Harnessing the Immune System to Eliminate and/or Control HIV

A viable, realistic and testable roadmap

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Disclosures

• Research support
  – Merck
  – ViiV
  – Gilead
HIV “Cure”:

Target

Product

Profile

Identifying Key Drivers of the Impact of an HIV Cure Intervention in Sub-Saharan Africa

Andrew N. Phillips, Valentina Cambiano, Paul Revill, Fumiyo Nakagawa, Jens D. Lundgren, Loveleen Banshi-Matharu, Travor Mabugu, Mark Sculpher, Geoff Garnett, Silvija Staps, Stephen Becker, Joseph Murungu, Sharon R. Lewin, Steven G. Deeks, and Timothy B. Hallett

Efficacy: aviremia in absence of therapy > 2 years; early failure is tolerable, late failures must be rare

Product: oral/parenteral; administered for limited period of time (e.g., 6 months); specialized (tertiary) care not required

Target Population: effective ART initiated at any stage and in all populations (gender, subtype), CD4+ T cell count > 350 cells/mm³

Long-term safety: comparable to ART, transmission risk negligible

Cost: < $1400 (RLS)
Viable pathways towards a durable remission/cure: Gene therapy

• Gene and cell therapy
  – Development of an HIV-resistant immune system
  – Excision of replication-competent HIV (CRISPR)

• Approach supported by success of the Berlin Patient and the near-success of the Boston Patients
Viable pathways towards a durable remission/cure: Early ART

• Prevention of latency
  – PEP
  – Mississippi baby
  – PrEP failures

• Preservation of immune function
  – Post-treatment control
Viable pathways towards a durable remission/cure: Shock and kill

• Shock and kill
  – Complete eradication
  – Reservoir reduction as an adjunct to other curative interventions

• Approach supported by recent success in reversing latency *in vivo*

*Unless all virus is eradicated (which might not be possible) some durable host mechanism of control will be needed to prevent late failures*
Viable pathways towards a durable remission/cure: Immunotherapy

- Immunotherapy
  - Durable host-mediated control of HIV in the absence of ART ("remission")
  - May not fully restore immune health
  - Zero tolerance for persistent viremia at a level which might be associated with transmission

- Approach supported by
  - Elite control and post-treatment control
  - Cancer immunotherapy
All models of durable SIV/HIV remission suggest that durable control of established infection will require (1) low disease burden, (2) low inflammation and (3) sustained T cell responses that are primed, reside in tissues, and target susceptible epitopes

*These same attributes apply to cancer immunotherapy*
Immunotherapy for HIV infection
Two decades of largely failed approaches

• Weak immunogenicity
  – Pre-existing immuno-dominant responses
  – CTL escape
• Inflammation and counter-regulatory immunosuppression
• High virus burden
• Immune-privileged tissues sanctuaries
Immunotherapy and HIV remission

**Enhanced T cell immunity**

Inhibition of harmful inflammatory responses

Low disease burden (reservoir)

Disruption of sanctuaries
Despite heroic efforts and multiple studies, no therapeutic vaccine has convincingly reduced set-point (post-ART).

Current generations of studies are focused on reducing reservoir.
T cell vaccines generally expanded pre-existing immunodominant clonotypes that failed to control initial infection

Dysfunctional T cells
CTL escape emerges in a few months and gets deposited in “reservoir”

Vaccines that shift responses to subdominant or non-classical epitopes needed
High levels of tissue-based CD8+ T-effector cells that recognize unusual and diverse epitopes, including those restricted by class II MHC molecules, that fully clears (cure) low-inoculum infections when present at time of exposure.
Novel Conserved-region T-cell Mosaic Vaccine With High Global HIV-1 Coverage Is Recognized by Protective Responses in Untreated Infection

Beatrice Ondondo¹, Hayato Murakoshi², Genevieve Clutton¹,³, Sultan Abdul-Jawad¹, Edmund G-T Wee¹, Hiroyuki Gatanaga²,⁴, Shinichi Oka²,⁴, Andrew J McMichael⁵, Masafumi Takiguchi²,⁶, Bette Korber⁷,⁸ and Tomáš Hanke¹,⁶

Six highly conserved regions of gag/pol carried by two mosaics and delivered by ChAdC63, MVA and/or DNA
Ad26/MVA Therapeutic Vaccination with TLR7 Stimulation in SIV-Infected Rhesus Monkeys

Ad26/MVA prime-boost vaccine with TLR7 agonist reduces reservoir during ART and controls SIV post-ART, with 3/10 animals exhibited durable “remission”
Multiple groups are now studying TLR agonists in the clinic

