“Towards an HIV Cure”
Global Scientific Strategy

1st Stakeholders Consultation Meeting

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International AIDS Society
Stronger Together

Melissa Churchill.
Ph.D LLB

towards an HIV cure
people focused
science driven

Definitions

- The definition of a "functional HIV cure" means:-undetectable viremia without ART;-no disease progression;-no CD4 loss;-lack of HIV transmission

- Eradication/Cure: complete eradication of HIV infected cells from the body

Cure Vs Functional Eradication

Cure	Functional Cure/Remission
Infectious Diseases model	Cancer model
Elimination of all HIV-infected cells	Long term health in absence of HAART
HIV RNA < 1 copy/ml	HIV RNA < 50 copies/ml
Sterilising cure (Eradication)	Functional cure

Barriers to cure

- Latently infected T-cells
- Residual viral replication
- Anatomical reservoirs

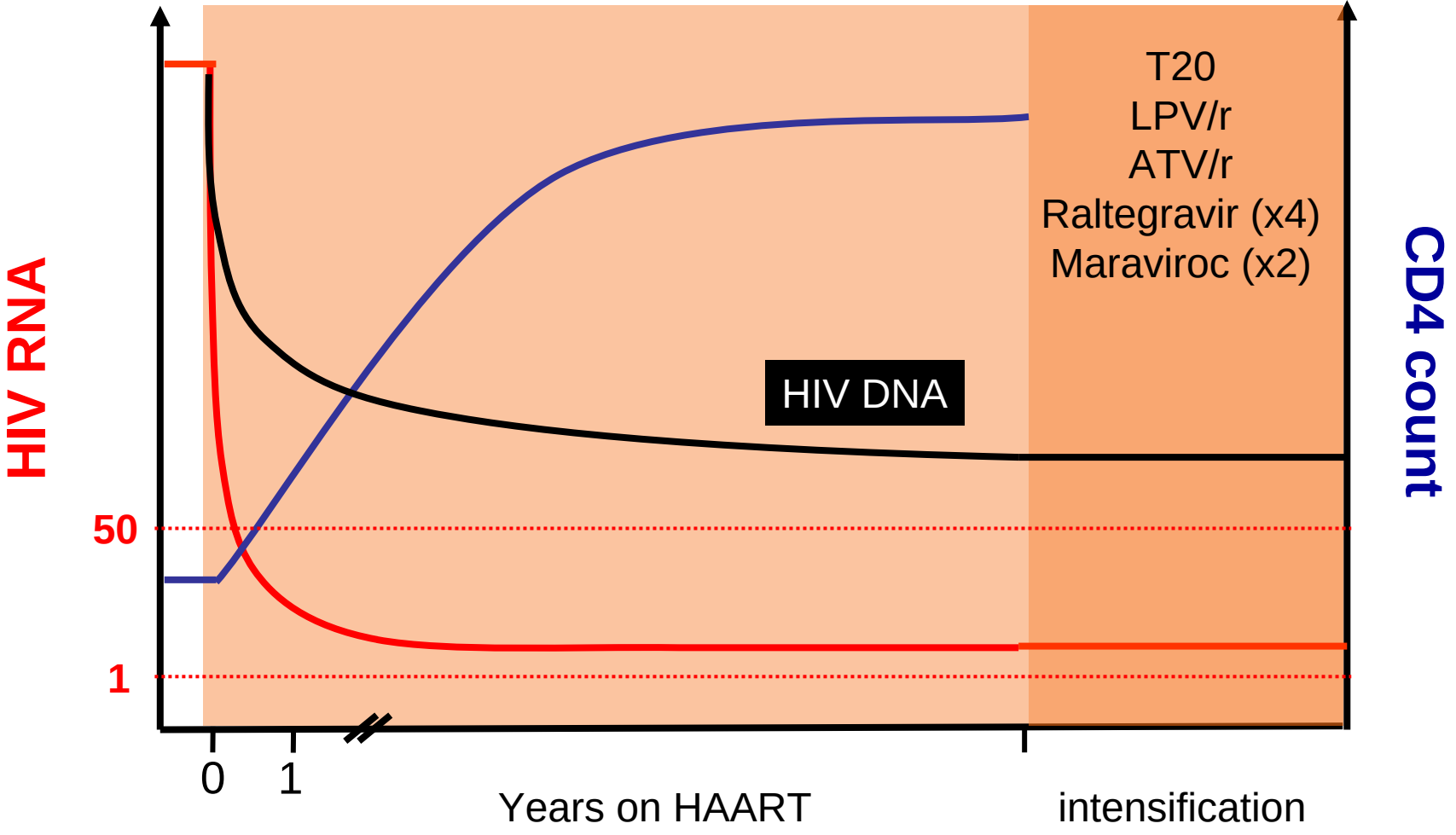
Current Strategies aimed at eradication/functional cure

