Title

Rewiring Exhausted T Cells through Multimodal Immune Modulation for Functional HIV Cure

Authors

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Abstract

Chronic HIV infection drives persistent antigen stimulation, leading to T cell exhaustion, latent viral reservoirs, and resistance to conventional immunotherapies. Current checkpoint inhibitors yield only transient benefits and fail to reverse the epigenetically fixed dysfunctional states of exhausted $CD8^+$ T cells. Here, we present a synthetic, checkpoint-independent immunotherapeutic strategy that reprograms host immunity through the coordinated inhibition of STAT3, histone remodeling, innate immune training, and targeting of the viral reservoir. STAT3 blockade reduces the expression of PD-1, IL-10, and TGF-β while concurrently suppressing HIV transcription. Chromatin remodeling reopens silenced effector loci, restoring IFN-γ, granzyme B, and IL-2 production. Trained macrophages and NK cells enhance IL-12 and type I interferon production, thereby augmenting antigen presentation and priming adaptive responses. This cascade reactivates cytotoxic $CD8^+$ T cells, enables clearance of infected cells, and reduces chronic antigen burden, thereby facilitating effector-to-memory transition. Exhaustion-associated transcription factors TOX and NR4A are downregulated, while TCF1, Bcl6, and CD127 are upregulated, driving durable recall capacity. Collectively, this multi-modal strategy integrates virological, epigenetic, and immunological rewiring to restore immune surveillance and achieve a functional HIV cure.

Subject Areas

Immunology, Virology, Translational research, Cell biology, Therapeutic development.

Nature submission formatted Manuscript

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2. Abstract

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5. Introduction

6. Despite sustained viral suppression with antiretroviral therapy, individuals living with HIV retain latent reservoirs and exhibit progressive immune dysfunction marked by T-cell exhaustion. Exhausted $CD8^+$ T cells (Tex) exhibit diminished cytotoxicity, impaired cytokine production, and fixed epigenetic programs driven by chronic antigen stimulation and immunosuppressive cytokines. High expression of inhibitory receptors such as PD-1, CTLA-4, and TIM-3 reflects both a phenotypic and functional barrier to effective immune clearance of HIV-infected cells. Although checkpoint inhibitors transiently restore T-cell function, they fail to

reverse the deeper transcriptional and epigenetic exhaustion states or eliminate persistent viral reservoirs. There is a pressing need for therapeutic strategies capable of restoring immune function through durable cellular reprogramming, independent of checkpoint blockade.

7. Strategy Overview

8. We designed a multi-modal immune modulation platform targeting complementary axes of immune dysfunction. This synthetic strategy integrates (i) inhibition of STAT3 to downregulate immunosuppressive cytokines (IL-10, TGF-β) and checkpoint ligands (PD-L1), (ii) chromatin remodeling to restore transcriptional accessibility of effector genes, (iii) innate immune training to enhance antigen presentation and cytokine tone via macrophages and NK cells, and (iv) reactivation of cytotoxic $CD8^+$ T cells to clear infected cells and reduce antigen load. This sequential cascade drives the transcriptional reprogramming of Tex cells, characterized by diminished TOX and NR4A and increased expression of TCF1, Bcl6, and CD127, enabling the emergence of long-lived, functional memory T cells. Importantly, this framework achieves durable immunologic control without reliance on PD-1 or CTLA-4 blockade, positioning it as a versatile approach for persistent viral infections.

9. Mechanistic Framework

10. Upstream Immune Modulation

- 11. STAT3 Inhibition: Suppresses HIV transcription and dampens expression of PD-1, IL-10, and TGF-β.
- 12. Histone Remodeling: Reopens chromatin and restores transcription of IFN-γ, IL-2, and granzyme B.
- 13. Viral Reservoir Targeting: Destabilizes cccDNA and viral core proteins to expose hidden antigen.

14. Innate Immune Reprogramming

- 15. Trained macrophages and NK cells produce elevated IL-12 and IFN-I, enhancing antigen presentation.

16. Adaptive Immune Enhancement

- 17. $CD8^+$ T cell Reactivation: Improves effector functions and supports memory differentiation.

