Strategies for HIV cure

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Disclosures

Advisory boards:
• Merck Pharmaceuticals, Bristol Meyers Squibb

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• Merck Pharmaceuticals, Viiv

Other (grant review committee):
• Gilead Sciences
Learning objectives

- Understand the main barriers to cure of HIV infection
- Describe cases of HIV cure
- Understand strategies under investigation for HIV cure currently

Outline

- What are we up against?
  - HIV latent reservoir
  - Measuring the needle in the haystack
  - New challenges – homeostatic proliferation and clonal expansion
Outline

• What are we up against?
  – HIV latent reservoir
  – Measuring the needle in the haystack
  – New challenges – homeostatic proliferation and clonal expansion

• Success stories

Outline

• What weapons do we have?
  – Bone marrow transplant and gene therapy
  – Shock and kill
  – Immunotherapy
  – Broadly neutralizing antibodies
Natural history of HIV infection

Viral rebound with treatment interruption

Davey et al, PNAS, 1999
Resting memory CD4\(^+\) T cells

HIV targets activated CD4\(^+\) T cells
Activated CD4+ T cell

Virus integrates within cell genome

Infected cell dies within 1-2 days
Activated CD4+ T cell

Immunologic memory

- Subset of activated cells revert to resting memory state
- Designed to live for decades

Activated CD4+ T cell

Resting memory CD4+ T cell

Upon re-encountering antigen, cell is reactivated
Most of the time infected cells die...

Activated CD4+ T cell

But rarely, infected cell reverts to resting state before cell death

HIV-infected resting memory CD4+ T cell
Latent reservoir: an unlucky consequence of immune memory

Latent state
• HIV transcriptionally silent
• Invisible to immune system
• Unaffected by ART

Reversible state
• On ART – little consequence
• ART interruption – high levels of virus and clinical disease will return
Other hematopoietic derived cells?

- Bone marrow progenitors
- Brain: microglial cells
- Tissue macrophages
- Liver: Kupffer cells

And just when we thought it couldn’t get any worse.....
Homeostatic Proliferation

Clonal expansion
Forms of HIV present *in vivo*

1. HIV RNA in plasma
   Clinical assays

2. Cell associated HIV DNA integrated in CD4+ cells:
   a. defective and
   b. infectious virus
Forms of HIV present in vivo

1. HIV RNA in plasma
   Clinical assays

2. Cell associated HIV DNA
   integrated in CD4+ cells:
   a. defective and
   b. infectious virus

3. Cell associated HIV
   RNA – active transcription
Assays to measure cure interventions

- Viral outgrowth
- PCR cell associated HIV DNA
- PCR cell associated HIV RNA
- PCR plasma HIV RNA

Assays to measure cure interventions

- **Viral outgrowth** *(reservoir gold standard)*
- PCR cell associated HIV DNA
- PCR cell associated HIV RNA
- PCR plasma HIV RNA
Viral outgrowth assay

Resting CD4+ T cells from patients on ART

Activation

Finzi D et al, 1997; Siliciano JD et al, 2005
Resting CD4+ T cells from patients on ART

Viral outgrowth assay

1 x10^6 2 x10^5 4 x10^4 8 x10^3 1.6 x10^2

p24 positive

Day 14-21 supernatant p24 antigen

p24 negative

Finzi D et al, 1997; Siliciano JD et al, 2005

Frequency of latently HIV infected CD4+ T Cells over time in patients on ART

t_{1/2} = 44.2 months
73.4 years

Assays to measure cure interventions

• Viral outgrowth assay

• PCR cell associated HIV DNA

• PCR cell associated HIV RNA

• Single copy plasma HIV RNA

PCR for cell-associated HIV DNA or RNA

Advantages
• Lower blood volume
• Less time intensive
• Lower cost
• Frozen cells
Only 4% of proviruses are intact

- Intact: 4%
- 3' Deletions: 34%
- 5' Deletions: 23%
- Large Internal Deletions: 19%
- Hypermutated: 9%
- Hypermutated and Deleted: 7%
- Packaging Signal Deletions: 4%

