18th Annual Conference of the British HIV Association (BHIVA)

Professor Mario Stevenson

University of Miami Leonard M Miller School of Medicine, Florida, USA

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Professor Mario Stevenson:	None
Date	**April 2012**

18-20 April 2012, The International Convention Centre, Birmingham

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.

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HAART IS EFFECTIVE:

- Rapidly achieves 4-6 log reduction in viremia to below detectable limits.
- Suppression to below detectable levels is rapid and durable.

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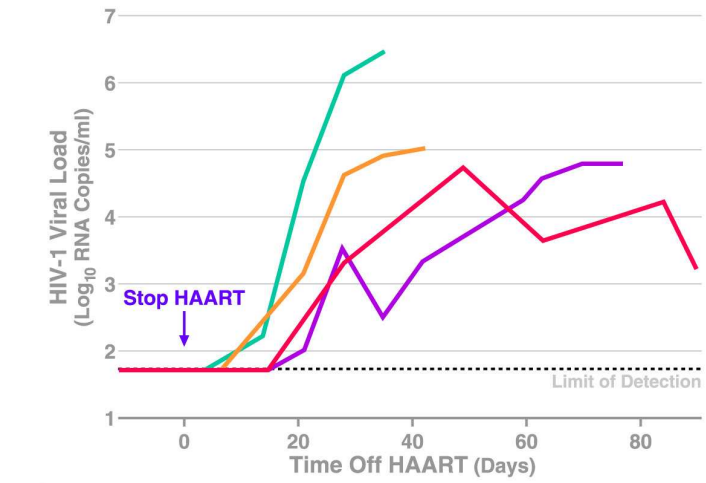
Viral Rebound After HAART Interruption



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What sustains HIV-1 in the face of HAART?

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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.

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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.

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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.

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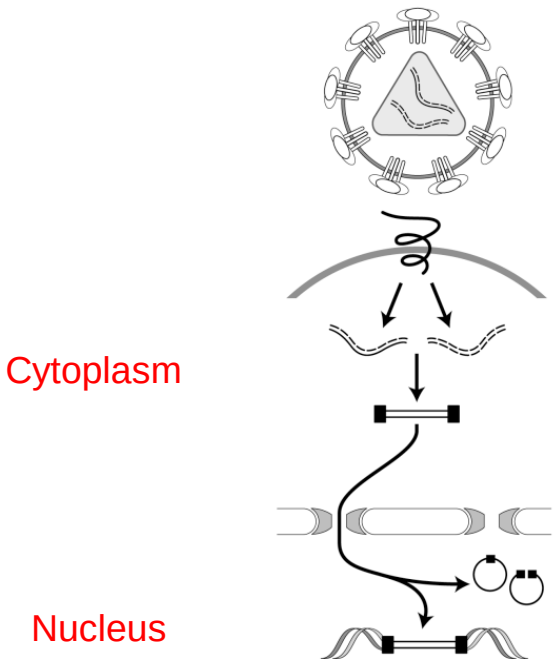
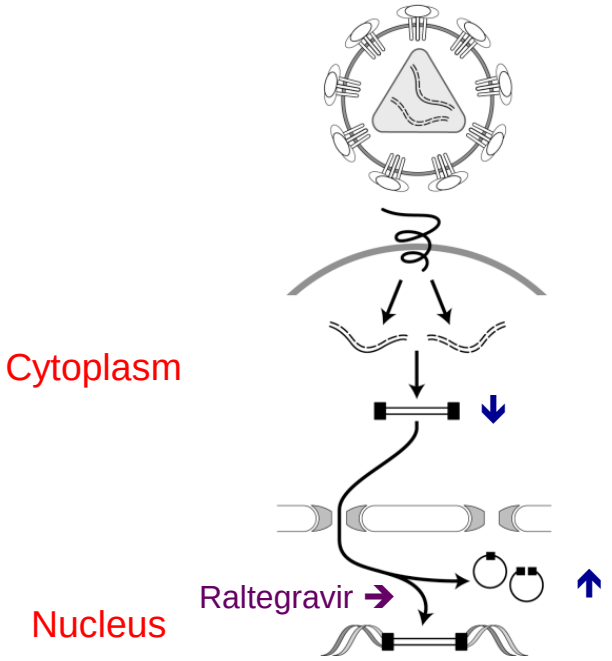
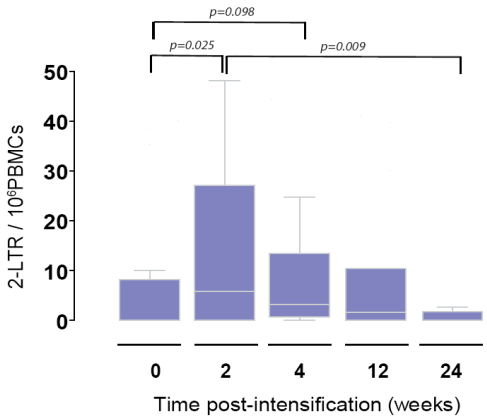
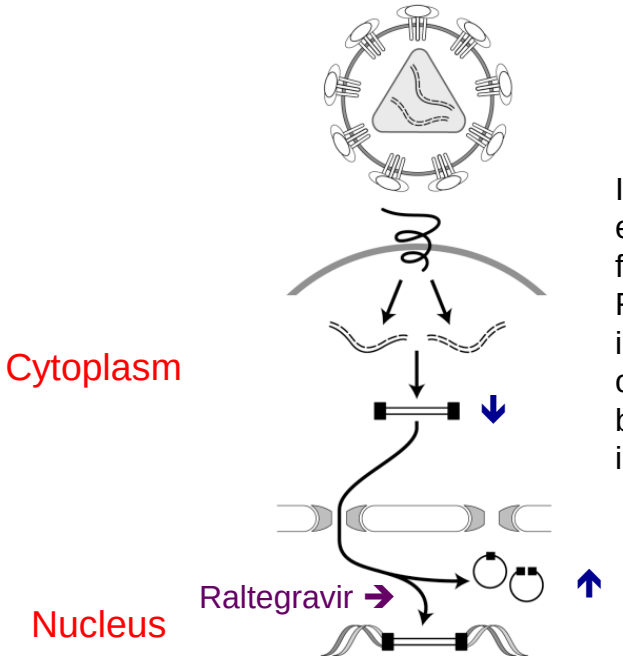




