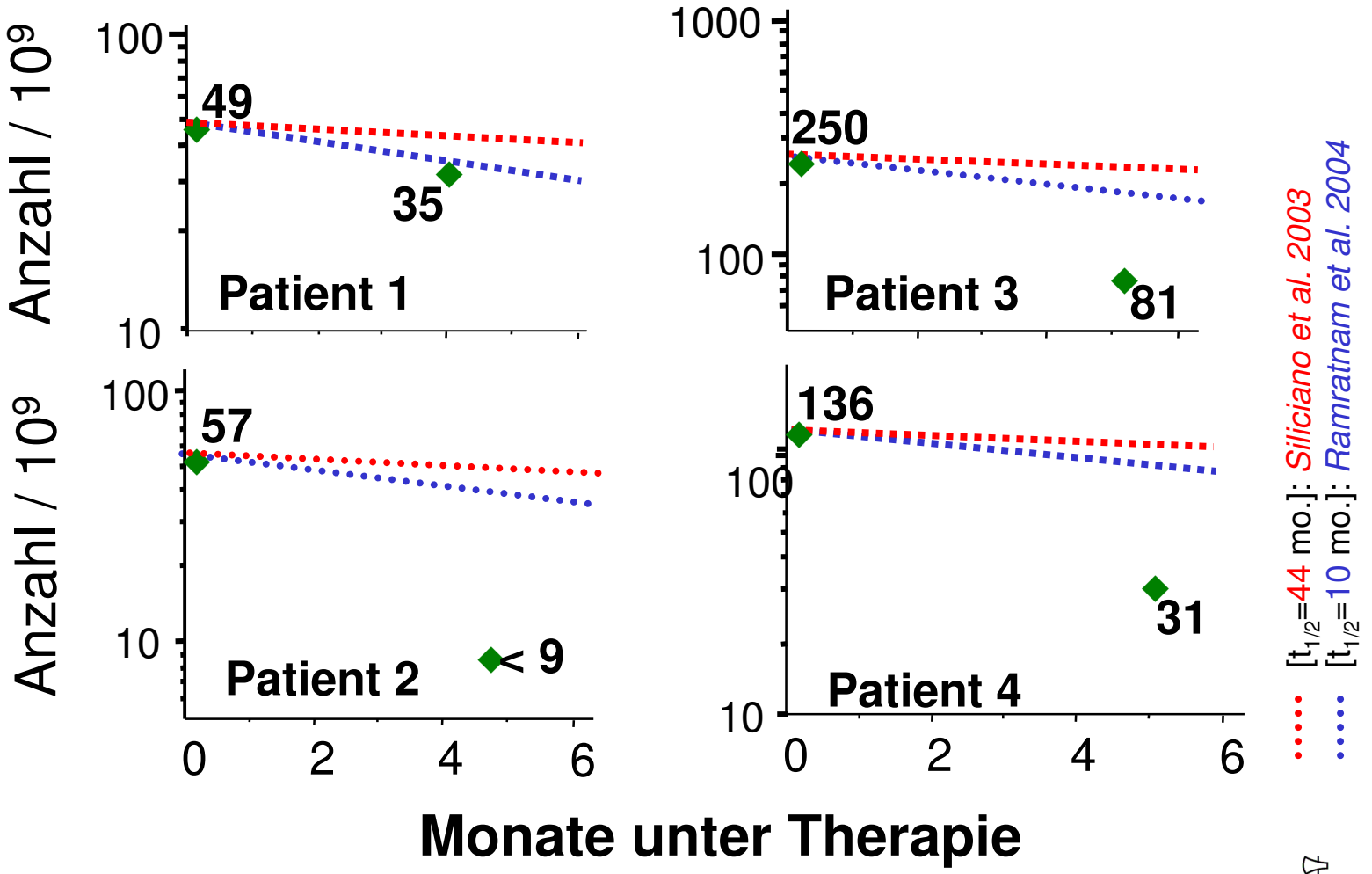
Study Design



Lehrman et al, Lancet 2005

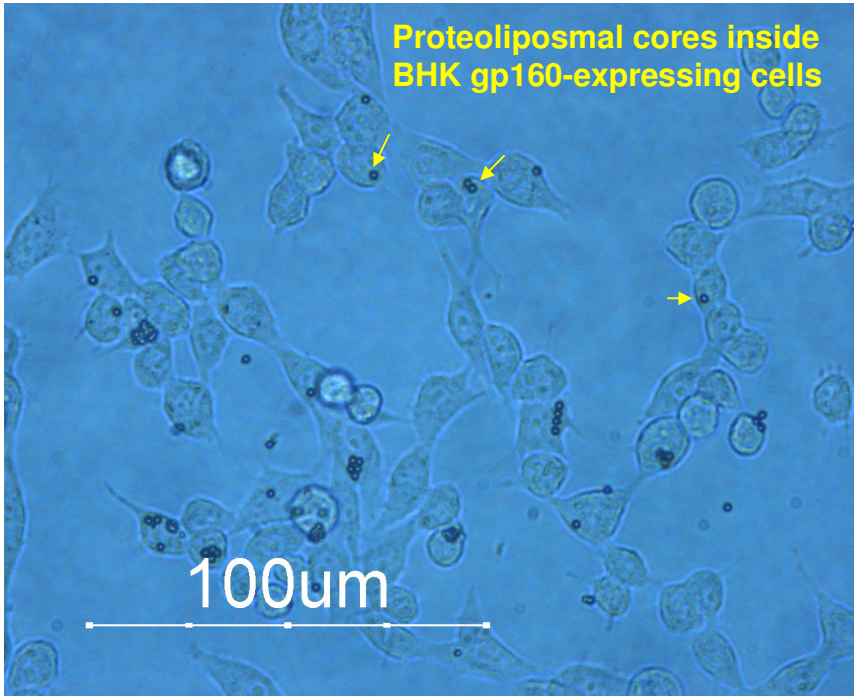
Pilot study

Decay of latently infected cells ⇑



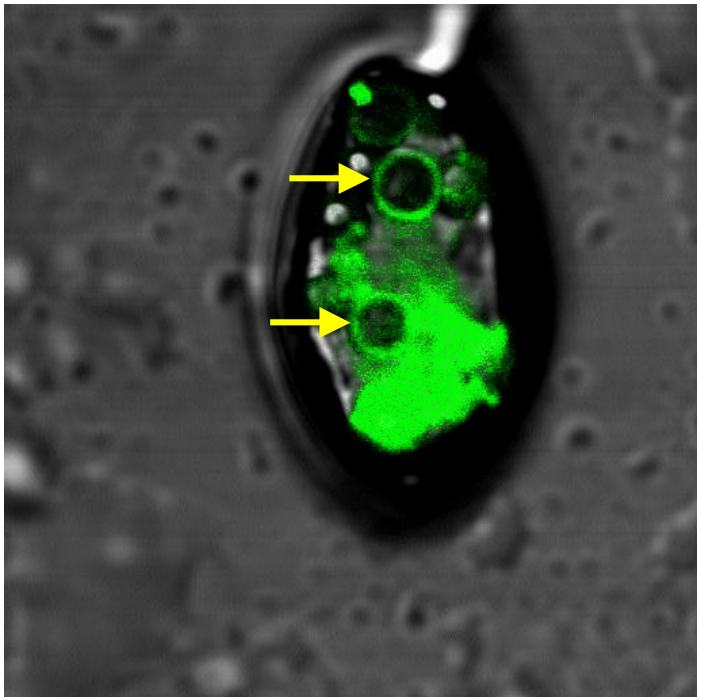
Lehrman et al, Lancet 2005

Specific Fusion Between CCR5-conjugated proteo-liposomes & gp160-expressing Cells



Liposomes fused with BHK gp160-expressing cells.

Bronshtein, IAS 2006, Toronto LB304



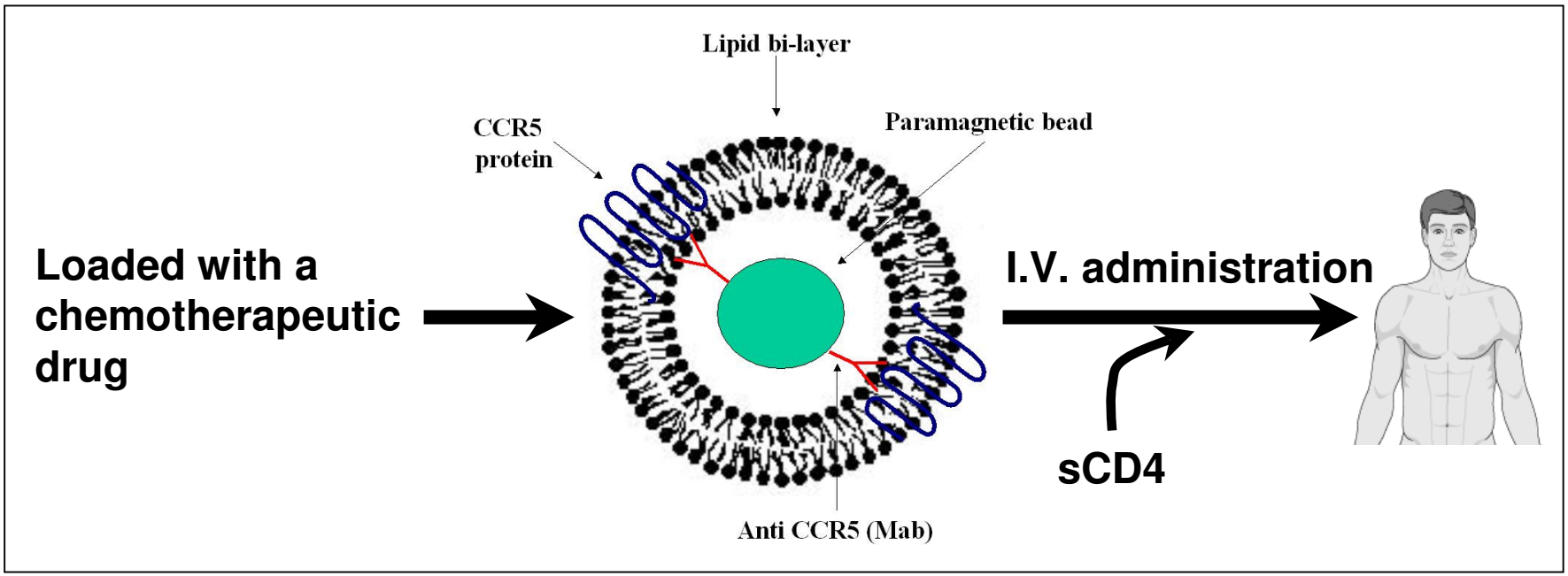
CCR5-conjugated proteol-liposomal cores localization inside BHK gp160-expressing cells.

New technologies

Proteo-liposomes to target cell

Long term goal

To develop CCR5 conjugated proteo-liposomal constructs for targeted drug delivery & inactivation of free virions



Future steps

- Improve targeting systems
- Simplify methods to count latently infected cells
- Define mechanism of nuclear retention
- Understand silencing

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Eradication

Should we be optimistic?

- Of course, we should!
- We can handle replicating virus
- Let’s understand latency
- Kick the dormant HIV out of the cell
- Design target systems
- Don’t forget silencing !

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