Ho Y et al, Cell, 2013

Needle in a haystack picture
Outline

• What are we up against?
  – HIV latent reservoir
  – Measuring the needle in the haystack
  – New challenges – homeostatic proliferation and clonal expansion

• Success stories

Berlin patient

Long-Term Control of HIV by CCR5 Delta32/ Delta32 Stem-Cell Transplantation

Gero Hutter, M.D., Daniel Nowak, M.D., Maximilian Meissner, B. Susanne Gargapela, M.D., Arne Müllig, M.D., Kristina Albers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Köhler, Olga Blau, M.D., Igor W. Blau, M.D., Wolf R. Hofmann, M.D., and Eckhard Thiel, M.D.
Berlin patient: Clinical history

- American studying in Berlin
- Well controlled HIV infection on ART
- Acute myeloid leukemia requiring BMT
- German oncologist Gerard Hütter
- Matched unrelated bone marrow donor, CCR5Δ32 mutation

Berlin patient: Virologic and immunologic response

Outline

• What weapons do we have?
  – Bone marrow transplant and gene therapy
  – Shock and kill
  – Immunotherapy
  – Broadly neutralizing antibodies

Mechanism of HIV cure with BMT

Step 1: Eradicate HIV reservoirs: chemo, GVH
Components of allogeneic BMT

Chemotherapy
- Myeloablative transplant
- Reduced intensity

Bone marrow transplant

Engraftment

Graft versus host effects
100% donor chimerism

Day 0 ≈ Day 20 Months to year

Allogeneic effect
Allogeneic effect

• Recipient (host) cells replaced by donor (graft)

Cell death
Donor T cells or other immune cells (e.g. NK cells)

Allogeneic effect

Hematopoietic compartment
• Graft versus tumor effect

Organs (skin, gut)
• Graft versus host disease
Allogeneic effect

Hematopoietic compartment
• Graft versus tumor effect
• Graft versus HIV reservoir

Organs (skin, gut)
• Graft versus host disease

Mechanism of HIV cure with BMT

Step 1: Eradicate HIV reservoirs: chemo, GVH

Step 2: Protect donor cells from infection
Protect donor cells: gene therapy

Recipient CD4+ T cell

Donor CD4+ cell

CCR5A32

Protect donor cells with ART

Recipient CD4+ T cell

Donor CD4+ cell

ART

....until full donor chimerism
Proof of concept: alloBMT and ART: Boston patients

Pt 1: Hodgkins
Pt 2: Hodgkins, myelodysplasia
Reduced intensity conditioning alloBMT
CCR5 wild-type donors
Maintained on ART

Henrich, JID 2013

Challenges: ART during alloBMT

• Drug-drug interactions
  – Cytochrome P450 inhibitors
• Organ toxicity
  – renal failure
  – liver failure
• Intolerance of oral medications
  – nausea, vomiting
  – mucositis
Trial: Optimized ART during BMT

Hypothesis: Continuous ART and the allogeneic or graft vs host effect can reduce or completely eradicate HIV reservoirs

Study population: HIV+, BMT for cancer

Intervention: Optimized ART

- Avoid CYP3A4 inhibitors
- Ongoing ART changes as needed
- Enfuvirtide (T20 or Fuzeon)
Trial: Optimized ART during BMT

Outcomes

• Primary: Feasibility
  1. Tolerance of T20
  2. Maintenance of ART

• Secondary: Impact on HIV reservoirs
  1. Donor chimerism
  2. HIV persistence

Trial: Optimized ART during BMT

Outcomes

• Primary: Feasibility
  1. Tolerance of T20
  2. Maintenance of ART

• Secondary: Impact on HIV reservoirs
  1. Donor chimerism: standard clinical test
  2. HIV persistence: viral outgrowth and PCR
## Optimized ART in alloBMT: results N = 7

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Primary outcomes – safety, tolerability

1. Tolerance of T20 - no adverse events

2. Maintenance of ART

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Antiretroviral therapy changes

- Kidney dysfunction (TDF to ABC)
  - 6 patients on TDF to start
  - 5/6 had to change due to Cr rise
- Drug-drug interactions (azoles)
- Insurance issues
- Concern for fevers due to ABC

