Repurposing BCL-2 and JAK-inhibitors to target myeloid reservoirs

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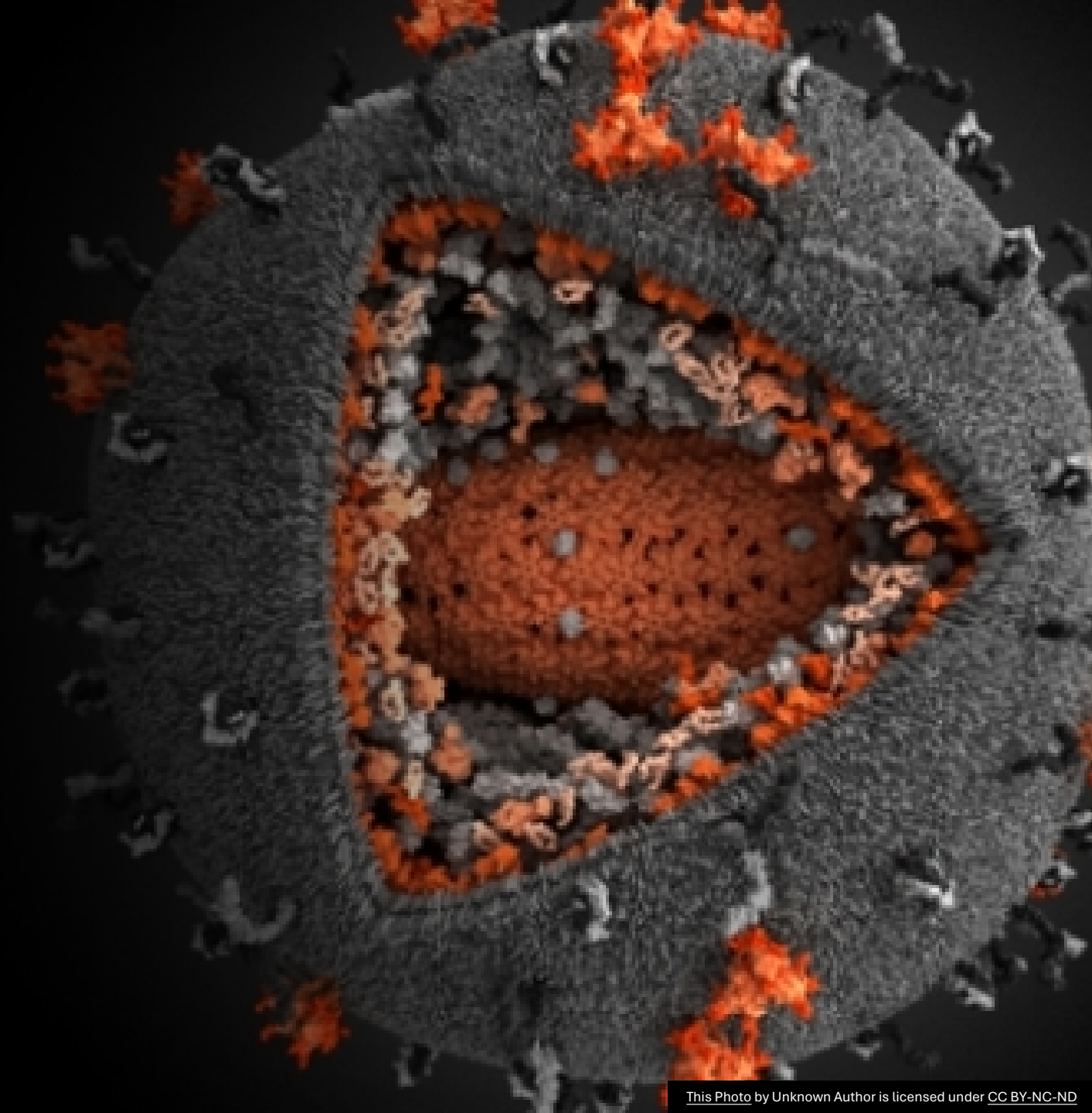
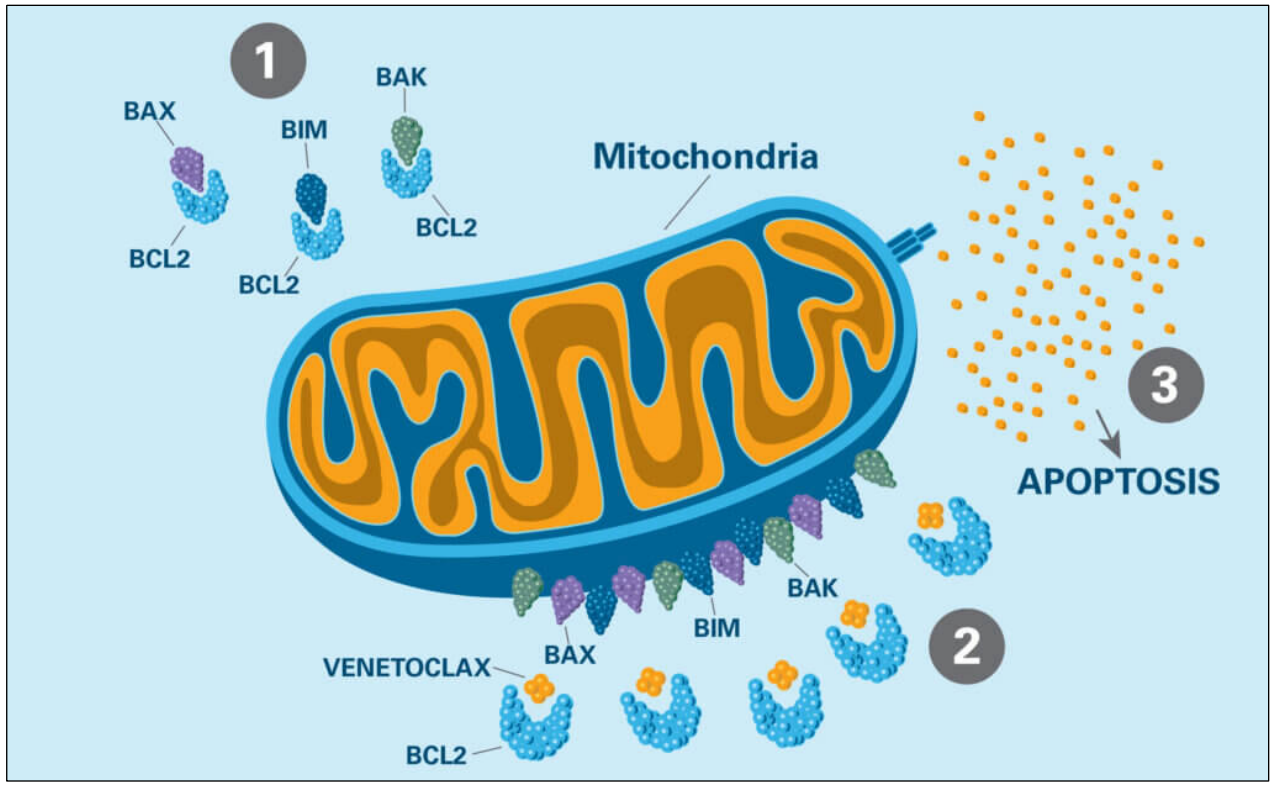