- Identification of reservoirs;
  - establishment
  - regulation
  - persistence

Strategies for cure

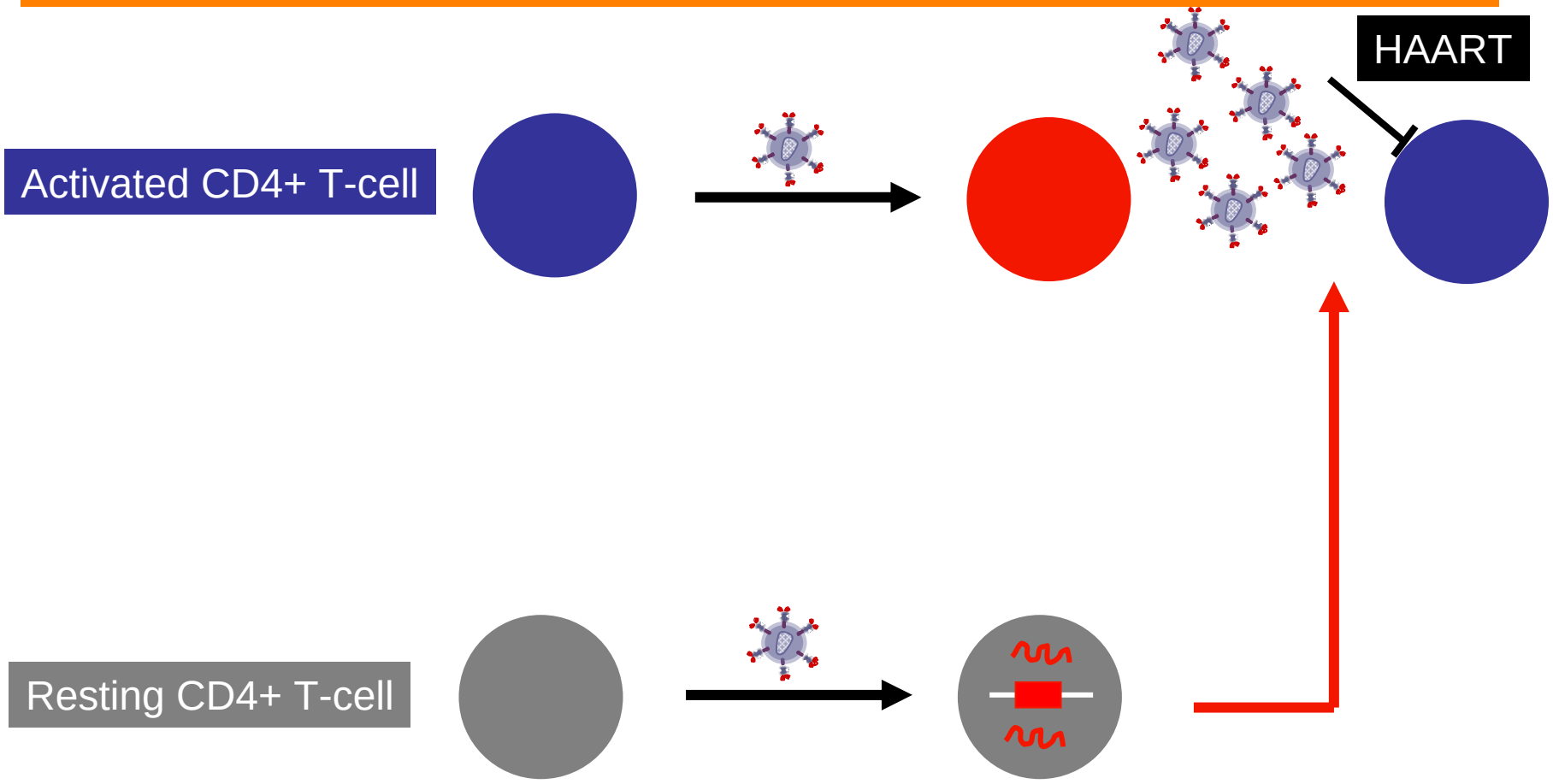
- Starting ART very early before reservoirs are fully established
- Eliminate residual virus replication by HAART intensification
- Eliminate latently infected cells
- Maintaining latency to keep proviral DNA permanently silenced
- Make cells “resistant” to HIV
- Enhance HIV-specific immunity