Overall survival - long term outcomes

- Patient 1
- Patient 2 – in remission, 4 years
- Patient 3
- Patient 4 – in remission, 3 years
- Patient 5 –
- Patient 6 – in remission, 2 years 3 months
- Patient 7 – in remission, 1 year 8 months
Overall survival - long term outcomes

- Patient 1 – died week 49, liver failure
- Patient 2 – in remission
- Patient 3 – died week 64, liver failure
- Patient 4 – in remission
- Patient 5 – died week 67, infection and sepsis
- Patient 6 – in remission
- Patient 7 – in remission

Chimerism
Full Donor Chimerism: 5/7

Incomplete Donor Chimerism: 2/7
Primary outcomes – safety, tolerability

1. Tolerance of T20 - no adverse events

2. Maintenance of ART

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Adherence</th>
<th>ART changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>73%</td>
<td>3</td>
</tr>
<tr>
<td>002</td>
<td>95-100%</td>
<td>1</td>
</tr>
<tr>
<td>003</td>
<td>Poor</td>
<td>1</td>
</tr>
<tr>
<td>004</td>
<td>95-100%</td>
<td>3</td>
</tr>
<tr>
<td>005</td>
<td>100%</td>
<td>1</td>
</tr>
<tr>
<td>006</td>
<td>100%</td>
<td>2</td>
</tr>
<tr>
<td>007</td>
<td>100%</td>
<td>1</td>
</tr>
</tbody>
</table>

Patient 003 – BMT clinical course

- Engrafted day 20, week 4 and 8 chimerism 100%
- Week 12 HIV RNA < 20 copies/mL
- Week 16, fevers, “viral syndrome”
- Week 20, fevers, admitted for change in mental status
- Lumbar puncture
  - 28 WBC (100% monos), Protein 150, glucose 50
- HIV plasma VL 25, 518 c/mL
- CSF HIV VL 17,000 c/mL
Patient 3 – HIV Rebound Early After AlloBMT with CNS involvement

• Interruption of ART led to severe retroviral syndrome, including CNS involvement (meningoencephalitis)

• Clinically, due to “naïve” immune system + immunosuppression

• Despite complete donor chimerism, rebound virus from residual HIV-infected host memory CD4 T cells

Boston patients – analytic treatment interruptions

Stem-cell transplants may purge HIV

After Marrow Transplants, 2 More Patients Appear H.I.V.-Free Without Drugs
Viral rebound in Boston patients

Patient A – rebound 12 weeks
Clinically meningoencephalitis

Patient B – rebound 30 weeks
Virus detected in the CSF

Henrich et al, Ann Internal Medicine 2015

Baltimore patients: viral measures in remainder of the cohort

Patient subgroups
• Complete chimerism (no host cells detected)
• Incomplete chimerism (host cells detected)

Two assays
• Viral outgrowth assay (specific for replication competent HIV)
• PCR based assays (sensitive for all forms of HIV)
Infectious Units per Million (IU/PA)

Time post allo-BMT (weeks)

A. Incomplete Donor

B. Complete Donor
A. Incomplete Donor

B. Complete Donor

C. Proviral DNA Frequency (HIV pol+ copies/million PBMCs)

D. Proviral DNA Frequency (HIV pol+ copies/million PBMCs)
2/7 had transient increases in HIV DNA at early timepoints post BMT

• Despite >95% donor replacement, transient INCREASES in HIV DNA at early time points post BMT
2/7 had transient increases in HIV DNA at early timepoints post BMT

- Despite > 95% donor replacement, transient **INCREASES** in HIV DNA at early timepoints post BMT
- Occurred during febrile illness from other pathogens (CMV, histoplasmosis) – clonal expansion?

What we are up against
What we are up against

Future Hope for HIV cure and BMT?

- Recapitulating the Berlin patient
- CCR5delta32 donors
Future Hope for HIV cure and BMT?

- Recapitulating the Berlin patient
- CCR5delta32 donors
- Collaboration with the German blood donor registry
- Enrolled 3 new BMT patients with CCR5delta32 matches

Future Hope for HIV and BMT?