Conflicts of Interest

- None

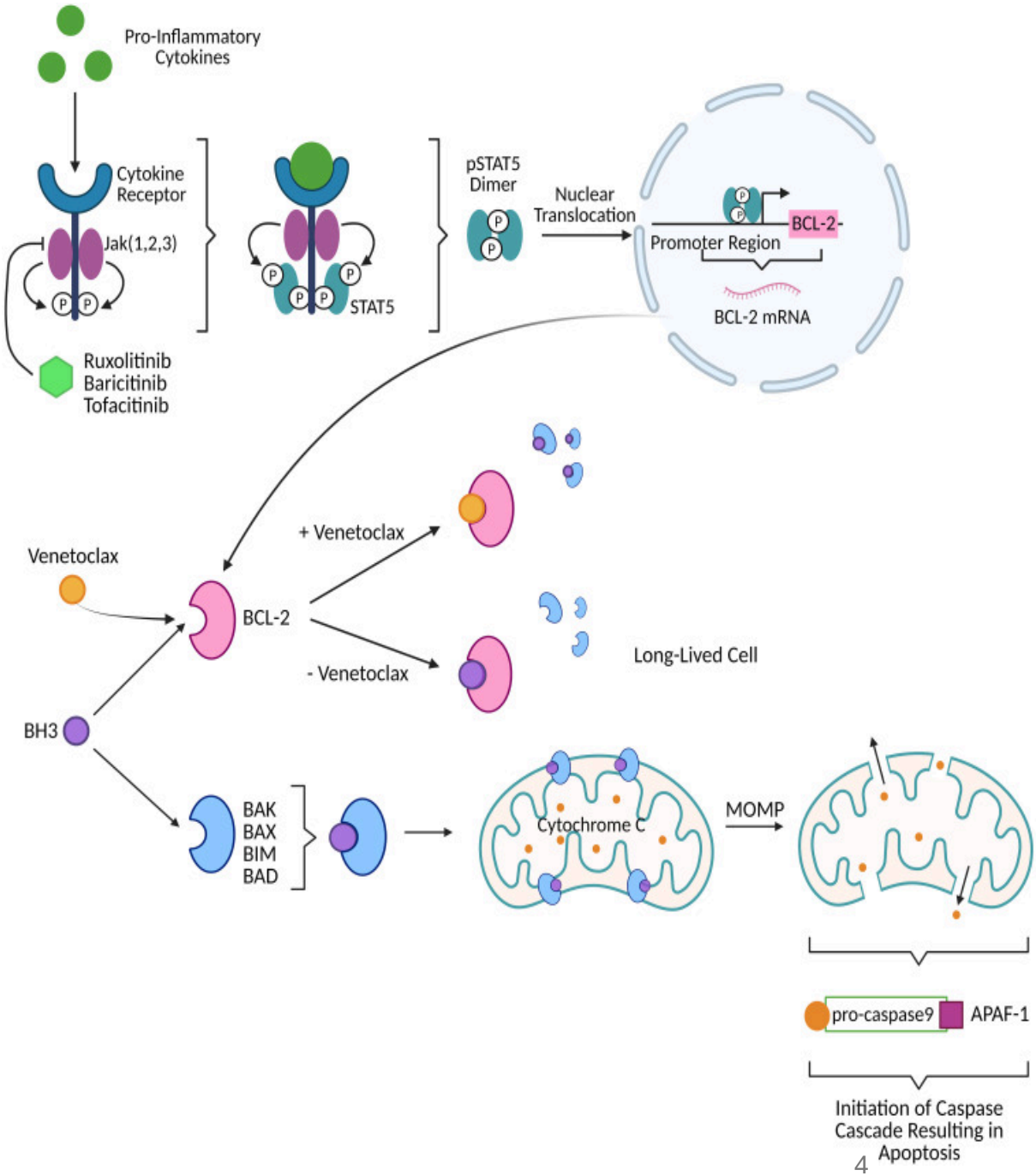
B Cell Lymphoma (BCL)-2 proteins are important regulators of cellular apoptosis



- Large protein family, key modulators of cellular lifespan.
- Several viruses and cancers induce BCL-2 to avoid cell death and improve survival.
- BCL-2 proteins are modulated by pathogen/host interactions and cytokines produced by tumor micro-environment or triggered by viral infections.
- Drugs targeting BCL-2 proteins have important roles in treatment of cancer and viral infections.

JAK-STAT signaling induces BCL-2 expression

- The JAK-STAT pathway regulates BCL-2 expression.
- Phosphorylated STAT5 binds to BCL-2 gene and enhances its transcription.
- Elevated BCL-2 is a marker for the pathogenesis of HIV-1.
- Inhibiting JAK-STAT signaling pathway reduces BCL-expression and decays the HIV-1 reservoir



Role of the JAK-STAT Pathway in maintaining the HIV reservoir

Ruxolitinib and Tofacitinib inhibit pSTAT5 and BCL-2 expression in CD4+ T cells stimulated with inflammatory cytokines in a dose dependent manner