Episomes increase upon Raltegravir intensification.



Buzon et al., Nature Med. 2010



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.

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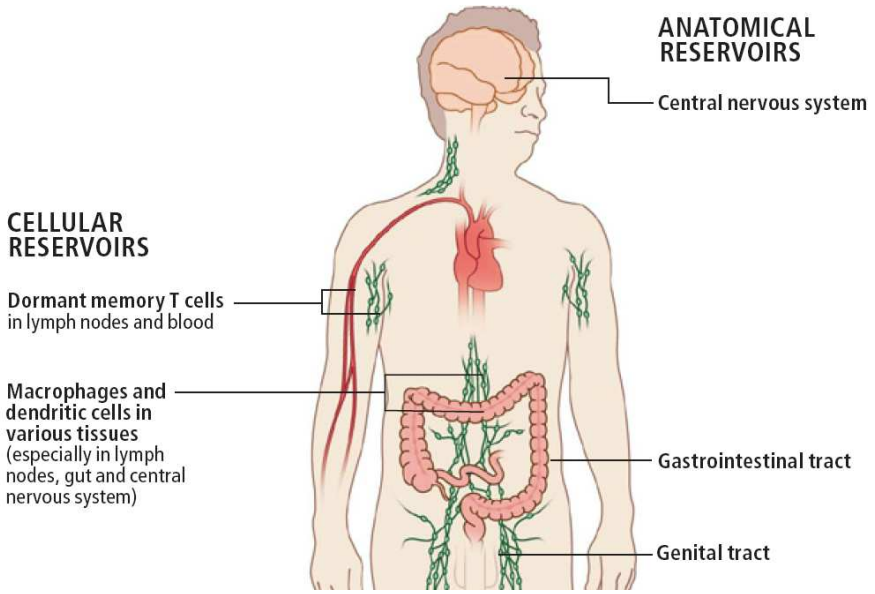
Reservoirs of HIV-1 persistence in HAART



M. Stevenson, Scientific American 2008

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.

