Deciphering HIV Pathogenesis: Implications for Therapy and Prevention

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The Global AIDS Pandemic: A Snapshot

- 12,000 new infections and 8,000 deaths every day-epidemic continues to expand
- Heterosexual transmission accounts for >80% of HIV infections worldwide
- 50% of infections occur in young people (15-25)
- Only 1 in 10 infected know that they are infected
- 1,600 children infected daily as a result of mother to child transmission
- >12 million children have been orphaned from the death of one or both parents from AIDS
AIDS Is Like an Indonesian Tsunami Every 4 Weeks

About 240,000 died in this disaster

The Global HIV Epidemic
Over 25 million infected in Africa

The sub-Saharan AIDS epidemic is very much about children.
Where Did the AIDS Virus Come From?

African Apes

Three separate transmissions of primate viruses since ~1930, one spawned the global AIDS pandemic
How was the source of the AIDS virus identified?
But the team did not trap or kill the apes...

Noninvasive collection of “ape droppings”
What type of ape transmitted the AIDS virus?

Chimpanzees
Pan troglodytes troglodytes
Actively hunted, skinned and sold in “bushmeat” markets (blood exposure)

Origin of HIV-1 Group M
Why one chimp virus has caused the current global HIV pandemic while the other chimp and gorilla viruses have not spread widely remains a mystery.

Other primate viruses are still lurking…
Only 9 genes, 15 proteins, and an RNA

But 40+ million HIV-infected and over 25 million already dead of AIDS
Protease Inhibitors

RT Inhibitors
HIV antiviral medications are not yet reaching those in greatest need

Only 1 out of 4 Africans needing treatment are receiving treatment
What new HIV drugs have recently become available?

Entry Inhibitors

Maraviroc

HIV-1 Life Cycle
**The CCR5 Δ32 Mutation Story:**
An Informative Experiment of Nature

**Wild-type CCR5**
- Wild-type protein expressed at cell surface
- Binds MIP-1α, MIP-1β, and RANTES chemokines which participate in the inflammatory response

**CCR5 Δ32 Mutation**
- Truncated receptor protein that is never expressed at the cell surface
- People homozygous for this mutation are healthy with no defect in inflammation suggesting chemokine receptor redundancy
- Found in 2–5% of Caucasians; less frequent in Asian and African races

**CCR5 Δ32/Δ32 Mutation Provides Protection from HIV Infection**

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<td>+/+</td>
<td>+/Δ32</td>
<td>Δ32/Δ32</td>
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<td>(85%)</td>
<td>(13–14%)</td>
<td>(1–2%)</td>
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- Susceptible to HIV infection
- Susceptible, but may clinically progress less rapidly
- Highly resistant to HIV infection
What is new and exciting on the therapeutic horizon?
Each of us in this room produces a potent innate antiviral factor that can potentially stop HIV “dead in its tracks”

APOBEC3G

- Antiviral factor active against HIV
- Member of a family of enzymes that “edits” viral RNA and DNA
- Incorporated into budding HIV virions and renders these virions non-infectious
In view of the potent anti-viral properties of APOBEC3G, why are we witnessing a global HIV epidemic?

...because HIV dedicates one of its nine genes, Vif, for neutralizing APOBEC3G
An exciting new target for development of an entirely new class of anti-HIV drugs
Facts About HIV

- Untreated patients produce 50-500 billion virions every day

- Each infected cell produces enough virus to infect 10 new cells (replicative rate of 10)

- >90% effective therapy (which we have) should reduce the replicative rate to <1 thereby extinguishing infection

- Why no cure for infected patients?
HIV Latency

- HIV can silently hide in one type of very long lived T cell

- While these cells are rare, clearing them from the body is predicted to require >60 years of treatment

- New approaches are urgently needed otherwise a “cure” for HIV infection will never become a reality

Genomic Structure of HIV-1

- Only 9 genes, 15 proteins, and an RNA
- But 40+ million infected and rising
HIV-1 Life Cycle

Genomic Structure of HIV-1

Potent transcriptional activator
How RNA Pol II Transcription Proceeds in the Absence of Tat

Genomic Structure of HIV-1

Regulator of structural gene expression
Rev and RNA Export through the Nuclear Pore
HIV Immunopathogenesis
How Does HIV Lead to T Cell Depletion?

- **The virus is cytopathic** - leads to accelerated destruction of both mature CD4+ T cells and immature progenitor cells

- **The virus is antigenic** - triggers a chronic inflammatory response that facilitates viral replication and spread

What might be driving immune activation beyond HIV?
HIV Causes Depletion of Gut-associated CD4+ T Cells and Breakdown of Mucosal Barrier

Brenchley et al, J Exp Med, 2004

Plasma LPS Levels Are Increased in Chronic HIV Infection

Brenchley et al, Nat Med 06
Common Theme

In the presence of chronic inflammation:

HIV $\rightarrow$ T Cell Depletion $\rightarrow$ AIDS

In the absence of chronic inflammation:

HIV $\rightarrow$ T Cell Depletion $\rightarrow$ AIDS

New Approaches to Immune Reconstitution in HIV Disease
Laura A. Napolitano, MD

The Human Thymus
Can We Find Therapies to Restore Thymic Function?

Growth Hormone Biologic Functions

- Regulates body growth and metabolism
  - Greatest activity: first two decades of life
  - Underappreciated role in the immune system
  - Restores function of the thymus in aged rodents and dogs
Growth Hormone Treatment Increases Thymic Density in HIV-Infected Adults

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Growth Hormone Treatment Increases Thymic Density and T Cell Numbers

![Graph showing change in thymic density and T cell numbers with and without GH treatment.](graph.png)

*significant difference
Growth Hormone Cessation Reverses the Gain in Thymus Tissue

T Cell Diversity in HIV Disease

Normal T cell Repertoire

Depletion

HIV

De novo T cell production

IL-2

Peripheral T cell expansion

Pre-study  6 Months on GH  12 Months off GH
### Prevention Approaches That Work on a Limited Basis

- **Voluntary Counseling and Testing**: stigma
- **Condoms**: no better than 20% use
- **Screening of the Blood Supply**: variable
- **Antivirals to Prevent Sexual and Mother to Child Transmission**: still not widely used
- **Clean Needles**: highly political issue

### New Prevention Approaches We Hope Will Work in the Future

- **Microbicides**: 5-10 years
- **Pre-exposure Prophylaxis**: testing now
- **HIV Vaccine**: a distant dream
- **Circumcision**: ???
Male Circumcision

- Oldest common surgery
- 20-25% of men circumcised
- Simple procedure that confers many benefits
- Procedure entails some risk particularly in adult males
- Benefits must be weighed against risks
- Cultural considerations
Circumcision Markedly Reduces Female-to-Male Transmissions of HIV

Male-to-Female Transmissions of HIV Also Reduced by Circumcision When Viral Load Is Low
Two large circumcision trials recently halted because > 50% protection was demonstrated; unethical to continue

Could anti-retroviral drugs be used to prevent HIV infection before it occurs?
Pre-Exposure Prophylaxis (PrEP)

- Used daily—can be initiated by women
- Prophylaxis is a proven medical concept (malaria, TB, birth control pills)
- Requires identification of high risk groups for proof of concept
PrEP works in experimentally infected monkeys (70-100%)

If successful, PrEP could “buy time” as we continue to try to develop an effective AIDS vaccine

Progress very limited so far; lead Merck vaccine just recently failed
Exciting New Avenues of Prevention

• Semen Enhancer of Viral Infectivity (SEVI)
But no medical or preventive interventions will work without increasing the health care infrastructure throughout Africa.