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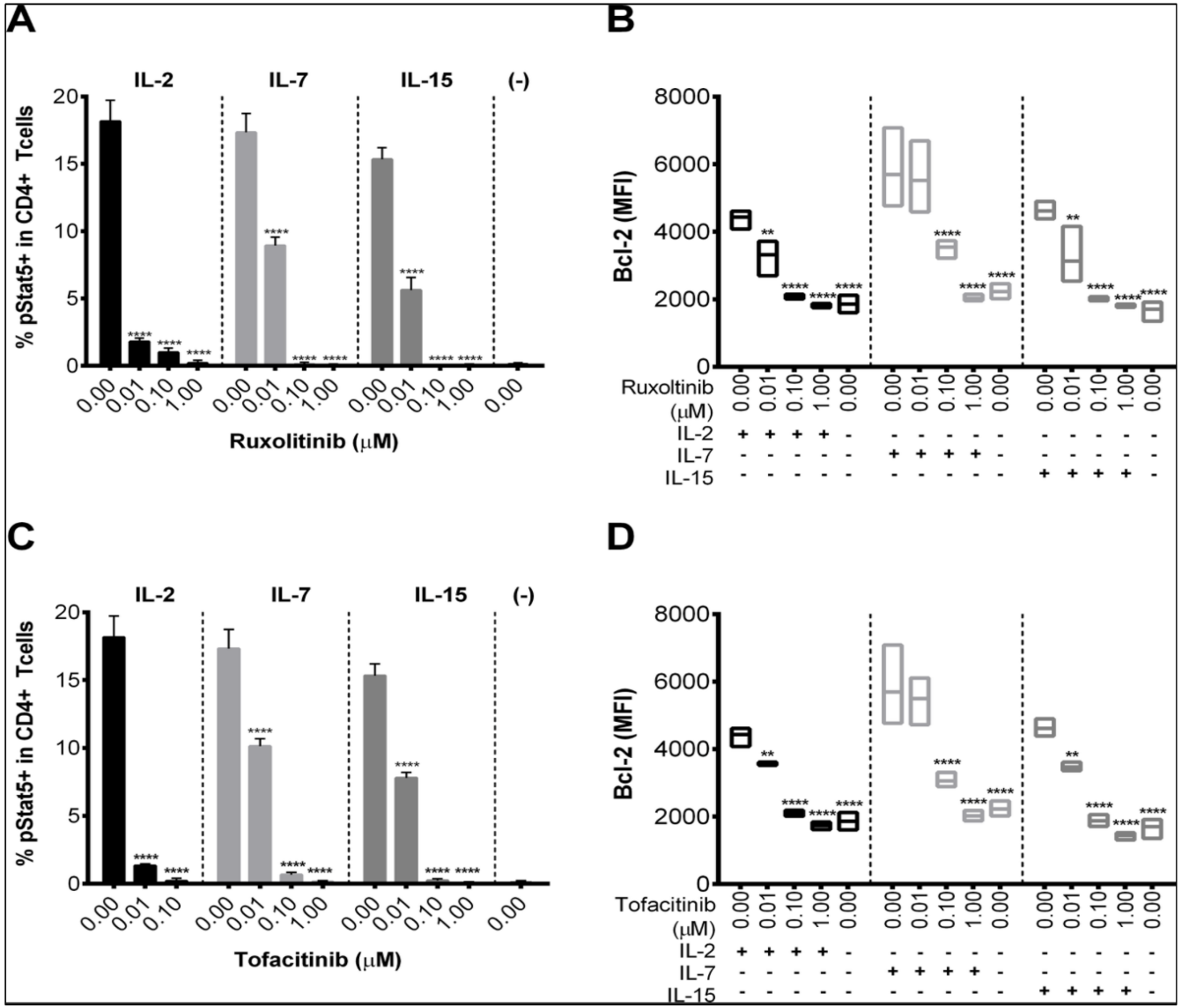
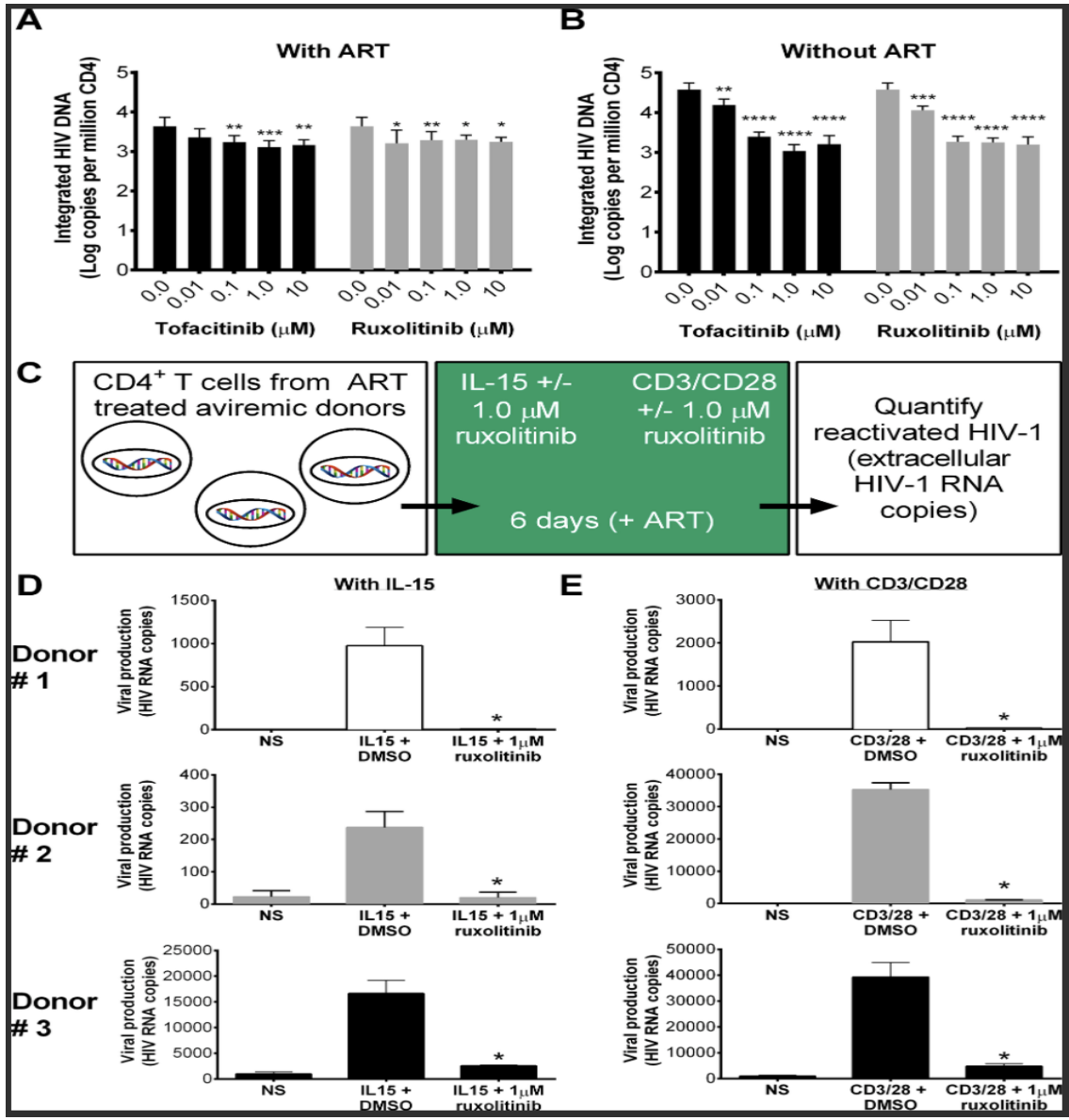


Reference: Gavegnano C, Brehm JH, Dupuy FP, Talla A, Ribeiro SP, Kulpa DA, et al. (2017) Novel mechanisms to inhibit HIV reservoir seeding using Jak inhibitors. PLoS Pathog 13(12): e1006740.

Role of the JAK-STAT Pathway in maintaining the HIV reservoir

Jak-inhibitors reduce frequency of cells harboring integrated viral DNA and IL-15 induced reactivation of latent HIV-1 in CD4+ T cells.