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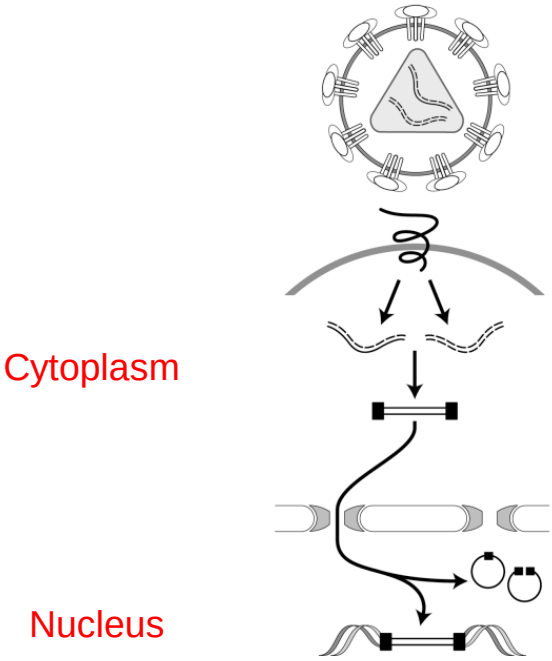

Results.

- 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.

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Results.

- Decay dynamics of viral replication intermediates follow 2 patterns:

  - Patients whose cDNA levels fall to below detectable by 6 months (3/10)

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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 (7/10).

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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.

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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

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New Therapeutic Targets:

Harnessing Cellular Restrictions.

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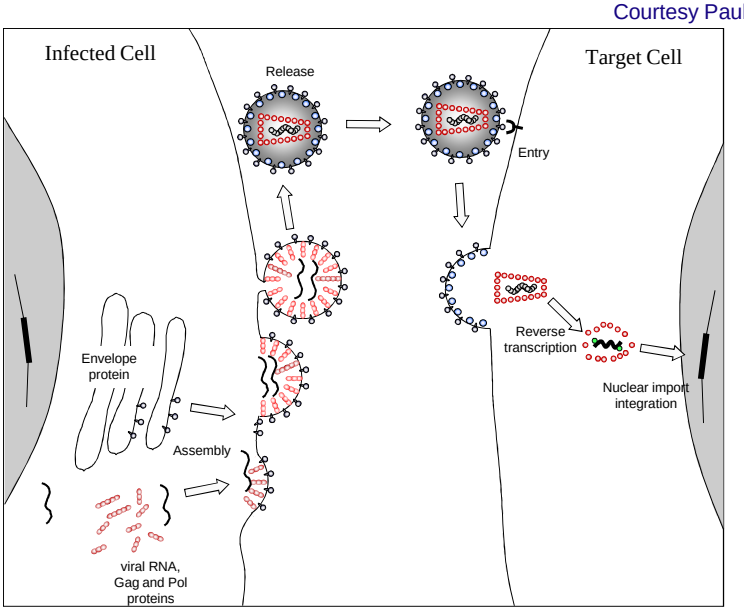
Retrovirus:Host interactions

Courtesy Paul Bieniasz



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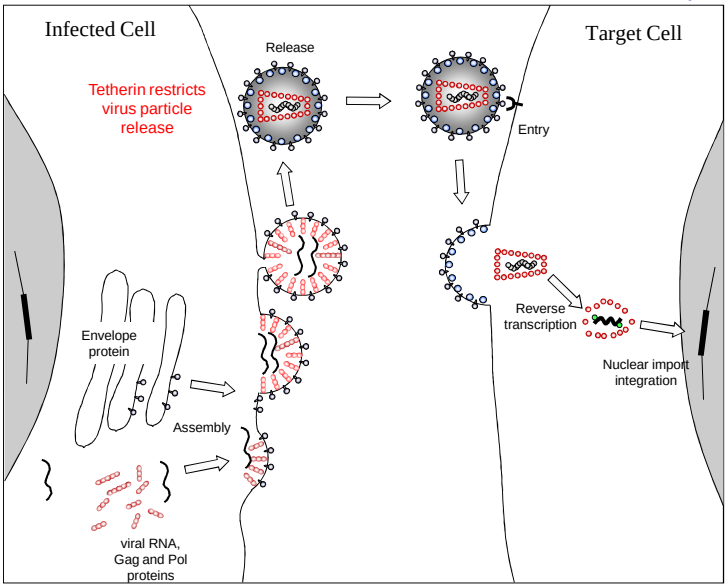

