HIV cure research: current strategies and challenges

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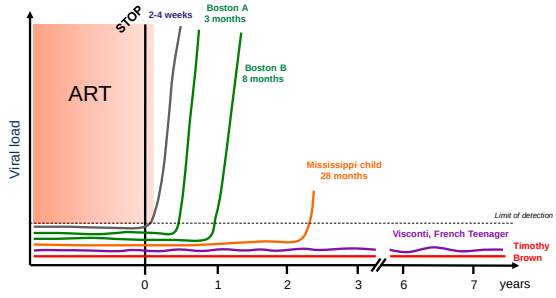
Sustained remission off ART is rare but achievable



Hütter et al. *N Engl J Med* 2009; Persaud et al. *N Engl J Med* 2013; Luzuriaga et al. *N Engl J Med* 2015; Henrich et al. *Ann Intern Med* 2014; Saez-Cirion et al. *Plos Path* 2013; Saez-Crion et al., *IAS 2015*, Vancouver 2015;.

Barriers to cure

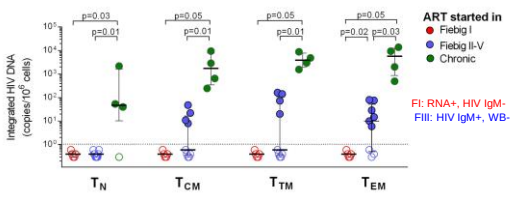
- Latently infected T-cells
- Residual viral replication
- Anatomical reservoirs

current **strategies** to eliminate latently infected cells

Eliminating latently infected cells

- Treatment during acute infection
- "Activating" latent infection
- Boosting HIV-specific immunity
- Allogeneic transplantation
- Reducing homeostatic proliferation(?)

Early ART limits persistence of HIV reservoir in all CD4+ T cell subsets



After 2 years of ART, integrated HIV DNA is undetectable in all subsets of Fiebig I individuals.

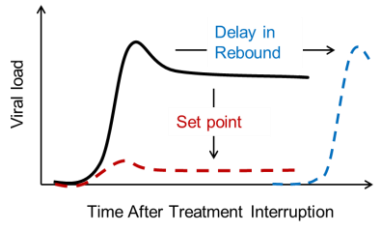
Nicolas Chomont and Jintanat Ananworanich

Post treatment control is rare following ART in acute infection

Published studies	n
Optiprim (Cheret A, Lancet ID 2015)	90
Spartac (Stohr W, Plos One 2013)	165
VISCONTI (Saez-Cirion A, Plos Pathogens 2013)	14
Swiss HIV Cohort Study (Gianella S, Antiviral Therapy 2011)	32
Primo-SHM (Grijsen ML, PLoS Medicine 2012)	173
ANRS CO6 PRIMO (Goujard C, Antiviral Ther 2012)	164
CASCADE (Lodi S, Arch Intern Med 2012)	259

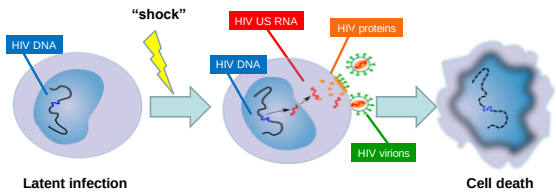
Ananworanich, Keystone Symposium on HIV cure, April 2015

We need a biomarker that can predict "cure" or "remission"



- **HIV DNA**: SPARTAC, Swiss HIV Cohort Study
- **CA-US HIV RNA**: ACTG ATI Cohort Study
- **PD1 expression** on CD4 and CD8 (prior to ART): SPARTAC

Activating latent infection



Latency reversing agents: many now in clinical trials

Epigenetic modifiers
HDACi
Methylation inhibitors
Methyltransferase inhibitor
Bromodomain inh

TLR agonists
TLR7 (GS9620)
TLR3 (polyICLC)
TLR 9
TLR4

Activators of NF-kB
Prostratin
Bryostatin
Ingenol B / PEP 005
SMAC mimetics

Other
Disulfiram
Quinolines
IL-15

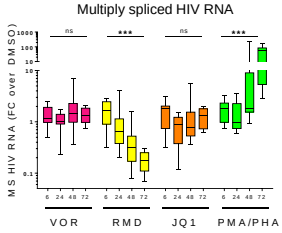
HDACi activate HIV latency in vivo

HDACi	Clinical development	HIV latency	US HIV RNA	Plasma RNA	HIV DNA
Vorinostat	Licensed (2006) CTCL	Single dose[1] Intermittent[2] Continuous[3]	↑	↔	↔