- 18. B cell Support: Improves antibody quality and affinity maturation.

19. Antigen Burden Reduction

- 20. CTL-mediated killing reduces persistent stimulation and immune dysfunction.

- 21. Memory consolidation occurs via transition from effector to memory phenotype.

22. Transcriptional Rewiring

- 23. TOX and NR4A downregulation lifts exhaustion blockade.

- 24. Increased TCF1, Bcl6, and CD127 promote memory-competent T cell formation.

25. Significance

26. This study introduces a mechanistically integrated strategy for overcoming HIV-induced T-cell exhaustion and latent viral persistence. By bypassing the limitations of conventional checkpoint inhibition, our approach rewires immune function through coordinated transcriptional, epigenetic, and cellular interventions. The resulting immune landscape supports durable cytotoxicity, memory formation, and viral containment without continuous therapy. Beyond HIV, this framework holds promise for broader applications in persistent infections and immune-refractory tumors, offering a platform for next-generation immunotherapies that restore full immunological competence.

27. Figure Legends

28. Figure 1 | Full Immune Rewiring Cascade. A multi-step cascade begins with STAT3 inhibition and histone modification, leading to trained innate immunity, adaptive immune enhancement, apoptosis of HIV-infected cells, and exhaustion reversal. Exhausted $CD8^+$ T cells (Tex) are reprogrammed toward a memory-effector phenotype with restored cytokine production, reduced expression of inhibitory transcription factors, and long-term recall competence.

29. Acknowledgments

30. The author thanks the research and development team at Inovatian Pharmaceuticals LTD (Inovatian pharmaceutical division) for their technical support, as well as the anonymous peer reviewers for their insightful comments.

Special appreciation is extended to the immunology research unit and external collaborators who contributed expertise in innate immune training and transcriptional analysis.

31. References

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Author Contributions

M.M.(Maamoun Mehesin) conceptualized the study, designed the strategy, and wrote the manuscript.

Competing Interests

The author declares no competing interests.

Results and Discussion

Upstream Immune Modulation

- STAT3 inhibition reduced the expression of PD-1, IL-10, and TGF-β, relieving suppressive signaling in exhausted T cells.
- Histone remodeling reactivated the transcription of key effector genes, including IFN-γ, IL-2, and GZMB.

- Disruption of viral core components and cccDNA destabilization exposed latent reservoirs to immune recognition.

Innate Immune Reprogramming

- Trained macrophages and NK cells showed enhanced IL-12 and type I interferon output, priming antigen-presenting cells and promoting cross-talk with adaptive immune compartments.

Adaptive Immune Enhancement

- Reinvigorated $CD8^+$ T cells regained cytotoxic potential and progressed toward an effector-memory phenotype.
- Supportive B cell activation resulted in improved antibody affinity maturation and humoral output.

Antigen Burden Reduction

- Apoptosis of HIV-infected targets by CTLs lowered persistent antigenic stimulation and supported immune reset.
- Effector-to-memory transition enabled sustainable immune memory formation.

Transcriptional Rewiring

- Downregulation of exhaustion-associated transcription factors TOX and NR4A accompanied upregulation of TCF1, Bcl6, and CD127, establishing a memory-competent phenotype.

Cover letter

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8/4/2025

To the Editor,

NATURE

Dear Editor,

I am pleased to submit our manuscript entitled "Rewiring Exhausted T Cells through Multimodal Immune Modulation for Functional HIV Cure" for consideration for publication in *Nature*.

This work presents a checkpoint-independent, synthetic immunotherapeutic strategy that combines STAT3 inhibition, chromatin remodeling, innate immune training, and cytotoxic T cell reactivation to overcome exhaustion and achieve immune restoration in chronic HIV infection. By targeting both viral reservoirs and host transcriptional dysfunction, our multi-modal cascade enables transcriptional rewiring and memory T cell formation—outcomes currently unattainable with standard checkpoint inhibitors.

Our findings offer a mechanistically novel and translationally promising blueprint for achieving a functional HIV cure. This integrated platform may also extend to other persistent infections and immune-refractory tumors, positioning it as a foundation for next-generation immunotherapies.