Retrovirus:Host interactions

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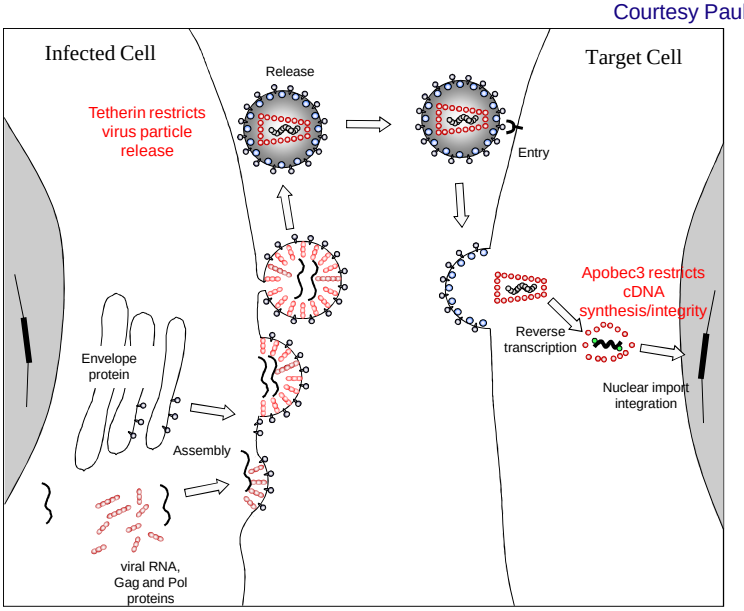
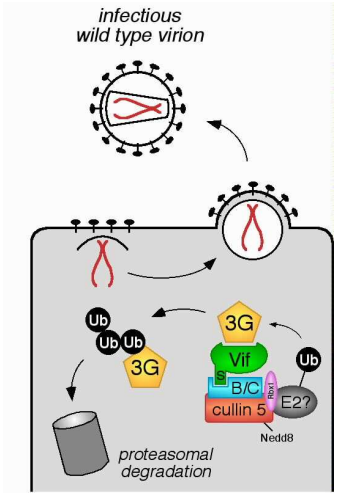


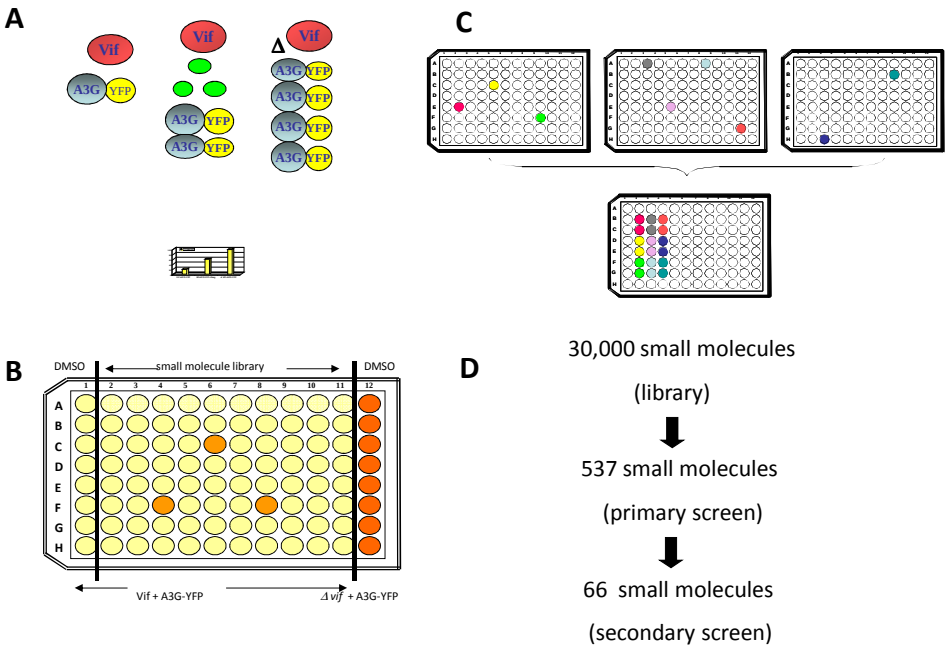
If our cells carry such potent restrictions, why are we still susceptible to HIV-1 infection?