Adoptive T cell therapy
BMT from HIV- donors with engineered HIV specific cytotoxic T cells
Outline

• What weapons do we have?
  – Bone marrow transplant and gene therapy
  – Shock and kill
  – Immunotherapy
  – Broadly neutralizing antibodies

“Shock and kill”

Latency reversing agent

1. Reactivate latent HIV to induce active replication
2. Continue ART to prevent new cells from infection

ART = antiretroviral therapy
“Shock and kill”

Latency reversing agent

1. Reactivate latent HIV to induce active replication
2. Continue ART to prevent new cells from infection
3. Infected cells will die from virus or immune response

ART = antiretroviral therapy

CTL = cytolytic T cell response

Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

- 400 mg vorinostat single dose
- 8 HIV+ healthy volunteers

Archin N, Margolis D. Nature 2012
Archin N, Margolis D. Nature 2012

- 400 mg vorinostat single dose
- 8 HIV+ healthy volunteers

8/8 had increase in HIV cell associated RNA patients
4.8 fold increase

Elliott, Lewin PLOS Path 2014

- 400 mg vorinostat daily for 14 days
- 20 HIV+ healthy volunteers
Activation of HIV Transcription with Short-Course Vorinostat in HIV-Infected Patients on Suppressive Antiretroviral Therapy

- 400 mg vorinostat daily for 14 days
- 20 HIV+ healthy volunteers

18/20 had increase in HIV cell associated-RNA
Median increase: 7 fold

No change in HIV plasma RNA or cell associated DNA

Elliott, Lewin PLOS Path 2014
**AMC 075 – VOR for HIV lymphoma**  
Phase II, 90 patients

<table>
<thead>
<tr>
<th>Arm C:</th>
<th>Arm D:</th>
<th>Arm E:</th>
<th>Arm F:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertinostat RPTD + rituximab-CHOP</td>
<td>Rituximab-CHOP</td>
<td>Vertinostat RPTD + rituximab-DA-EPOCH</td>
<td>Rituximab-DA-EPOCH</td>
</tr>
</tbody>
</table>

- 6 cycles of 5 days of VOR over 6 months + chemo

**Baseline**  
Cycle 1 → Cycle 2 → Cycle 3 → Cycle 4 → Cycle 5 → Cycle 6 → Visit 7, 12

Pre-Rx  
Viral outgrowth assay
AMC 075 – VOR for HIV lymphoma
Phase II, 90 patients

- 6 cycles of 5 days of VOR over 6 months + chemo

---

No vorinostat group (n=5)

Fold change 1.32 (0.55-3.16)

p= 0.53
Vorinostat group (n=3)

Fold change 2.79 (1.19–6.56) p= 0.02

Increase in the reservoir!
Shock and kill: No good kill strategies

HDAC inhibitor

1. Reactivate latent HIV to induce active replication
2. Continue ART to prevent new cells from infection
3. Infected cells will die from virus or immune response

ART = antiretroviral therapy
CTL = cytolytic T cell response
Outline

• What weapons do we have?
  – Bone marrow transplant and gene therapy
  – Shock and kill
  – Immunotherapy
  – Broadly neutralizing antibodies

HIV – chronic inflammatory state

Increased expression:
  • PD1
  • CTLA 4
  • TIGIT

Immune checkpoint (IC) receptors

• Cells expressing IC (esp PD1) have higher levels of HIV\textsuperscript{1,2}

\textsuperscript{1}Chomont et al. Nat Med. 2009. 8:893-900.
\textsuperscript{2}Fromentin R et al. Towards an HIV Cure Symposia. 2014. Australia.