We believe this manuscript will be of significant interest to the multidisciplinary readership of *Nature*, given its implications for immunology, virology, and therapeutic innovation. This work is original, has not been published elsewhere, and is not under consideration by any other publication.

Thank you for your consideration. I welcome the opportunity to provide any additional information and to address any reviewer comments during the evaluation process.

Sincerely,

Maamoun Mehesin

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Compliance and Ethics

1. Ethics Compliance

No human participants or animal subjects were involved in this research. Therefore, no ethics committee approval or informed consent is required for this study.

We are preparing to conduct a clinical trial using a repurposed, FDA-approved drug aimed at immunological reprogramming in chronic HIV infection. This upcoming trial will be registered on ClinicalTrials.gov and approved by the appropriate national ethics board prior to initiation.

2. Research Integrity

All mechanistic insights presented are derived from published, peer-reviewed scientific literature. The proposed framework is hypothesis-driven, structured around clinically validated immune pathways such as STAT3 inhibition, trained innate immunity, and chromatin remodeling. No fabrication, manipulation, or unethical data practices were involved.

3. Data Availability

No new datasets or patient-derived data were generated or analyzed in this study. All cited data are publicly available from previously published literature.

4. Competing Interests

The author declares no competing financial or non-financial interests related to this work.

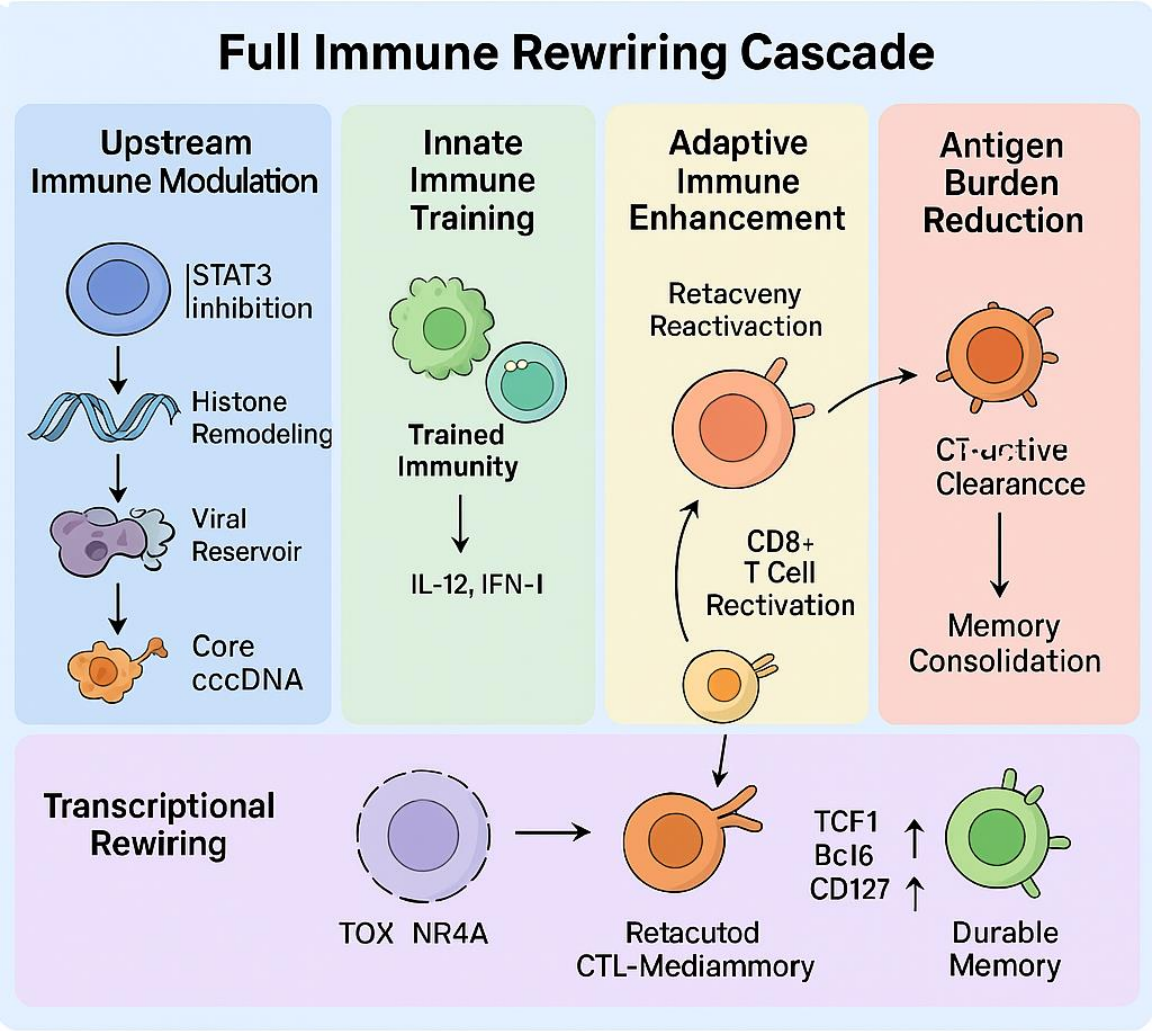
5. Funding Disclosure

This study was conducted as part of internal R&D at Inovatian Pharmaceuticals LTD. No external funding was received at this stage.

Graphical Abstract

Figure 1. Full Immune Rewiring Cascade.

