Learning Objectives

After attending this presentation, participants will be able to:

- Describe the primary objectives of different cure approaches
- Contrast the benefits and drawbacks of different cure approaches
- Describe how different approaches may achieve a cure goal

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The Cascade

<table>
<thead>
<tr>
<th>Number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care in the United States</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Number of Individuals</td>
</tr>
<tr>
<td>100%</td>
</tr>
</tbody>
</table>

Even with drugs that are 100% effective at suppressing virus we are unable to achieve this in 100% of infected people

This is one reason we need a cure

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The Cascade

Even with drugs that are 100% effective at suppressing virus we are unable to achieve this in 100% of infected people

This is one reason we need a cure
Three Histories of HIV-infected Cells In Vivo

Multiple mechanisms govern these events

Ongoing HIV Viremia During cART

- cART reduces plasma HIV RNA > 6 to 7 log_{10}
- But viremia persists indefinitely (0.1-3 copies RNA/mL)
- Source of viremia unknown

How To Cure HIV-Infected People

- Multiple mechanisms account for HIV persistence
- Unifying theme: find and diminish size of the HIV reservoir
  - Reduce seeding of latent pool with early/more ART
  - Reverse latency (shock and kill)
  - Increase HIV-specific immune function (vaccines)
  - Reduce immune activation
  - Gene therapy targeting the virus and the host
  - Allogeneic stem cell transplantation
- Combination therapy may be necessary
Even though this procedure works, it is highly unlikely that it will ever translate into an accessible approach.

Despite 1000–10,000 fold reductions in reservoir size, virus rebounded. Modeling: latent reservoir will have to be depleted > 10^5 fold (Hill, PNAS '14)

A single virus accounts for recrudescence.

Shock and Kill

Activate the infected T cell

"Shock"

Virus is produced

Immune system kills the cell

ART stops new infections
**Current Status of LRA Clinical Trials**

- Numerous LRAs identified in studies with cell lines and primary T cells
- Relative to T cell activation, few LRAs work well ex vivo with cells from patients
- In clinical trials, evidence for increase in cell-associated and plasma HIV RNA
- In clinical trials, no reduction in the reservoir yet demonstrated

**The Kill?**

Reactivate the virus with LRA and then clear the infected cells

**Will the virus kill the infected cells?**

- "After reversal of latency in an in vitro model, infected resting CD4 T cells survived despite viral cytopathic effects" (Shan, Immunity 2012)

**Can the immune system help?**

- Most of the virus has mutated to escape the immune response and escape variants dominate in the latent reservoir of chronic subjects (Deng, Nature 2015)

**Therapeutic vaccination?**

- Transient expansion of T cells that do not recognize escaped HIV epitopes (Koup, JID 2014)

**The Kill?**

How to improve the kill in context of latency reversal

- bnAbs (see later)
- CMV-based vaccination (Picker)
- TLR-7 (Geleziunas)
- Immune checkpoint blockade (Chomont/Sekaly)
- Very early ART (Ananworanich)
- mTOR inhibition (Deeks)
**Gene Therapy**

Deliver a therapeutic agent to a cell using a gene

**Provide something to inhibit or kill HIV**
- Anti-HIV antisense RNA, fusion inhibitor C46, transdominant Rev

**Remove something that HIV needs: CCR5**
- Using antisense RNA, intrabodies, targeted DNA nucleases

**Real lesson we learned from the Berlin and Boston patients:**
- You need to remove the virus and the target cells

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**Lentiviral Vector Based Gene Therapy Targeting HIV**

<table>
<thead>
<tr>
<th>Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH: Lentiviral gene transfer to HSC during auto-HSCT for AIDS lymphoma</td>
<td>Completed</td>
</tr>
<tr>
<td>COB: Lentiviral gene transfer to HSC after AIDS lymphoma therapy</td>
<td>Active, enrolling</td>
</tr>
<tr>
<td>UCLA/Calimmune: Lentiviral gene transfer to CD4 T cells and HSC during auto-HSCT for AIDS lymphoma</td>
<td>Active, enrolling</td>
</tr>
<tr>
<td>FHCRC/Calimmune: Lentiviral gene transfer during auto-HSCT for AIDS lymphoma</td>
<td>Pending</td>
</tr>
</tbody>
</table>

**Trials in setting of HSCT for AIDS-associated lymphoma**

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**Nuclease Based Gene Therapy Targeting CCR5**

**Endpoints:**
- Safety
- CD4 counts and HIV levels
- CCR5 editing

**3 trials complete, 2 recruiting:**
- majority on ART and aviremic
- CD4 counts 200-750 cells/µl
- no CXCR4 tropic virus
HIV Cures and Immunotherapy:
New Horizons