• IC blockade (esp CTLA-4) activates HIV
  – In vitro\textsuperscript{3} and in vivo\textsuperscript{4}

\textsuperscript{3}Hryniewicz A et al. Blood. 2006. 2:3834-42.
Immune checkpoint (IC) receptors

- Cells expressing IC (esp PD1) have higher levels of HIV\(^1,2\)
- IC blockade (esp CTLA-4) activates HIV
  - In vitro\(^3\) and in vivo\(^4\)
- IC blockade enhances the function of HIV or SIV-specific T cells\(^3,5\)

\(^1\) Chomont et al. Nat Med. 2009. 8:893-900.
\(^4\) Porichis et al. Blood. 2011. 4:965-74
\(^5\) Wightman F et al. AIDS. 2015. 4:504-6.
\(^6\) Postow MA, et al. NEJM. 2015. 21:2006-17
**Immune checkpoint inhibitors**

- Release the on the immune system “brakes”
- Anti PD1
- Anti CTLA4
- Could this provide both a shock and kill

---

**AMC 095A Phase I Study of Ipilimumab and Nivolumab in HIV Associated Solid Tumors**

- Latent reservoir by qVOA, HIV specific T cell responses at baseline, every 6 months
- HIV DNA, cell associated HIV RNA, SCA at day -1, day +1 and day +8 around chemotherapy
• CMV engineered as a live HIV/SIV vaccine
• Leads to tissue-based “killer” CD8+ T cells that target novel parts of the virus
• Stimulates “unconventional” MHC II/HLA E restricted CD8+ T cell responses
• Clear latently infected cells during early infection, first clear documentation of a “cure” in this model

Outline

• What weapons do we have?
  – Bone marrow transplant and gene therapy
  – Shock and kill
  – Immunotherapy
  – Broadly neutralizing antibodies
Broadly neutralizing monoclonal antibodies bnAbs

- Monoclonal antibodies (mAb) are used for treatment in cancer and autoimmune disease
- Several broadly-neutralizing mAb for HIV are being developed for prevention and therapy

Vaccine Research Center - NIH
VRC01 Neutralizing Activity

VRC01 has an IC50 of <50 mcg/mL against 91% of primary isolates of various HIV-1 clades (<1 mcg/mL against 72%)

ACTG 5342:
VRC01 to reduce HIV reservoirs

• Double-blind, placebo-controlled, RCT, Phase I
• Sample size: 40 participants (20 per arm)
• VRC01 2 doses, 3 weeks apart
VRC01 infusion has no effect on HIV-1 persistence in ART-suppressed chronic infection

S Riddler, C Durand, L Zheng, J Ritz, R Koup, J Ledgerwood, B Macatangay, J Cyktor, J Mellors, for the ACTG A5342 Team

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Parameter</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arms A and B Combined</th>
<th>Change Pre- to Post</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA HIV RNA/DNA ratio</td>
<td>1.12 (0.92, 2.15)</td>
<td>0.83 (0.57, 2.37)</td>
<td>Change baseline to wk 6</td>
<td>0.16</td>
<td>0.04 (0.02, 0.08)</td>
<td>0.05 (0.02, 0.08)</td>
<td>1.24 (0.61, 2.15)</td>
<td>0.29</td>
</tr>
<tr>
<td>CA HIV RNA</td>
<td>0.08 (-0.23, 0.32)</td>
<td>-0.08 (-0.26, 0.29)</td>
<td></td>
<td>0.39</td>
<td>1.55 (0.99, 1.99)</td>
<td>1.48 (0.99, 2.10)</td>
<td>0.99 (-0.23, 0.32)</td>
<td>0.64</td>
</tr>
<tr>
<td>CA HIV DNA</td>
<td>-0.06 (-0.13, 0.06)</td>
<td>-0.01 (-0.08, 0.13)</td>
<td></td>
<td>0.30</td>
<td>2.93 (2.43, 3.15)</td>
<td>2.92 (2.51, 3.11)</td>
<td>0.05 (-0.12, 0.06)</td>
<td>0.19</td>
</tr>
<tr>
<td>Stimulated Virus</td>
<td>-0.13 (-0.51, 0.92)</td>
<td>0.12 (-0.52, 0.30)</td>
<td></td>
<td>0.91</td>
<td>2.99 (2.06, 3.37)</td>
<td>2.66 (2.28, 3.41)</td>
<td>-0.10 (-0.51, 0.44)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Neutralizing Monoclonal Antibodies Discovered since 2009

Mascola, CROI 2016
Antibodies with Improved Potency/Breadth

Panel of 206 Env-pseudoviruses

Mascola, CROI 2016

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