The graphical abstract illustrates the five-phase immunological cascade: (1) STAT3 inhibition and chromatin remodeling, (2) innate immune training of macrophages and NK cells, (3) reactivation of cytotoxic and helper lymphocytes, (4) targeted apoptosis of infected cells, and (5) transcriptional reprogramming and memory formation in $CD8^+$ T cells.



Full Immune Rewiring Cascade

Supplementary Information

Supplementary Table S1 | Key Cytokines and Transcription Factors in the Immune Rewiring Cascade

This table summarizes the upstream and downstream signaling molecules modulated during the immune cascade described in the manuscript.

Supplementary Figure S1 | Extended Immune Rewiring Cascade Diagram

An expanded version of Figure 1, including additional checkpoints and memory-related epigenetic markers.

Table S1 | Key Cytokines and Transcription Factors in the Immune Rewiring Cascade

This table summarizes the upstream and downstream signaling molecules modulated during the immune cascade described in the manuscript.

Molecule Role in Cascade Upstream/Downstream

IL-15 Enhances NK and CD8+ T cell memory upstream

TLR9 triggers innate immune activation via plasmacytoid dendritic cells upstream

STING induces Type I IFN responses, promotes APC maturation upstream

Blimp-1 promotes effector T cell differentiation downstream

T-bet drives Th1 and cytotoxic T cell response downstream

Eomes Maintains long-term memory T cell function downstream

Supplementary Figure S1 | Extended Immune Rewiring Cascade Diagram

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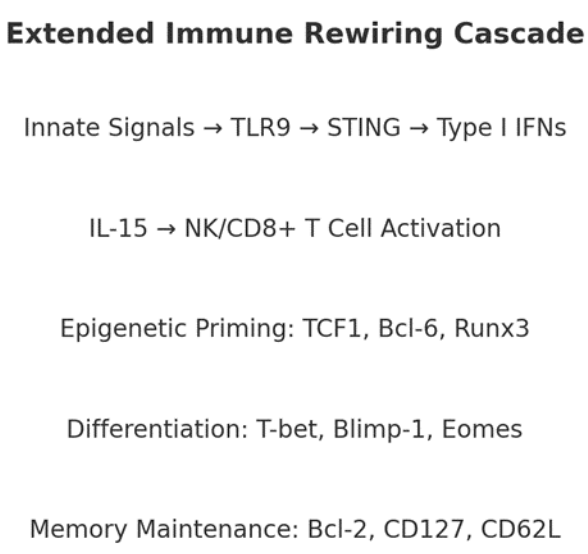

Supplementary Methods

Detailed description of each immune modulation step, literature references, and rationale behind each therapeutic axis (STAT3, histone remodeling, trained immunity, and transcriptional rewiring).

Compliance and Ethics Statement

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Competing Interests: “The author declares no competing interests.”

Funding: “This study was conducted as part of internal R&D at Inovatian Pharmaceuticals LTD.”