Vif inhibits APOBEC3G by inducing proteasome-mediated degradation



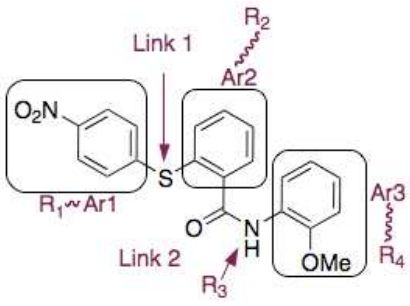
Mariani *et al.*, Stopak *et al.,* Sheehy *et al.,* Marin *et al.,* Conticello *et al.,* Yu *et al.,* Mehle *et al.*

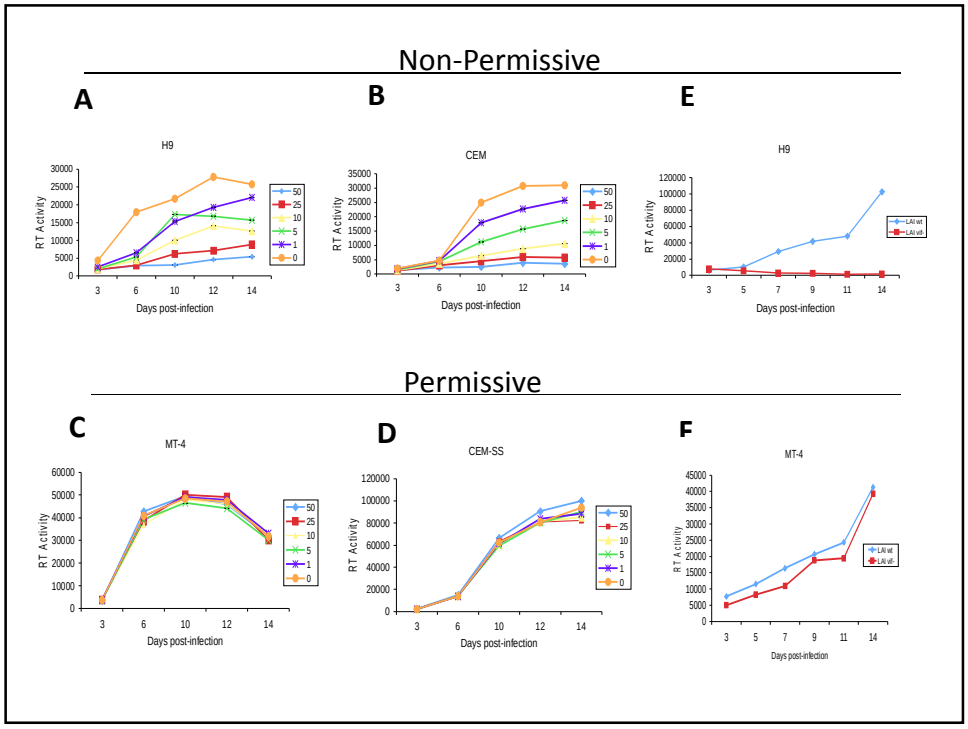
Cell-based screen for Vif antagonists



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).