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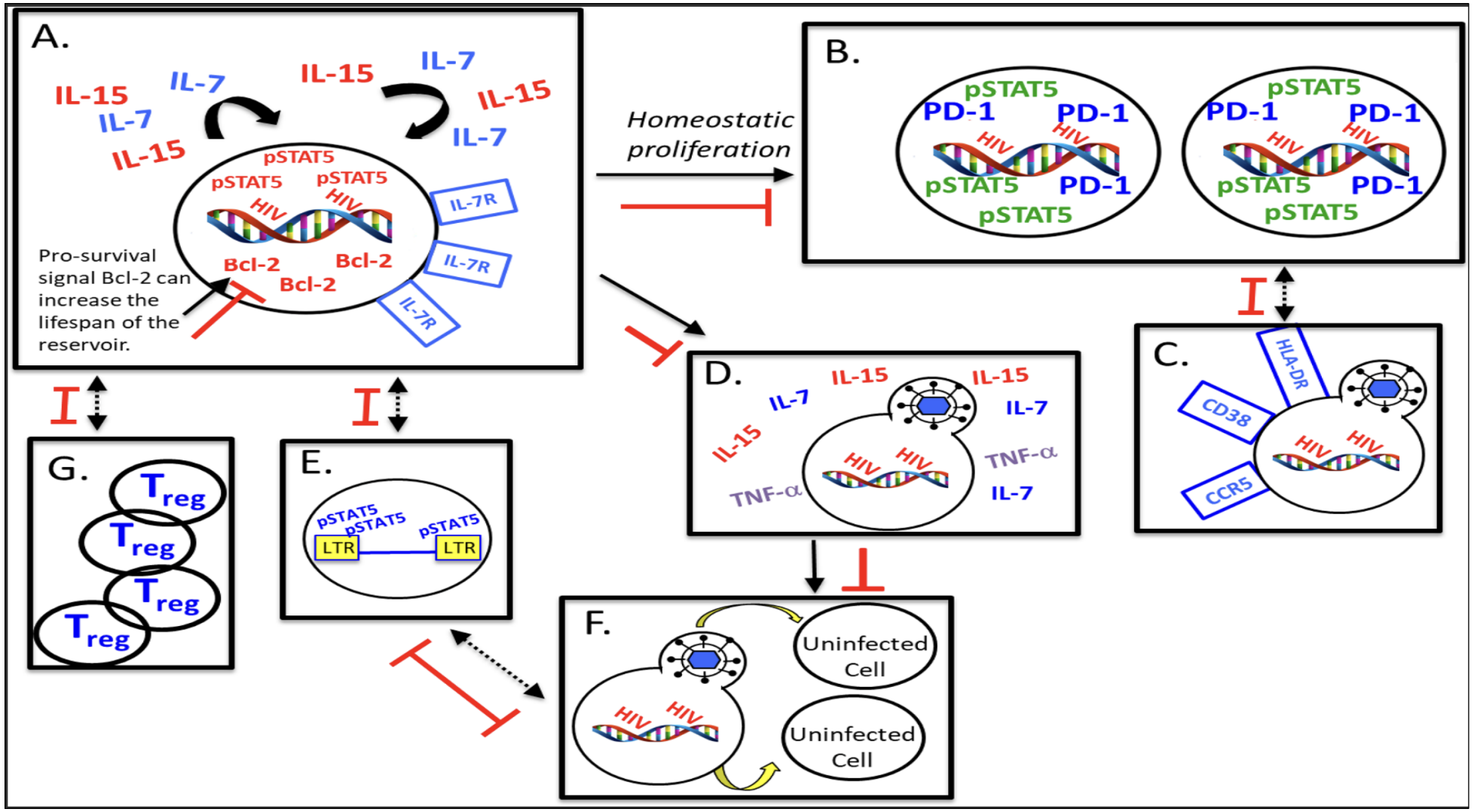
Reference: Gavegnano C, Brehm JH, Dupuy FP, Talla A, Ribeiro SP, Kulpa DA, et al. (2017) Novel mechanisms to inhibit HIV reservoir seeding using Jak inhibitors. PLoS Pathog 13(12): e1006740.

Immunologic mechanisms of viral persistence and impact of Jak inhibitors on the viral reservoir



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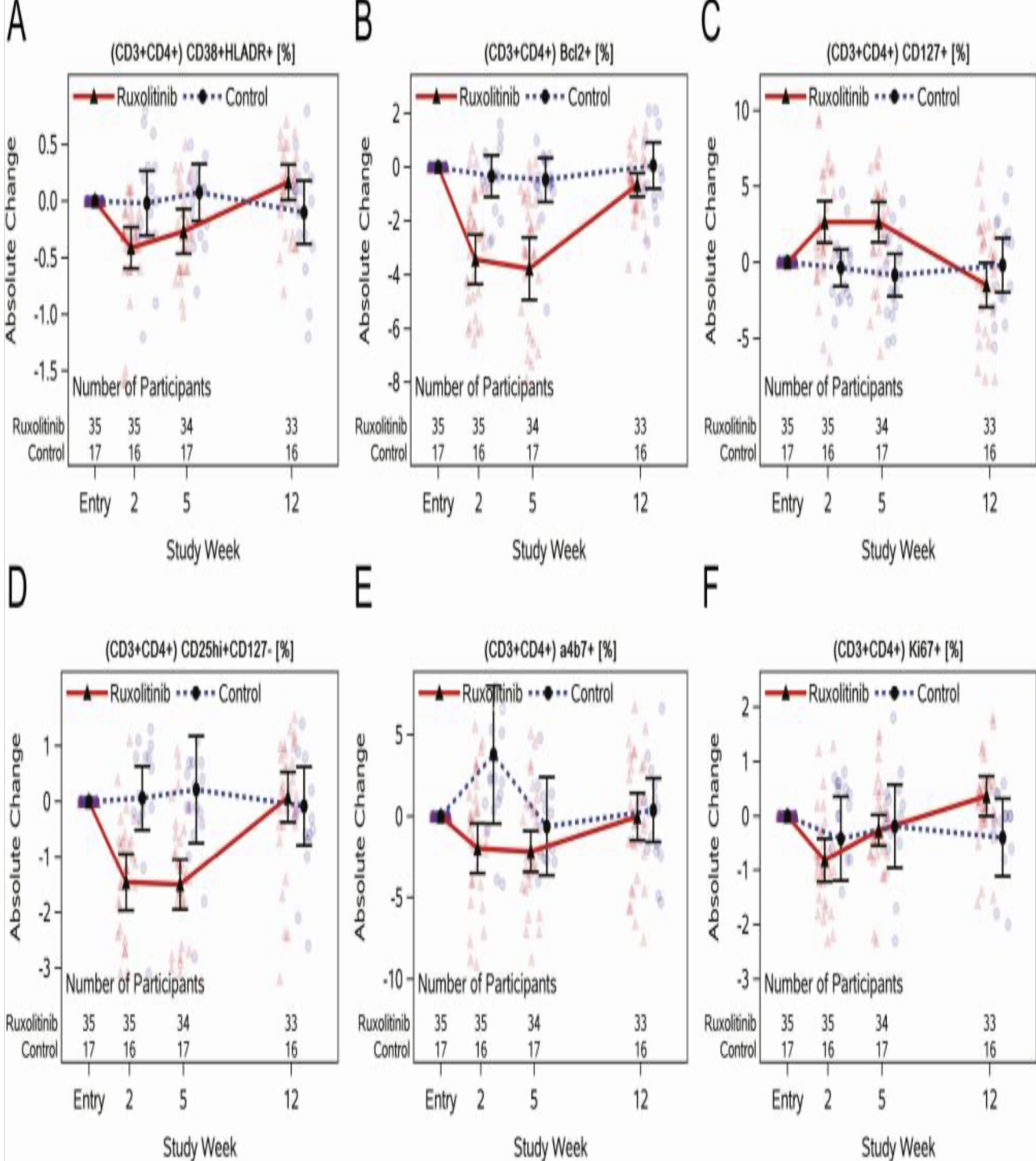
Reference: Gavegnano C, Brehm JH, Dupuy FP, Talla A, Ribeiro SP, Kulpa DA, et al. (2017) Novel mechanisms to inhibit HIV reservoir seeding using Jak inhibitors. PLoS Pathog 13(12): e1006740.