[1] Archin et al., *Nature* 2012; [2] Archin et al., *J Infect Dis* 2014; [3]Elliott J et al., *Plos Pathogens* 2014; [4]Rasmussen et al., *Lancet HIV* 2014; [5]Sogaard et al., *Plos Pathogens* 2015 (in press)

CTCL – cutaneous T-cell lymphoma

Adverse effects on HIV RNA splicing following activation with potent HDACi



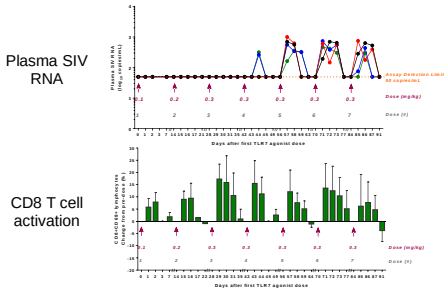
Changes over time for each LRA: Kruskal-Wallis; *** $p \leq 0.001$; **** $p \leq 0.0001$

Talia Mota

HDACi have adverse effects on HIV-specific immunity (in vitro) and host gene changes

Jones et al., *Plos Path* 2014; Elliott et al, *Plos Path* 2014

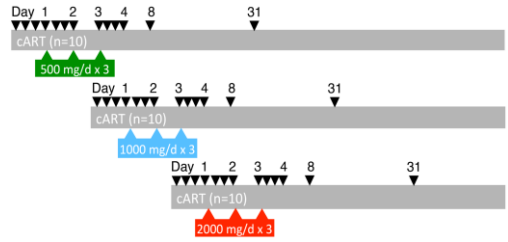
TLR7 agonist activates HIV latency in SIV infected macaques



Human clinical trial of a similar TLR7 agonist currently enrolling

Whitney et al., *CROI 2015*, Seattle 2015

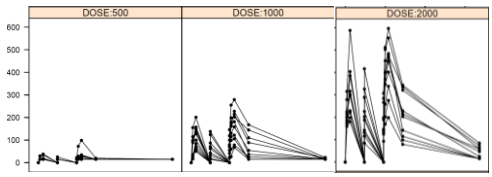
Disulfiram dose escalation study to activate HIV latency



DARE

Elliott JH et al., CROI, Seattle 2015. Abstract 428LB

High dose disulfiram increases cell associated and plasma HIV RNA

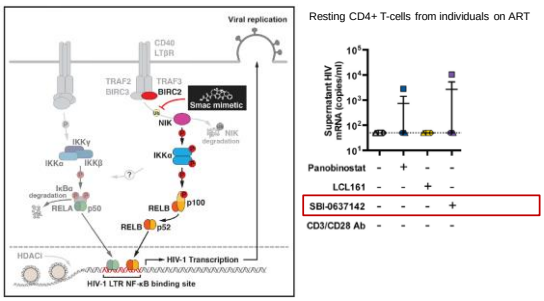


A modest (2 fold) but significant increase in cell associated and plasma HIV RNA with disulfiram 2g/day

DARE

Elliott JH et al., CROI, Seattle 2015. Abstract 428LB

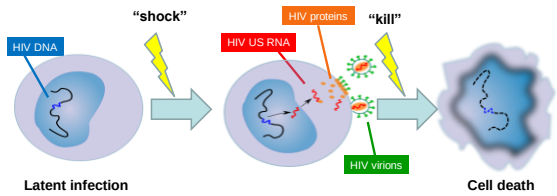
Activation of non-canonical NFKB pathways: synergism with HDACi



Pache et al., Cell Host Microbe 2015

Boosting HIV-specific immunity

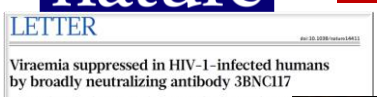
"shock (tickle) and kill"



"reduce and control"

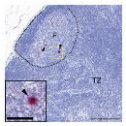
Therapeutic vaccination: bNABs and CMV vaccine

Combination cure studies
Romedepsin + Vacc x4
Romdepsin + 3BNC117



Phase 1 human studies
to start in 2016

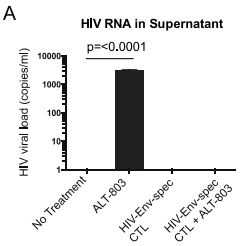
B cell follicles in lymph node might be a barrier