Eliminating viral replication: treatment intensification

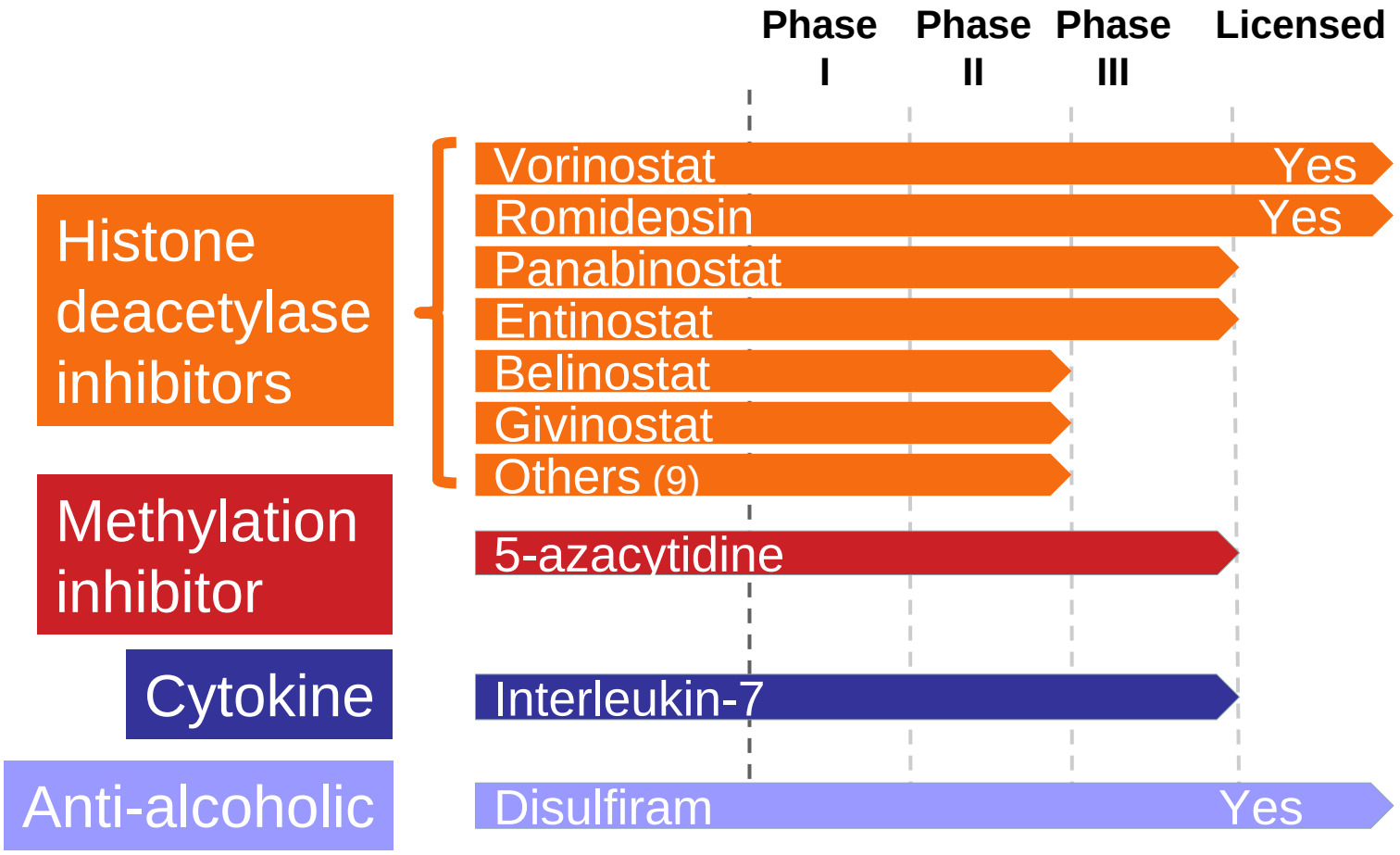


Dinoso et al., *Proc Natl Acad Sci U S A*, 2009. 106(23): 9403-8; McMahon et al., *Clin Infect Dis*, 2010. 50(6): 912-9; Ghandi et al., *J Infect Dis*. 2010.201(2):293-6 and CROI 2011 ; Buzon et al., *Nat Med*, 2010 16: 460; Ghandi et al., *Plos Med* 2011; Yukl et al., *AIDS* 2010; Hatano et al., *J Infect Dis* 2011