Safety and Efficacy of Ruxolitinib in PWH on ART

- Phase 1/2 study including 60 PWH well controlled on ART
- Ruxolitinib was safe and well tolerated.
- No significant impact on markers of inflammation (IL-6, sCD14).
- Reduction in CD4+ T cells expressing HLA-DR/CD38 and in BCL-2 expression.

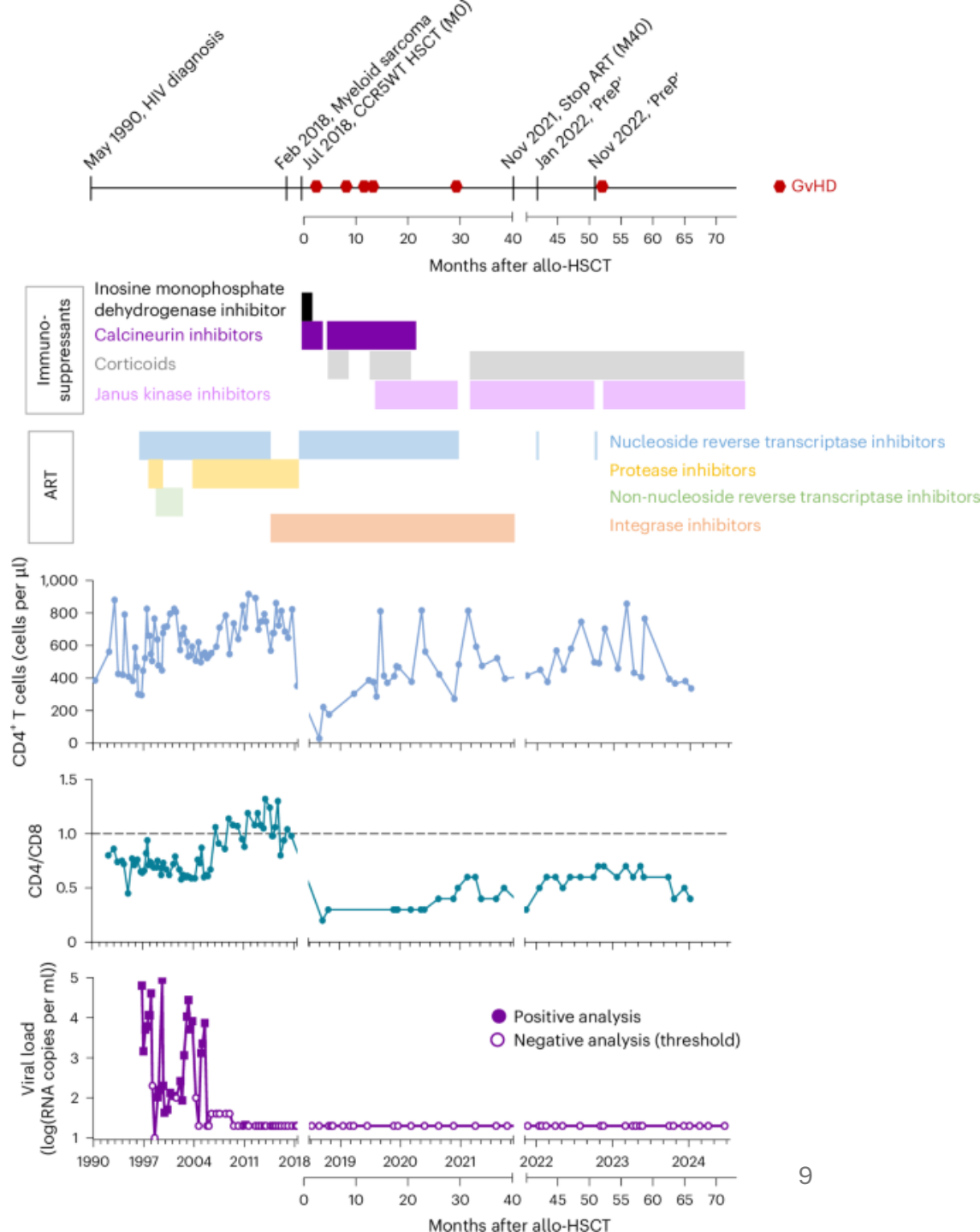
Vincent Marconi

Raymond Schinazi



JAK-inhibitors in HIV functional cure approaches

- Sustained HIV remission following allogenic HSCT with wild type CCR5 donor cells.
- Patient developed graft vs. host disease post HSCT
- Treated with Ruxolitinib
- Sustained virologic control for 32 months off ART.



Reference :Sáez-Cirión, A., Mamez, AC., Avettand-Fenoel, V. *et al*. Sustained HIV remission after allogeneic hematopoietic stem cell transplantation with wild-type CCR5 donor cells. *Nat Med* (2024).