B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers

Yoshinori Fukazawa[1,2], Richard Lum[1,2], Afam A Okoye[1,2], Haesun Park[1,2], Kenta Matsuda[3], Jin Young Bae[1,2], Shoko I Hagen[1,2], Rebecca Shoemaker[4], Claire Deleage[4], Carissa Lucero[4], David Morcock[4], Tonya Swanson[1,2], Alfred W Legasse[1,2], Michael K Axthelm[1,2], Joseph Hesselgesser[5], Romas Geleziunas[5], Vanessa M Hirsch[3], Paul T Edlefsen[6], Michael Piatak, Jr[4], Jacob D Estes[4], Jeffrey D Lifson[4] & Louis J Picker[1,2]

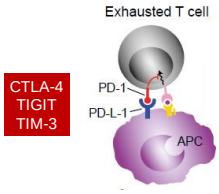
ALT-803 (IL15 superagonist) acts an an LRA and boosts CTL



Ex vivo model using 500 million resting CD4+ T-cells (6 billion PBMC) from patients on ART co-cultured with autologous CTL

Brad Jones et al., Keystone Symposium on HIV Cure, Boston, MA, April 2015

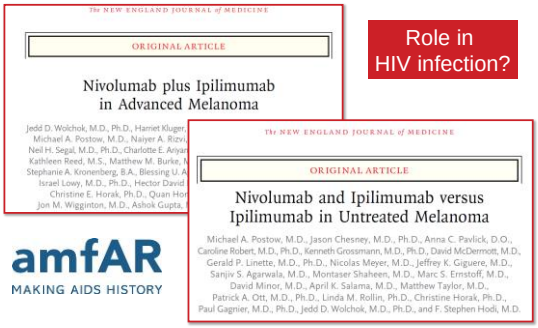
Blocking immune checkpoint markers to boost immune function



Drug	Company	Target	Registration	HIV
Nivolumab	BMS	PD-1	FDA approved: melanoma	no
Pembrolizumab	Merck	PD-1	FDA approved: melanoma and lung cancer	no
BMS-963559	BMS	PD-L1	Phase III: solid organ malignancy	On hold
Ipilimumab	BMS	CTLA-4	FDA approved: melanoma	Case reports

Wightman et al., *AIDS* 2015;29(4):504-6

Combination immune checkpoint blockade: greater efficacy in melanoma

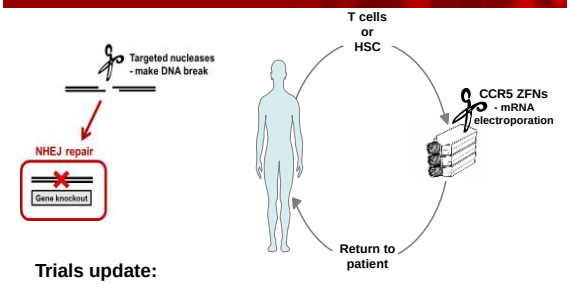


Role in HIV infection?

amfAR
MAKING AIDS HISTORY

making cells resistant to HIV

Gene therapy: ZFNs to knockout CCR5



Trials update:

- Several Phase I/II trials ongoing modifying T cells (NCT01543152, NCT02225665, NCT02388594)
- First HSC trial anticipated opening July 2015

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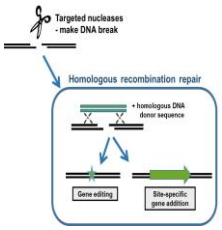
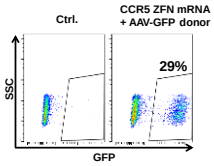
Targeted nucleases allow precise gene editing or site-specific gene addition





GFP insertion at CCR5 in HSC

- Beyond gene (CCR5) knockout, this opens up the possibility of editing host genes such as restriction factors, or inserting anti-HIV genes at a specific site

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Conclusion

- Several interventions have been shown to significantly **reduce the frequency** of latently infected cells including very early ART and transplantation – but this rarely translates into prolonged remission
- Activation of **latent HIV possible in vivo** with HDACi, disulfiram and TLR7 agonists but remains a need for more potent, less toxic and more specific LRAs
- **Combination activation** and/or **enhanced immunity** through vaccination or immune check point inhibition currently being evaluated
- "Knock out" or "knock in" **gene therapy** may play a role

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