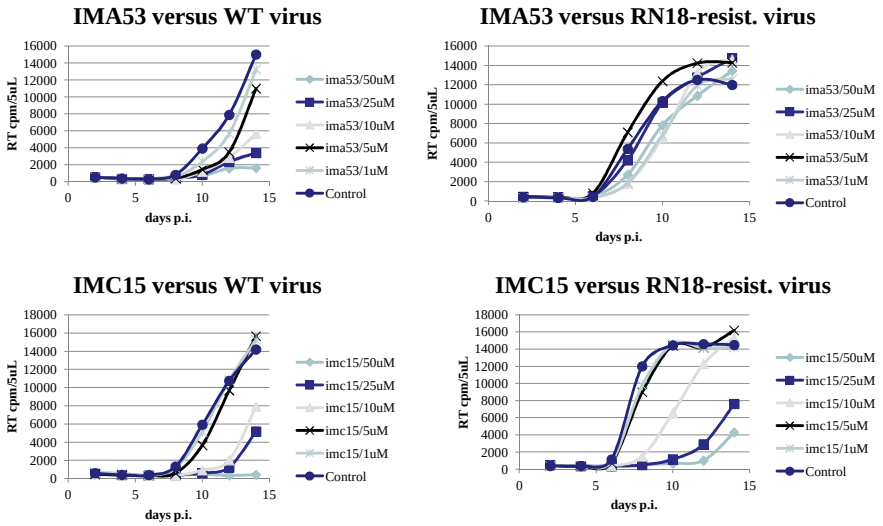




RN18-resistance profiles.

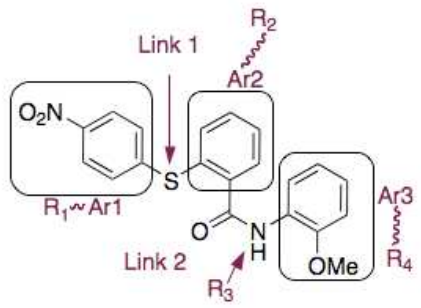
- Experience with other classes of ARVs predicts that viruses acquiring resistance to an agent will also exhibit resistance to related compounds.
- Examine sensitivity of RN18-resistant virus to RN18 analogs

RN18-resistant virus retains sensitivity to some 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:

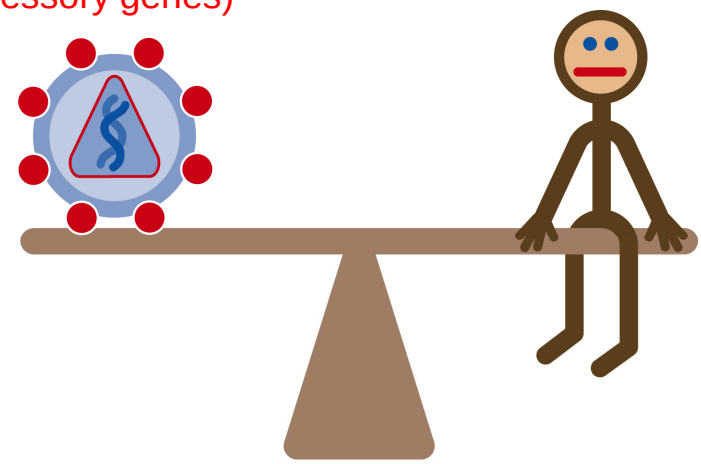
RN18 is a *bona fide vif* antagonist -restricts viral replication only in the presence of its target and increases the extent of deamination in viral cDNA (*Nathans et al., Nature Biotech.)*

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

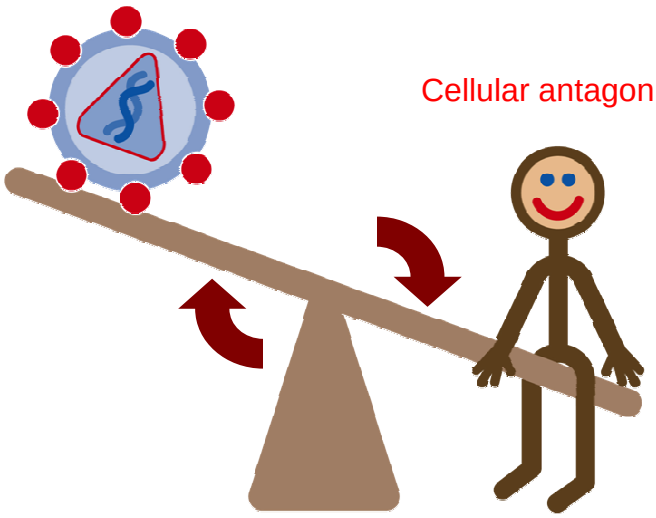
RN18 is a drug-like molecule. Preclinical development of these novel antagonists is underway (NIH UO1 and Industry support)

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

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