JAK-inhibitors and reservoirs in the CNS

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Recruiting

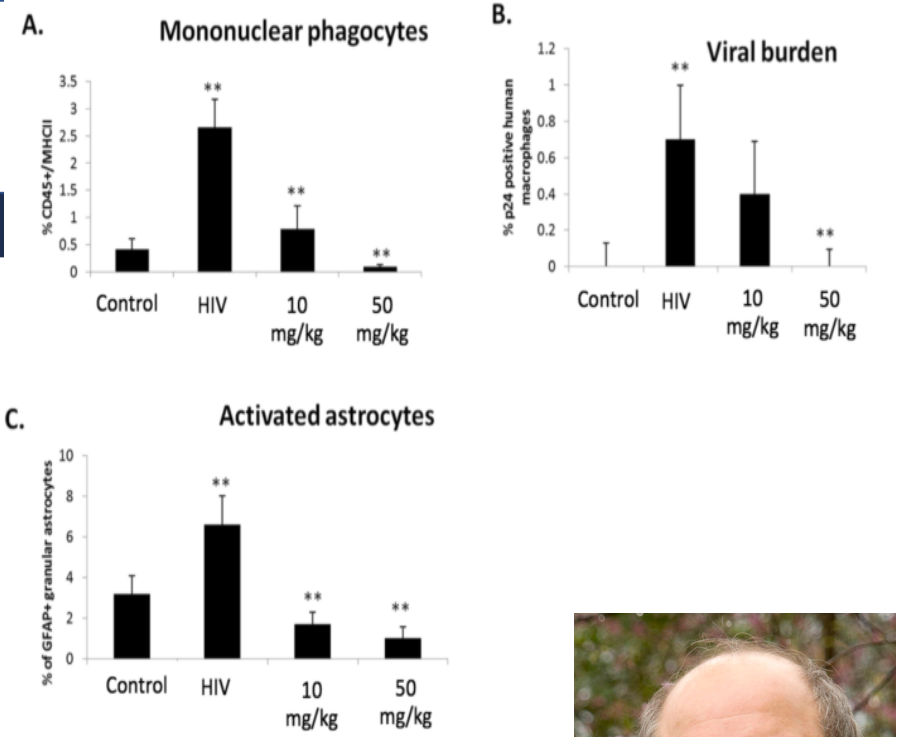
Baricitinib for Reduction of HIV - CNS

ClinicalTrials.gov ID NCT05452564

Sponsor William Tyor

Information provided by William Tyor, Emory University (Responsible Party)

Last Update Posted 2024-04-02



a SCID mouse model

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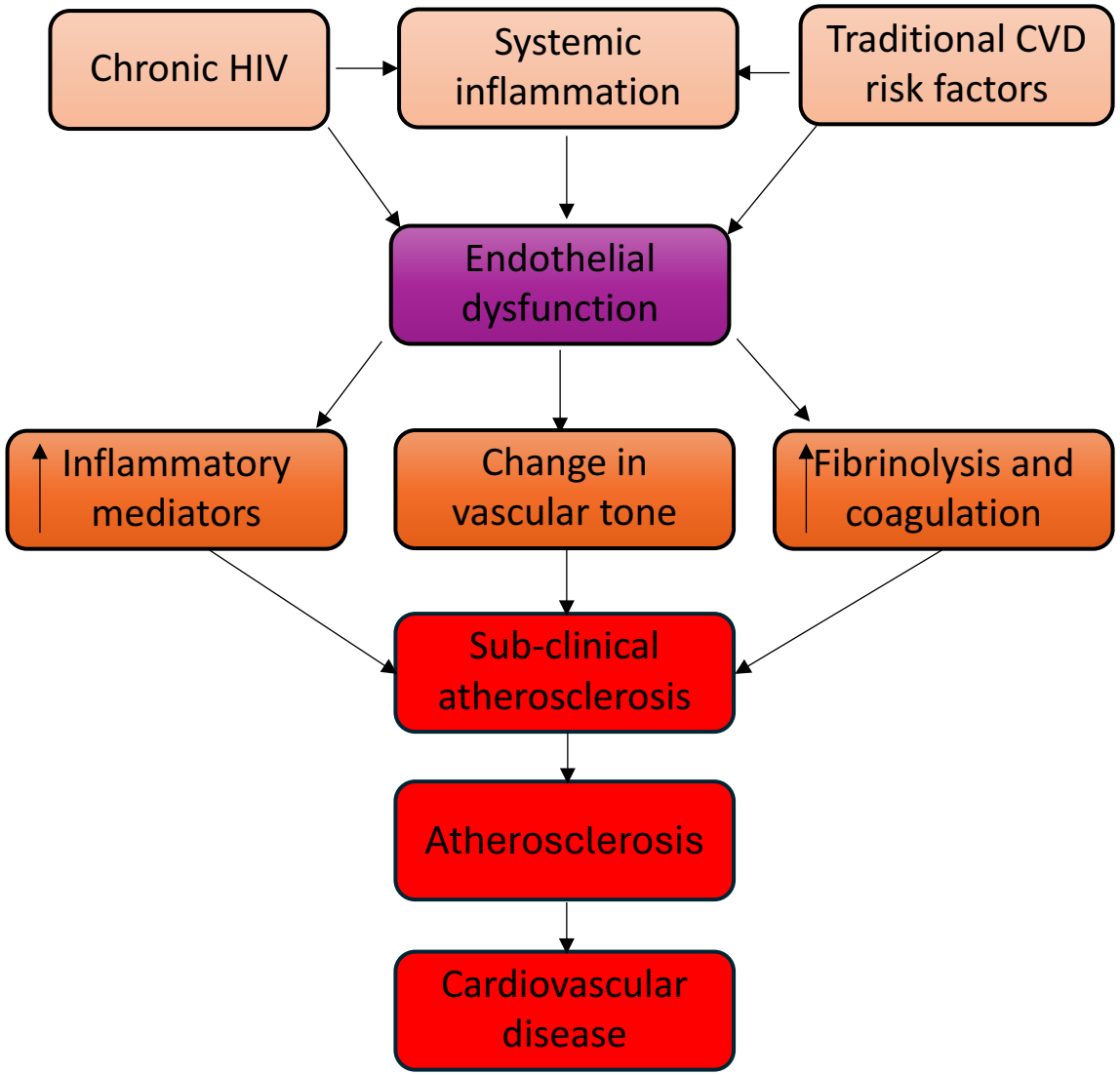
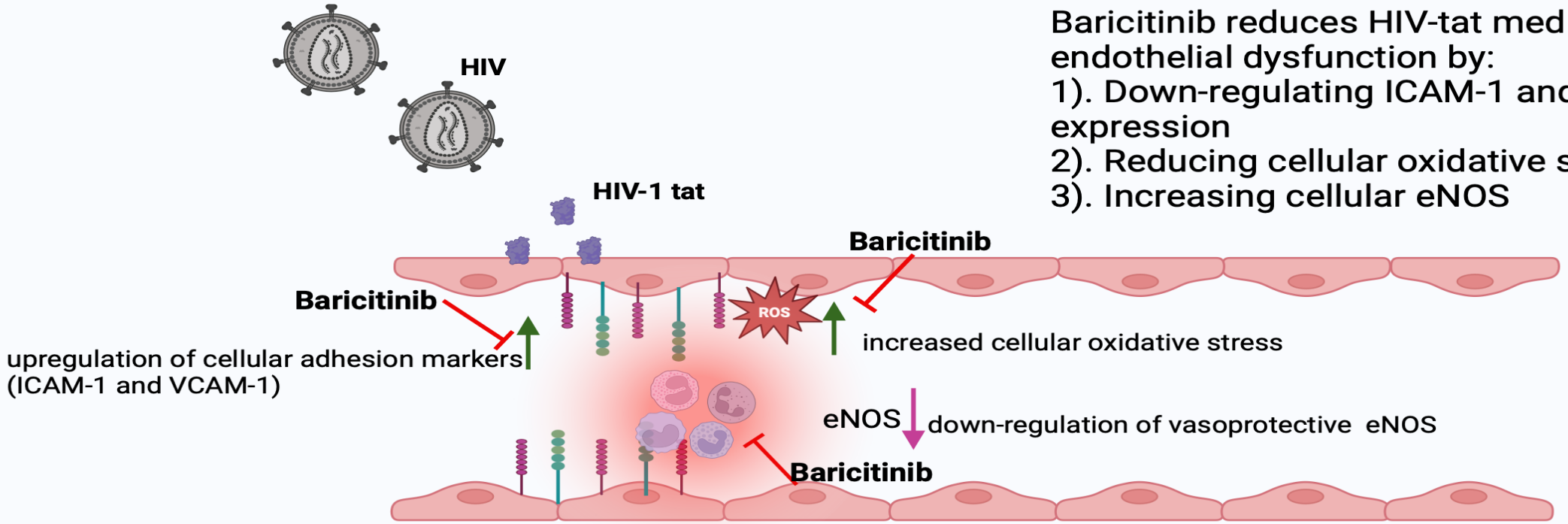
HIV myeloid reservoirs and the cardiovascular system