- TLR2, TLR3, TLR4, TLR7/8 and TLR9 agonists
  - Latency reversal
  - Enhanced NK cell function
  - Enhanced CTL
- UCSF amfAR Institute: Public/private partnership (UCSF/Gladstone/OHSU/IDRI and Gilead)
  - NHPs: TLR7 agonists alone or in combination with TLR4 agonist
  - First clinical trial pending
Immunotherapy and HIV remission

Enhanced T cell immunity
Inhibition of harmful inflammatory responses
Low disease burden (reservoir)
Disruption of sanctuaries
T-cell “activation” is lower in treated than untreated adults, but consistently higher than “normal”

Similar trends consistently observed with multiple measures of inflammation, including IL-6, sCD14, sCD163 and PD-1 expression of T cells
Oncology model: The inflammatory response in cancer tissue stimulates a potent and durable anti-inflammatory response

- Upregulation of checkpoint blockers (PD-1, CTLA-4)
- Immunosuppressive cytokines (TGF-β, IL-10, IDO)
- Immunosuppressive immune cells (T-regs, MDSCs)
Cancer immunotherapy is reshaping a fatal and progressive disease much as ART reshaped HIV in the 1990s.
ICB Clinical Trials: HIV and cancer

I pilimumab (anti-CLTA-4) increases cell-associated RNA and decreases viremia (“chock and kiil”)

Cell Associated US-HIV RNA

Plasma Single copy HIV RNA

Ipilimumab treatment cycle
Careful assessment of safety and efficacy of immunotherapies in HIV/cancer will provide pathway for developing curative interventions

- **CITN 12**: Phase I Study of pembrolizumab (anti-PD-1) in patients with HIV and relapsed/refractory or disseminated malignant neoplasm

- **AMC 095**: Phase I study of ipilimumab (anti-PD-1) and nivolumab (anti-CTLA-4) in advanced HIV-associated tumors (including anal CA and KS)
Sirolimus (rapamycin)—which reduces T cell activation and T cell proliferation and enhances generation of memory—is associated with low “reservoir” size post-renal transplant.
Translational research within DARE
*Multiple targets have been characterized ex vivo and are now being studies in vivo (NHPs and humans)*

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<tr>
<th>Intervention</th>
<th>Pathway</th>
<th>Status</th>
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<td>Nivolumab</td>
<td>PD-1</td>
<td>NHP studies pending AMC multi-center clinical trial (cancer/HIV)</td>
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<tr>
<td>Ipilimumab</td>
<td>CLTA-4</td>
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<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>CITN multi-center clinical trial (cancer/HIV)</td>
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<td>CMV vector</td>
<td>Vaccine</td>
<td>NHP studies ongoing (Picker/DARE)</td>
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<td>Sirolimus</td>
<td>mTOR</td>
<td>Proof-of-concept studies ongoing (ACTG, UCSF)</td>
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<td>Everolimus</td>
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<td>Canakinumab</td>
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<td>Ruloxitinib</td>
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<td>Methotrexate</td>
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<td>TLR4/7 agonists</td>
<td>Immune adjuvant</td>
<td>NHP studies ongoing (Okoye/DARE/IDRI)</td>
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<tr>
<td>Anti-CD20 antibodies</td>
<td>B cell follicle</td>
<td>NHP studies ongoing (Okoye/DARE/IDRI)</td>
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<td>Alemtuzumab</td>
<td>CD52</td>
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<td>Anti-CCL20</td>
<td>CCR6</td>
<td>NPP studies in development (Lewin/GSK)</td>
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Immunotherapy and HIV remission

*Enhanced T cell immunity*

*Inhibition of harmful inflammatory responses*

*Low disease burden (early ART)*

*Disruption of sanctuaries*
The estimated reservoir size rises rapidly during the first few four weeks.

At about the time HIV RNA becomes detectable, the reservoir size begins to increase dramatically, with an apparent 100-fold increase over the next two weeks.

Reservoir largely established by week 4 of infection.
Can we use ART to prevent latency?