Tuesday, August 23, 2016

Daniel C. Douek, MD, MRCP, PhD

Slide 20 of 35

• Infusion of CCR5-specific zinc-finger nuclease-treated ex vivo expanded autologous T cells is generally safe and well tolerated
• Durable increases seen in both CD4 and total T cell counts
• CCR5 modified T cells persist long-term in vivo and persist longer than unmodified cells during treatment interruption

Summary of Findings

All subjects in a cohort of chronically infected INR saw long-term CD4 T cell reconstitution and HIV reservoir decay (Sekaly, Lalezari, Blick CROI 2016)

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Antibodies Used In Virus Infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Product Description</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Polio</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus Immune Globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Immune serum globulin (ISG)</td>
<td>Prevention (travel)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B Immune Globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>RSV</td>
<td>Palivizumab prophylaxis in infants</td>
<td>Prevention</td>
</tr>
<tr>
<td>VZIG</td>
<td>Varicella Zoster Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>Ebola</td>
<td>Zmapp (3 mAbs)</td>
<td>Post Exposure</td>
</tr>
</tbody>
</table>

NHP studies going back to 1999 show that anti-HIV mAb can completely protect against acquisition of infection

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Potential Targets for Neutralization

HIV Envelope

CD4 Binding Site
PG04, GT11, 12A12, VRC13, VRC01, VRC01LS, VRC07-523LS, 3BNC117, N6

N332 Glycan Supersite
PGT128, DH542, PGT121, 10-1074

gp41 MPER
2F5, 4E10, 10e8

V1V2 Glycan
PG9, PG16, PGT141

PGT141-145, CAP26.25, VRC01LS, VRC01

CD4 Binding Site
PG04, GT11, 12A12, VRC13, VRC01, VRC01LS, VRC07-523LS, 3BNC117, N6

NHP studies going back to 1999 show that anti-HIV mAb can completely protect against acquisition of infection
Antibody Potency/Breadth

Panel of 206 HIV Env pseudoviruses (from all major clades)

Breadth: % of Envs neutralized

Panel of 206 HIV Env pseudoviruses (from all major clades)

Clinical Use of HIV-Specific Antibodies

Prevention and treatment with antibodies are different

Prevention
- Prevent acquisition of infection
- Block transmission

Treatment
- Have to deal with greater viral diversity
- Different mechanism of action?
- mAbs complementary to ARV
- Potential to reduce HIV reservoir (Cure)

Block virus entry
Cell killing

Clinical Use of HIV-Specific Antibodies

- During acute HIV infection, with ARVs, to rapidly reduce viremia and limit seeding the virus reservoir
- To maintain long-term viral suppression induced by ARV
e.g: LA-ARV + mAb given once every 2-3 months
- Reduce cell-associated virus reservoir by cell-mediated killing
  – functions distinct from ARVs; combine with LRAs?

Stimulate viral expression (LRA)
- Latently infected cell
- Macrophage phagocytosis

Natural killer cell lysis
- Clinical Use of HIV-Specific Antibodies
Phase I Trial of VRC01: Single Infusion

3 Patterns:
- Profound and maintained suppression
- Transient suppression
- No suppression

Pre-Infusion HIV Sensitivity to VRC01

The two low-responder participants had most resistant virus quasi-species before VRC01 infusion

Phase I Trials of VRC01 During ATI

• Majority of participants rebounded by week 5 even with high plasma concentrations of VRC01
• Modestly delayed virus rebound compared to historical controls
Profile of a 2nd Generation mAb Product

- Cost comparable to ARV drugs
- Cover 98-99% of virus diversity
- 10-fold more potent than current mAbs
- Given by SQ injection once every 3-4 months (vs IV infusion every 2 months)

Combined mAbs: Improved Potency and Breadth

Combination of 2+ mAbs improves potency and breadth

Mutations to Increase Half-Life

At least 3 - 4 fold increase in half-life in healthy adults
Decreases dose needed by 5-10 fold
Potentially extends dosing interval to every 6 months
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**Bifunctional Antibodies**

- Bispecific T cell engager (BITE)
- Dual-affinity re-targeting protein (DART)

Potential to mediate cell killing of infected CD4 T cell
Products exist and have entered clinical trials for cancer
Little in vivo data for treatment of HIV, even in animal models

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**Bifunctional Antibodies: Proof of Concept**

BITEs and DARTs mediate killing of HIV-infected cells in vitro

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**Conclusions for an HIV Cure**

- LRAs show poor reactivation and no reduction in reservoir size
- Gene therapy may be used to target HIV and/or CCR5
- Clinical studies are ongoing and some show reservoir reduction
- Env-specific mAbs are in promising proof of concept studies
- More potent mAbs and combinations of mAbs are on the horizon
- New approaches to cell-mediated killing of infected T cells
- Combinations of approaches may be used:
  - LA-ARVs + mAbs, LRAs + BITEs, gene therapy + mAbs + LRAs
SUGGESTED READINGS