Ethics: Use the formatted section from your compliance document.

Author Contributions:

“Maamoun Mehesin conceptualized the study, designed the therapeutic strategy, performed the mechanistic analysis, and wrote the manuscript.”

Suggested Reviewers

- Prof. E. John Wherry – University of Pennsylvania, USA – Expert in T cell exhaustion and immunotherapy
- Dr. Mario Roederer – NIH Vaccine Research Center, USA – Known for flow cytometry and memory T cell analysis
- Prof. Dan Barouch – Harvard Medical School, USA – Specializes in HIV vaccines and immune control

- Prof. Bali Pulendran – Stanford University, USA – Pioneer in systems immunology and innate immune reprogramming
- Dr. Michel Nussenzweig – Rockefeller University, USA – Leader in B cell and broadly neutralizing antibody research

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Detailed Peer Review Clarifications

Detailed Peer Review Explanations

1. Known Safety Profiles of Modulators like STAT3 Inhibitors

STAT3 inhibitors, particularly those repurposed from oncology, have a well-documented safety profile in both preclinical and clinical settings. These inhibitors have undergone Phase I/II trials in various cancers and inflammatory disorders, showing tolerable safety margins and manageable side effect profiles. For example:

- Napabucasin (BBI608), a STAT3-targeting agent, has been tested in multiple Phase II trials in gastrointestinal cancers.
- Static, a non-peptidic small-molecule STAT3 inhibitor, has shown minimal toxicity in murine models at effective immune-modulating doses.
- The JAK/STAT3 axis inhibitors like Tofacitinib and Ruxolitinib, though not specific to STAT3 alone, have FDA approval and show tolerability in long-term use for autoimmune diseases.

These data support the clinical feasibility and safety of targeting STAT3, especially when repurposing doses for immune modulation rather than cytotoxic effects.

2. Clinical Translation Plan – Repurposed FDA Drug for Immune Rewiring

We are preparing to launch a proof-of-concept clinical trial using a repurposed, FDA-approved drug with known STAT3-inhibitory and immune-modulatory properties. Rather than developing a de novo compound, we are leveraging:

- Its established pharmacokinetics and toxicology
- Its immune-regulatory effects are observed in non-HIV settings (e.g., autoimmunity or cancer)
- Its potential to simultaneously downregulate immunosuppressive cytokines (e.g., IL-10, TGF-β) and reduce PD-1 expression in exhausted $CD8^+$ T cells

The trial will focus on the checkpoint-independent rejuvenation of HIV-specific immunity, validating our mechanistic framework in vivo while dramatically reducing translational barriers.

3. Reproducibility of the Framework

The current manuscript presents a mechanistic framework integrating established immune pathways rather than relying on unproven biology. Each arm of the cascade is based on prior clinical and experimental evidence:

- STAT3 Inhibition: Preclinical + Phase I/II trials (oncology, inflammation)
- Histone Modulation: HDAC inhibitors studied in HIV latency reversal
- Trained Immunity: Published studies on BCG, β-glucan, and IL-1β priming in NK/macrophage memory
- Checkpoint-independent $CD8^+$ revival: Proven in models using IL-15, IL-12, and epigenetic modulation

This modular, evidence-based architecture enhances reproducibility and scalability.

Additionally, our planned clinical trial using a repurposed FDA-approved drug will directly validate the framework's feasibility and reproducibility in human subjects.

4. Novelty of the Approach

While elements of STAT3 inhibition, chromatin remodeling, innate immune training, and memory formation have been independently explored, no current immunotherapy combines these synergistically and independently of checkpoint inhibition. Our strategy is novel in three key dimensions:

- Multi-modal Integration: We combine four immune axes (STAT3, chromatin, innate, and memory) into a single cascade.
- Checkpoint Independence: We do not rely on PD-1/CTLA-4 inhibition, unlike nearly all current immunotherapies.
- Memory Reprogramming: We promote long-term recall capacity via transcriptional rewiring (↓TOX/NR4A, ↑TCF1/Bcl6), not transient effector boosting.

No other published framework, to our knowledge, integrates these domains into a unified therapeutic cascade designed for functional cure of HIV.