- HIV-infected macrophages have been detected in atherosclerotic plaque suggesting presence of a “cardiovascular” reservoir.
- HIV is a now well-established risk factor for cardiovascular disease mediated through chronic inflammation.
- Natalizumab a mAb that blocks monocyte/macrophage trafficking to heart tissues was associated with decreased cardiac fibrosis, inflammation, and cardiomyocyte degeneration in a primate model.
- JAK-inhibitors may have a role to play In reducing cardiac fibrosis and inflammation and potentially targeting the cardiac reservoir.



JAK inhibitors to target endothelial dysfunction, inflammation and CVD



Baricitinib reduces HIV-tat mediated endothelial dysfunction by:
1). Down-regulating ICAM-1 and VCAM-1 expression
2). Reducing cellular oxidative stress.
3). Increasing cellular eNOS

Inhibition

upregulation

downregulation

eNOS=endothelial nitric oxide synthase

ROS= reactive oxygen species

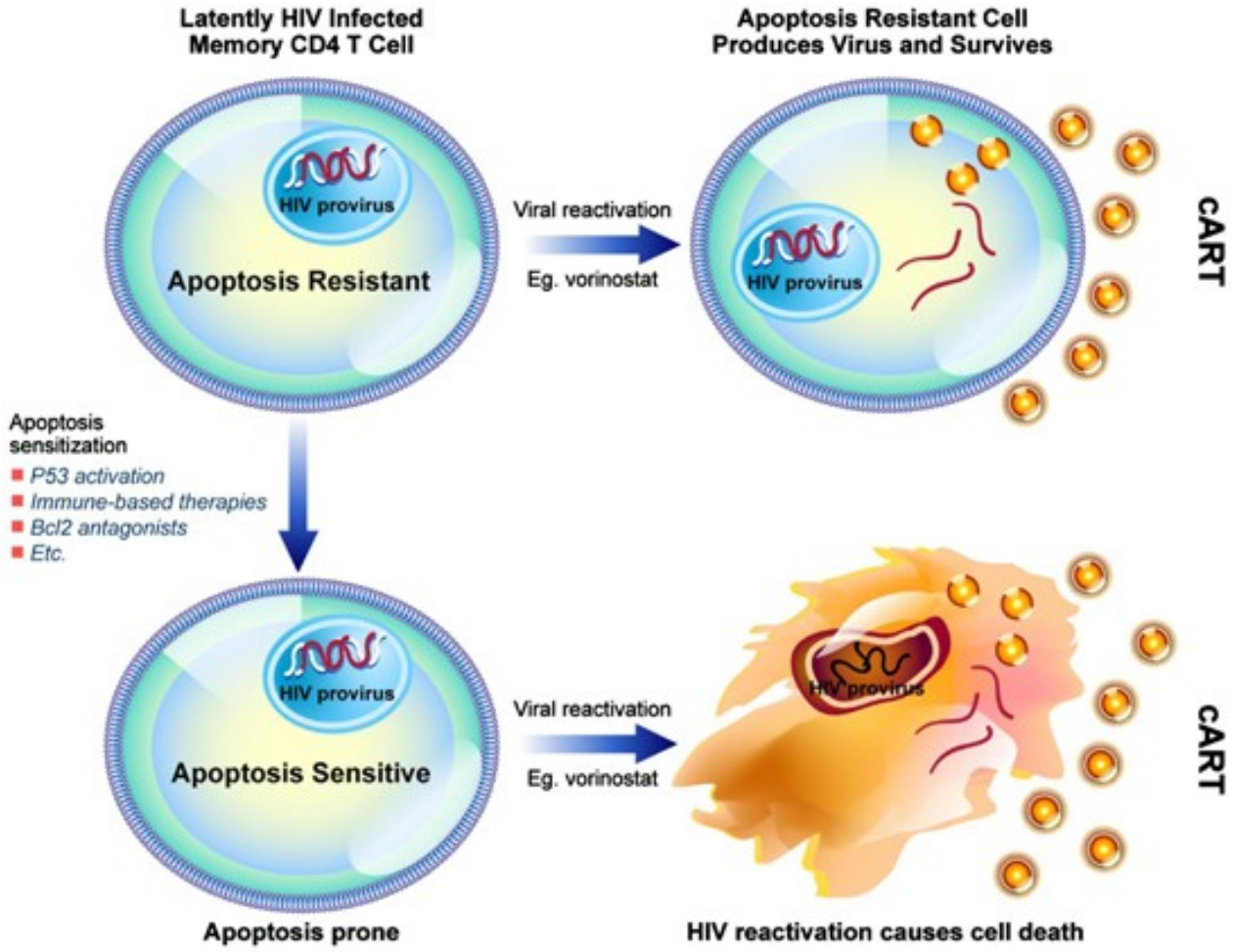
ICAM-1 = intercellular adhesion molecule-1