Eliminate latently infected T-cells: activate latent HIV



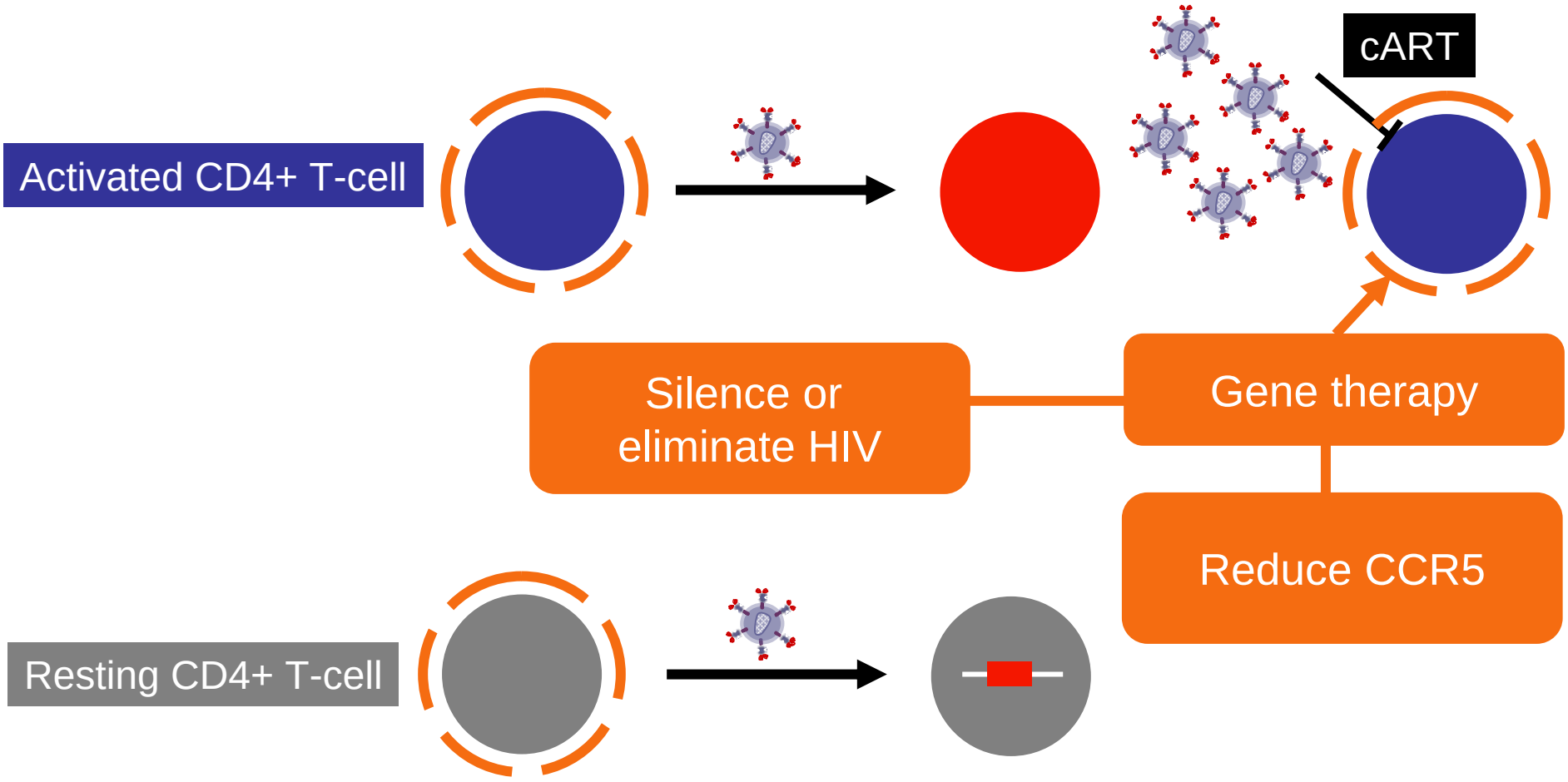
Licensed drugs that activate latently infected cells



* Total number of trials listed on http://clinicaltrials.gov (July 2011)

Prince et al. *Clin Canc Res* 2009;15:3958; Contreras et al, *J Biol Chem* 2009; 284: 6782; Archin et al *AIDS Res Hum Retroviruses* 2009;25:207; Xing et al., *J Virol*; 2011;85(12):6060-4; Friedman et al., *J Virol*. 2011;85(17): 9078-89; Matalon et al., Mol Med. 2011 May-Jun;17(5-6):466-72 Saleh et al., *Retrovirology* 2011 (in press)

Make cells “resistant” to HIV: gene therapy



Amado et al., *Hum Gene Ther* 2004: 15:251-62; An et al., *PNAS* 2007: 104:13110-5; Digiusto et al., *Science Transl Med* 2010; 2:36; Holt et al., *Nature Biotechnol* 2010;28(8):839-47; Lalezari et al., 18th CROI, Boston, Feb 2011 abstract 46; Tebas et al., 18th CROI, Boston, Feb 2011 abstract 165

Scientific challenges

- Multiple barriers to eradication meaning a **combination approach** will be likely
- Better **in vitro** and **animal models** to evaluate new strategies, alone and in combination
- **Drug development** to increase specificity for latently infected cells and/or enhanced tissue delivery
- Better understanding of the **immune system** in controlling low level viral replication

Clinical and implementation challenges

- **Universal access** to cART must remain a top priority
- PLWHA on cART are **doing well** so low threshold for toxicities related to an intervention
- Clinical **endpoints** for successful “eradication” unclear. When will a treatment interruption be OK?
- Multiple **unknowns with gene therapy**: uncertain safety of delivery vectors and zinc finger nucleases