Jak inhibitors employ novel mechanisms to block reservoir seeding and HIV persistence

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Background: Barriers to an HIV Cure and potential crosstalk to malignancies

- Current HAART cannot eliminate HIV-1.
  - Viral reservoirs:
    - Myeloid (including brain/CNS).
    - Lymphoid.
    - Pharmacological sanctuaries.
  - Ongoing inflammation (sCD14, IL-6, TNF-α, IL-7/15, D-dimer, sCD163, IL-1-α/β, others) even in individuals with well-controlled viremia contributes to reservoir:
    - Establishment, maintenance, and expansion.

Unmet clinical need = safe, specific, potent inhibitors of HIV-induced inflammation.
Our group and more recently others demonstrated that Jak inhibitors can block HIV replication and associated inflammation in macrophages and T cells *in vitro* and *in vivo*.


*Ruxolitinib and tofacitinib are potent and selective inhibitors of HIV-1 replication and virus reactivation in vitro.*

Gavegnano C¹, Detorio M, Montero C, Bosque A, Planelles V, Schinazi RF.


*The Janus kinase inhibitor ruxolitinib reduces HIV replication in human macrophages and ameliorates HIV encephalitis in a murine model.*

Haile WB¹, Gavegnano C², Tao S², Jiang Y³, Schinazi RF⁴, Tyor WR⁵.

**Retrovirology**

*Janus kinase inhibition suppresses PKC-induced cytokine release without affecting HIV-1 latency reversal ex vivo*

Adam M. Spivak², Erin T. Larragoite²*, McKenna L. Coletti², Amanda B. Macedo², Laura J. Martins², Alberto Bosque² and Vicente Planelles²
Hypothesis:
Blockade of HIV-induced inflammation with a Jak inhibitor could lead to purge of the viral reservoir, resulting in a functional cure or elimination of HIV-1.

Reservoir cell with current HAART

Reservoir persists, divides, expands.

Inability to eliminate HIV-1

Reservoir cell with ruxolitinib as HAART add on

Reservoir cells will die and reservoir could be eliminated.

- Possibility to remove HAART without viral rebound.
- Functional cure or elimination of HIV-1.
- Shorter duration of treatment.

- Decreased reservoir lifespan.
- Block reservoir expansion, reseeding.
Advantages of baracitinib versus ruxolitinib

**Jak 1/2 inhibitors that are nanomolar in vivo inhibitors of IL-6, IL-1α/β, TNF-α, CRP, D-Dimer, other inflammatory markers.**

**Ruxolitinib**
- FDA approved for myelofibrosis (2011).
- FDA approved for polythemia vera (2014).
- Orally available bid dosing (10-15 mg).
- Hepatic clearance.
- No approval for pediatric population.
- ACTG sponsored multi-site Phase 2A study “A Randomized, Pilot Study of Ruxolitinib in Antiretroviral-Treated HIV-Infected Adults in HIV-infected subjects” (n = 60; underway).

**Baracitinib**
- EU and Japan approval for rheumatoid arthritis.
- FDA approval pending in the United States.
- Orally available qid dosing (1, 2, 4 mg).
- Renal clearance.
- Second generation Jak inhibitor with reduced toxicity profile.
- Approved in pediatric populations (EU, Japan).
Markers of the Jak-STAT pathway and homeostatic proliferation are associated to HIV reservoir size \textit{in vivo}.

Jak inhibitors block reservoir establishment, maintenance, and expansion in primary monocytes/macrophages \textit{in vitro}.

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<th>Drug</th>
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<th>EC$_{50/90}$ in macrophages, µM</th>
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- No observed toxicity $\geq 50$ µM across all cells tested.
- Therapeutic window $> 100$ for all measures reported.
- All concentrations that block pro-HIV events are physiological.

Gavegnano and Schinazi et al, AAC, 2013 and unpublished work.
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Summary for Preclinical Evaluation of Baracitinib

• Baracitinib demonstrated potent, specific inhibition of key events that prevent eradication of HIV-1 in macrophages and T cells, which is a unmet clinical need for HIV-infected individuals.
  - Reservoir establishment, maintenance, lifespan, reseeding.
  - Reservoir maintenance.
  - CNS infection and HIV-induced encephalitis and neurocognitive impairments (HAD/HAND).

• Blockade of HIV-specific inflammatory events by baracitinib could reduce or prevent inflammatory-driven malignancies in HIV-infected individuals.

• Baracitinib could represent an add-on therapy to HAART that could decay the viral reservoir, eventually allowing for withdrawal of HAART without viral rebound.

• Human studies are underway with ruxolitinib, a similar Jak 1/2 inhibitor:
  – Phase 2a ACTG sponsored study (A5336) “A Randomized, Pilot Study of Ruxolitinib in Antiretroviral-Treated HIV-Infected Adults” (n = 60).
Acknowledgements

Team members

- Raymond F. Schinazi, PhD, DSc
- Vincent Marconi, MD
- William Tyor, MD
- Guido Silvestri, MD
- Woldeab Haile, PhD
- Rafick Sekaly, PhD
- Jessica Brehm, PhD
- Franck Dupuy, PhD
- Selwyn Hurwitz, PhD
- Catherine Montero, BS
- ACTG team

Funding:
NIH 4RO1MH10099904
CFAR NIH grant P30AI050409
Emory Center for Drug Discovery
and NIH ACTG
Extra slides
Jak inhibitors confer inhibition of multiple pro-HIV cytokines

PRO HIV CYtokines are boxed

- IL-2
- IL-7
- IL-15
- IL-6
- IFN-α/β
- IL-10
- LIF
- gp130 family
- IL-11, OSM

Baracitinib and Ruxolitinib

Tofacitinib (primarily Jak3)

Jak 1

Jak 2

Jak 3

Tyk2

Baracitinib and Ruxolitinib