VCAM-1=vascular cell adhesion molecule-1

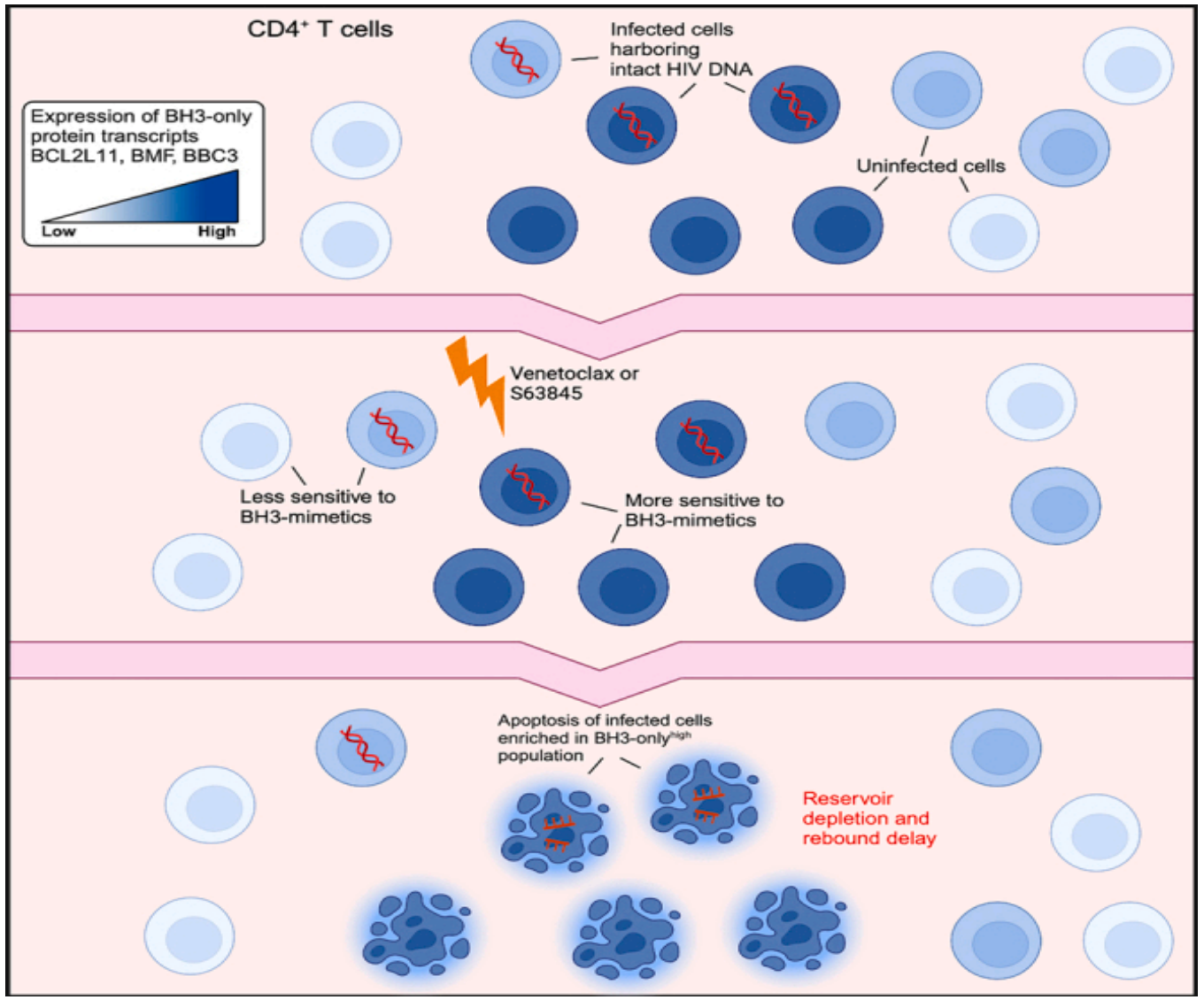
Manuscript in preparation

Promising BCL-2 inhibitors

- Mimic BH3-binding domains, binding to and inhibit anti-apoptotic BCL-2 proteins, thereby promoting apoptosis.
- BCL-2 antagonists can induce apoptosis in latently HIV-infected T cells by preventing BCL-2 from sequestering pro-apoptotic factors generated by HIV protease.
- Venetoclax has shown efficacy in reducing latent HIV reservoirs in T cells from ART-treated individuals when combined with T cell activation
- Venetoclax selectively kills HIV-infected primary T cells during active infection, possibly reducing latency establishment.



Reference: Badley, A., Sainski, A., Wightman, F. *et al.* Altering cell death pathways as an approach to cure HIV infection. *Cell Death Dis* **4**, e718 (2013). https://doi.org/10.1038/cddis.2013.248



CellPress
Cell Reports Medicine

Cell Rep Med. 2023 Aug 30;4(9):101178. doi: 10.1016/j.xcrm.2023.101178

Venetoclax, alone and in combination with the BH3 mimetic S63845, depletes HIV-1 latently infected cells and delays rebound in humanized mice

Philip Arandjelovic [1,2,9], Youry Kim [3,9], James P Cooney [1,2], Simon P Preston [1,2], Marcel Doerflinger [1,2], James H McMahon [4], Sarah E Garner [1,2], Jennifer M Zerbato [3], Michael Roche [3,8], Carolin Tumpach [3], Jesslyn Ong [3], Dylan Sheerin [1,2], Gordon K Smyth [5,6], Jenny L Anderson [3,10], Cody C Allison [1,2,10], Sharon R Lewin [3,4,7,10], Marc Pellegrini [1,2,10,11,*]

- Venetoclax delays viral rebound in a humanized mouse model of HIV infection
- Venetoclax depletes intact HIV DNA *ex vivo* in cells from people living with HIV on ART
- The HIV reservoir is enriched in cells with higher expression of BH3-only proteins

Beyond HIV – JAK-inhibitor use for COVID

- Cytokine storm and inflammation key to COVID pathogenesis.
- Baricitinib FDA approved for severe COVID treatment.
- JAK-inhibitors currently in clinical trials for long-COVID

JOURNAL ARTICLE

Use of Baricitinib in Patients With Moderate to Severe Coronavirus Disease 2019 FREE

Boghuma K Titanji, Monica M Farley, Ashish Mehta, Randi Connor-Schuler, Abeer Moanna, Sushma K Cribbs, Jesse O'Shea, Kathryn DeSilva, Bonnie Chan, Alex Edwards, Christina Gavegnano, Raymond F Schinazi, Vincent C Marconi

Clinical Infectious Diseases, Volume 72, Issue 7, 1 April 2021, Pages 1247–1250, https://doi.org/10.1093/cid/ciaa879

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Abstract

Hyperinflammation is associated with increased mortality in coronavirus disease 2019 (COVID-19). In this retrospective, uncontrolled patient cohort with moderate -severe COVID-19, treatment with baricitinib plus hydroxychloroquine was associated with recovery in 11 of 15 patients. Baricitinib for the treatment of COVID-19 should be further investigated in randomized, controlled clinical trials.

Conclusions

BCL-2 and JAK inhibitors are emerging therapies for HIV cure strategies.

JAK-inhibitors through their anti-inflammatory effects may be important for chronic neurologic and cardiovascular complications of HIV.

These agents will likely be used in conjunction with other approaches.

Further characterization of the mechanism by which they impact the HIV reservoir is needed as well as clinical studies to understand their utility in this space