PEP/PrEP/Cure Continuum

Barouch and Deeks, Science 2014
PrEP “Failures”: A platform to discover if early ART can be curative

Plasma HIV-1 RNA (copies/mL)

- PrEP Baseline Visit: Day 10 of HIV infection, TDF/FTC started
- Day 18 of HIV infection, DRV/r/RGVTDF/FTC started
- HIV RNA: 4.7 copies/mil CD4
- HIV DNA: ND

- Ultrasensitive plasma HIV RNA (<0.06 copies/mL): ND
- Total Inducible Virus Recovery: ND
- HIV DNA: ND

- Rectum/Leukapheresis: HIV RNA/DNA: ND
- Viral outgrowth assay, TILDA: ND
- HIV DNA (ddPCR) x2: ND
- CSF, BM: ND
- LN, ileum/rectum: ND

LLOD (<40 copies/mL)

Estimated Months since HIV Infection
• 20 adults (and one child) who started therapy early, remained on therapy for years, and had only transient rebound after stopping therapy

• Correlates: Low reservoir size, low T cell activation and as of yet a poorly defined immune mechanism of control
Immunotherapy and HIV remission

*Enhanced T cell immunity*

*Inhibition of harmful inflammatory responses*

*Low disease burden* *(shock and kill)*

*Disruption of sanctuaries*
Shock and Kill: Reservoir reduction with a goal of eradication, or reducing virus level below some theoretical level that it will not rebound

*Theoretical basis for most first generation cure strategies*

*Deeks, Nature 2012*
Administration of vorinostat disrupts HIV–1 latency in patients on antiretroviral therapy

N. M. Archin¹, A. L. Liberty¹, A. D. Kashuba¹, S. K. Choudhary¹, J. D. Kuruc¹, A. M. Crooks¹, D. C. Parker¹, E. M. Anderson², M. F. Kearney², M. C. Strain³, D. D. Richman³, M. G. Hudgens¹, R. J. Bosch⁴, J. M. Coffin², J. J. Eron¹, D. J. Hazuda⁵ & D. M. Margolis³

Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial

Thomas A Rasmussen, Martin Tolstrup, Christel R Brinkmann, Rikke Olesen, Christian Erikstrup, Ajantha Solomon, Anni Winckelmann, Sarah Palmer, Charles Dinarello, Maria Buzon, Mathias Lichterfeld, Sharon R Lewin, Lars Østergaard, Ole S Søgaard

The Depsipeptide Romidepsin Reverses HIV-1 Latency In Vivo

Ole S. Søgaard¹, Mette E. Graversen¹, Steffen Leth¹, Rikke Olesen¹, Christel R. Brinkmann¹, Sara K. Nissen¹, Anne Sofie Kjaer¹, Mariane H. Schleimann¹, Paul W. Denton¹, William J. Hey-Cunningham⁴, Kersten K. Koelsch⁴, Giuseppe Pantaleo⁵, Kim Krogsgaard⁶, Maja Sommerfelt⁶, Remi Fromentin⁷, Nicolas Chomont⁷, Thomas A. Rasmussen¹, Lars Østergaard¹, Martin Tolstrup¹

Short-term administration of disulfiram for reversal of latent HIV infection: a phase 2 dose-escalation study

Julian H Elliott, James H McMahon, Christina C Chang, Sulggi A Lee, Wendy Hartogensis, Namandje Bumpus, Rada Savic, Janine Roney, Rebecca Hoh, Ajantha Solomon, Michael Piatak*, Robert J Gorelick, Jeff Lifson, Peter Bacchetti, Steven G Deeks, Sharon R Lewin
PKC agonists (prostratin, bryostatin) are most potent latency reduces identified to date

Associated with significant toxicity
Immunotherapy and HIV remission

*Enhanced T cell immunity*

*Inhibition of harmful inflammatory responses*

*Low disease burden (reservoir)*

*Disruption of sanctuariers*
B cell follicles (high frequency of CD4+ Tfh cells; no CTL or NK cells) for HIV replication
Transient disruption of the B cell follicle with anti-CD20 antibodies enables CTL-mediated elimination of SIV (and perhaps HIV)
Experimental medicine

Large immunotherapy program now emerging for HIV cure

Probe studies: safety feasibility, biologic activity
Immune modification often generates immediate and complex counter-regulatory responses making it impossible to predict what will happen.
α4β7 integrin expression enables migration of T cells to gut mucosa (site of massive HIV replication)

Anti-α4β7 integrin antibody administration during ART increased mucosal CD4+ T cell levels and reduced mucosal SIV DNA

Treated animals controlled SIV post-ART
Combination strategies will likely be needed to achieve a durable remission

A number of viable combinations should be available for testing in a few years

- Reverse immune suppression
  - Immune-modifiers

- Enhanced CTL
  - CMV vector
  - Adjuvants (TLR)
  - ICBs

- CTL Escape
  - Unconventional CTL (CMV vector)
  - Early ART

- Low Reservoir
  - Shock and Kill
  - Early ART

HIV Remission