New strategies in HIV Cure

Block, Lock, & Excise

Lishomwa (Lish) Ndhlovu MD, PhD
Professor in Immunology in Medicine and Neuroscience
Division of Infectious Diseases | Department of Medicine
Conflict of interest disclosure

Received Consulting fees/honoraria from Abbvie and ViiV Healthcare

Ownership Interest (stocks, stock options, or other ownership interest excluding diversified mutual funds) with Cytodyn and service on the board directors and will not be discussing the off-label or investigational use of products.

No research support is received.
HOPE Scientific Program

**BLOCK**  Inhibiting HIV transcription

**LOCK**  Keeping the virus blocked without therapy

**EXCISE**  Inactivating proviral DNA in the genome

*Using epigenomic and genomic approaches to permanently inactivate HIV*
HOPE  Accelerating HIV’s natural path to an endogenous retrovirus
HOPE Scientific Program

ACTIVE

LATENT

SILENCED

EXCISED
HOPE Scientific Program

ACTIVE

Towards an HIV Cure

Histone Acetylation
HOPE Scientific Program

ACTIVE

Target Virus

Tat

SEC

Target Host

Histone Acetylation
HOPE Scientific Program

LATENT

Recruit Repressors

Paused Pol II

Target Polymerase
HOPE Scientific Program

ACTIVE
LATENT
SILENCED

Remove or alter HIV genome
HOPE Scientific Program

EXCISED
RF1: Define HIV silencing by targeting host and viral factors

Co-Directors
- Valente
- Greene

Members
- Feschotte
- Kumar
- Murthy
- Ndhlovu
- Nixon
- Roan
- Ott
- Verdin
Goal 1
Identify host regulators of HIV proviral silencing

Goal 2
Learn from endogenous retroviruses how to silence HIV

Goal 3
Define role of Tat in HIV silencing

Goal 4
Characterize -omics of HIV silencing

RF1 Hypothesis:
HIV transcription and chromatin structure offer unique targets for silencing
CRISPRi efficiently blocks HIV transcription
**RF2: Develop next-generation HIV silencing approaches**

<table>
<thead>
<tr>
<th>Co-Directors</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ndlovu</td>
<td>Agan</td>
</tr>
<tr>
<td>Roan</td>
<td>Nath</td>
</tr>
<tr>
<td>Ake</td>
<td>Nixon</td>
</tr>
<tr>
<td>Feschotte</td>
<td>Ott</td>
</tr>
<tr>
<td>Hsu</td>
<td>Smith</td>
</tr>
<tr>
<td>Kallas</td>
<td>Valente</td>
</tr>
<tr>
<td>Kibuuka</td>
<td>Verdin</td>
</tr>
<tr>
<td>Kumar</td>
<td>Weibel</td>
</tr>
<tr>
<td>Mwesigwa</td>
<td></td>
</tr>
</tbody>
</table>
RF2 Hypothesis:
Viral rebound is suppressed with silencing-promoting agents (SPA) after ART is stopped

Goal 1
Determine *in vivo effects* of candidate SPAs

Goal 2
Develop **novel SPAs**

Goal 3
Apply **sequence-specific** SPAs *in vivo*

**Screen single dose**
Tat-TAR toxicity assays

**Confirmation single dose**

**Dose response**

**Counterscreen TNF-α Assay**

- 579,443 small molecules
- 1024 hits
- 30 hits
- 5 leads
Tat inhibitors silence HIV transcription

Towards an HIV Cure IAS

Susana Valente
RF3: Disable the HIV provirus by targeted genome engineering

Co-Directors
- Kumar
- Ott

Members
- Chemnitz
- Feschotte
- Greene
- Hsu
- Hauber
- Lange
- Murthy
- Ndhlovu
- Nixon
- Valente
**RF3 Hypothesis:**

*In vivo* delivery of genome-engineering therapeutics permanently inactivates HIV without genotoxicity

---

**Goal 1**

Develop **double strand break-free** genome engineering method

---

**Goal 2**

Establish *in vivo delivery* platforms

- Virus-like-particles (VLP)
- PLGA nanoparticles (PLGA-NP)
- Protein/Peptide conjugates
In vivo delivery of $\alpha$CD7 VLPs targets CD4 T cells in mice
Teaching-learning model 'through the arts' and 'with the arts’ to understand complex HIV CURE research concepts and for researchers to better understand what it is like living with the infection.
Publications and IAS Abstracts

**Human endogenous retrovirus expression in HIV-associated diffuse large B-cell lymphoma**
Matthew L. Bendall,1, Jez L. Marston,1, Bhavaya Singh1, Gisalaine Curty2, Luis P. Iliguez1, Fabio E. Leal1, Ethel Cesaran1, Cedric Fescher,1, Douglas F. Nixon1

1Division of Infectious Diseases, Department of Medicine, Weill Cornell Medicine, New York, New York, USA.
2Oncovirolgy Program, Instituto Nacional de Cancer, Rio de Janeiro, Brazil.
3Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, New York, USA.

**Off-target effects on retroelement expression in T-cells Treated with Histone deacetylase inhibitors**
G. Curty 1, L.P. Iliguez 2, D.F. Nixon 3, M.A. Soares 1, M. de Mulder Rougvie 2, 3

1Instituto Nacional de Cancer, Oncovirolgy Program, Rio de Janeiro, Brazil, 2Weill Cornell Medicine, Division of Infectious Diseases, New York, United States, 3Weill Cornell Medicine, Department of Genetic Medicine, New York, United States.

**Endogenous Retrovirus Expression Distinguishes Latent From Actively Infected Cells In Novel Dual-Reporter HIV Latency Model**
Marston, Jez L. 1, 2, Randall, Kipchoie 2, Yesmeen Elgabor 2, Nixon, Douglas F. 2

1Department of Infectious Diseases, Weill Cornell Medical College, New York, NY
2Gateways to the Laboratory Program, Weill Cornell/New York-Presbyterian Sloan Kettering Tri-Institutional MD-PhD Program, New York, NY
3San Jose State University, San Jose, CA

**Effect of novel latency reversal agents on transposable element expression profile in T-cell memory subsets of HIV clinical samples**
G. Curty 1, L.P. Iliguez 2, M.A. Soares 1, D.F. Nixon 2, M. de Mulder Rougvie 2, 3

1Instituto Nacional de Cancer, Oncovirolgy Program, Rio de Janeiro, Brazil, 2Weill Cornell Medicine, Division of Infectious Diseases, New York, United States, 3Weill Cornell Medicine, Department of Genetic Medicine, New York, United States.
Learn More

HOPEforHIVcure.org

A fundamentally different “block-lock-excite” approach to cure HIV/AIDS

Follow us on @HOPEforHIVcure