Professor Mario Stevenson
University of Miami Leonard M Miller School of Medicine, Florida, USA

COMPETING INTEREST OF FINANCIAL VALUE

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<td>Professor Mario Stevenson</td>
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Date: April 2012
ART now, ART to come: Is there a need for new ARVs?

BHIVA, Birmingham, April 2012.

Mario Stevenson, Ph.D.
University of Miami Miller School of Medicine.

HAART IS EFFECTIVE:

• Rapidly achieves 4-6 log reduction in viremia to below detectable limits.
• Suppression to below detectable levels is rapid and durable.
What sustains HIV-1 in the face of HAART?
What accounts for the extreme persistence of the viral reservoir? - predictions

- HAART stops active replication. Latency allows lifelong persistence of the virus.
  - Prediction, intensification won’t change anything.
- Incomplete virologic suppression creates conditions for reservoir replenishment.
  - Prediction, different treatments may perturb the viral reservoirs.

How do we probe the viral reservoirs that persist in the face of HAART?

- New classes of antiretroviral agents widen treatment options for infected patients but also offer reagents with which to probe the reservoirs that persist in the face of HAART.
Monitoring the impact of therapy intensification:

- INTegRAL study in collaboration with J. Picado & B. Clotet: impact of Raltegravir intensification.
- 69 patients on suppressive 3 drug HAART regimen randomized to intensify with Raltegravir (n=44) or to continue HAART (n=24).
- Episomal cDNA and immune activation parameters were monitored.
Episomes increase upon Raltegravir intensification.
Increase in episomes following Raltegravir intensification can only be explained by *de novo* infection.

Reservoirs of cryptic replication?

- If treatment intensification impacts the viral reservoir, does this indicate incomplete suppression?
- Some tissue reservoirs may not reflect what is happening in the blood.
- Do these reservoirs constitute sanctuary sites for viral replication?
- Attention has focused on the lymphoid tissue in the gut since it is the predominant site of viral replication.
The role of lymphoid tissue in viral persistence.

- PO1 collaboration to identify the virologic response in tissue to ART.
- Baseline and sequential sampling over 6 months of gut and lymph node from patients initiating suppressive ART.
- Examination for viral infection intermediates (episomal, proviral, unintegrated linear cDNA) cell associated RNA and intracellular drug levels.
Results.

- Decay dynamics of viral replication intermediates follow 2 patterns:
  - Patients whose cDNA levels fall to below detectable by 6 months.
  - Patients whose cDNA levels at 6 months in 1 or more tissue compartments remain detectable or increase over entry-point or 1 month levels.
Results.

• Decay dynamics of viral replication intermediates follow 2 patterns:
  - Patients whose cDNA levels fall to below detectable by 6 months (3/10)
  - Patients whose cDNA levels at 6 months in 1 or more tissue compartments remain detectable or increase over entry-point or 1 month levels (7/10).
Basis for incomplete virologic response in lymphoid compartments:

• Does a suboptimal virologic response in tissue occur in the face of effective drug sequestration in the tissue?
• Determine intracellular drug levels relative to concentrations in peripheral blood lymphocytes.

Improving virologic response in tissue reservoirs:

• Despite suppressive HAART, de novo viral infection persists in lymphoid tissue (esp. LN).
• Inability to sequester antivirals in tissue lymphocytes may create conditions for replenishment of the viral reservoirs.
• These findings have implications for strategies aimed at viral control
New Therapeutic Targets:
Harnessing Cellular Restrictions.

Retrovirus: Host interactions

Courtesy Paul Bieniasz
Retrovirus: Host interactions

Courtesy Paul Bieniasz

Tetherin restricts virus particle release

Apobec3 restricts cDNA synthesis/integrity

Nuclear import integration
If our cells carry such potent restrictions, why are we still susceptible to HIV-1 infection?

**Vif inhibits APOBEC3G by inducing proteasome-mediated degradation**

Mariani et al., Stopak et al., Sheehy et al., Marin et al., Conticello et al., Yu et al., Mehle et al.
Validation of RN18 as vif antagonist:

- Since vif is required only in cells that express Apobec3, a vif antagonist would be predicted only to exert antiviral activity in non-permissive cells (i.e. in cells that express Apobec3).
RN18-resistance profiles.

- Experience with other classes of ARVs predicts that viruses acquiring resistance to an agent will also exhibit resistance to related compounds.
- Examine sensitivity of RN18-resistant virus to RN18 analogs
**Structure Activity Relationship on RN18: conclusions**

- SAR on approx. 500 analogs of RN18
- SAR has identified active compounds with superior numbers that are drug like molecules.
- Novel resistance profiles: virus resistant to RN18 remains sensitive to its analogs.
Development of small-molecule Vif antagonists:

RN18 is a *bona fide* vif antagonist - restricts viral replication only in the presence of its target and increases the extent of deamination in viral cDNA (*Nathans et al., Nature Biotech.*)

Proof-of-principle evidence that cellular restrictions can be harnessed as novel antivirals.

RN18 is a drug-like molecule. Preclinical development of these novel antagonists is underway (NIH U01 and Industry support)

Viral countermeasures (accessory genes)  Innate cellular defenses
Accessory Gene inhibitors

Cellular antagonists

Collaborators:

IRSI Caixa, Barcelona
Ventura Clotet
Javier Picado
Roger Paredes

University of Minnesota
Tim Schacker
Ashley Haase
Cavan Reilly

University of Nebraska
Courtney Fletcher

Burnham Institute
Tariq Rana

Vaccine Research Center, NIH
Danny Douek

UCSF
Steve Deeks
Mike McCune