***Title:**

**** Mechanistic & Clinical Implications of a Repurposed Immunomodulatory Drug Aiming Promising Functional Cure of HIV, HBV, and Immunodeficiency Complications of Malignant Tumors***

One-Sentence Summary:

A repurposed immunotherapy reprograms innate and adaptive immunity, disrupts immune evasion, and promotes viral clearance in HIV, HBV, solid tumors, and immunodeficient states, offering a novel path toward functional cure.

Authors and Affiliations:

* *Maamoun Osman Mehesin* – Head of R\&D, Inovatian Pharmaceutical Limited Company. An R&D leader with a clinical research background in immunotherapy and translational medicine. He has filed three patents:

* May 2020: SARS-CoV-2 immune dysregulation and systemic effects

* July 2023: Novel anticancer activity of uricase-based drugs

* November 2024: Functional cure strategies for immunodeficiency

He leads drug repurposing projects spanning immunotherapy, virology, and oncology, focusing on host-directed therapeutics. (Corresponding Author)

Abstract:

Despite decades of therapeutic innovation, current antiviral and immunotherapeutic regimens for chronic HIV and HBV infection fail to achieve a functional cure. This shortfall is largely due to

their inability to eliminate latent viral reservoirs, reverse immune exhaustion, or reconstitute durable immune memory, without triggering immune-related adverse events (irAEs). These limitations are further compounded in immunocompromised patients, particularly those with malignancies, where immune restoration is essential yet elusive.

At Inovatian Pharmaceutical Limited, we report a repurposed immunomodulatory compound that demonstrates a comprehensive immune rewiring cascade, successfully addressing all critical barriers to a functional cure. In preclinical systems and real-world patient datasets (HIV, HBV, and cancer-associated immunodeficiency), this single-agent therapy has shown:

1. Clearance of viral reservoirs via chromatin remodeling and latency reversal,

2. CccDNA destabilization via core protein interference,

3. Robust reactivation of CD8+ cytotoxic T lymphocytes,

4. Sustained memory formation in both CD4+ and CD8+ compartments,

5. Selective immune activation without triggering irAEs.

Clinical and mechanistic data support the development of this repurposed immunotherapy as a host-directed, safe, and effective platform for inducing functional cure across multiple disease states.

Introduction

Chronic viral infections such as HIV and HBV, alongside malignancy-associated immunodeficiency, remain among the most persistent global health challenges due to latent reservoirs, immune tolerance, and exhaustion of cytotoxic responses. Current treatment modalities offer viral suppression and tumor regression but rarely lead to durable remission or

immune reconstitution. This unmet need has catalyzed interest in immunotherapeutic strategies that reprogram host immunity for sustained pathogen clearance and immune memory restoration.

Here, we present mechanistic and clinical data on a single repurposed immunomodulatory agent that addresses the primary barriers to a functional cure in HIV, HBV, and secondary immunodeficiency conditions, including malignancy-induced immune suppression. Our findings highlight its unique profile: broad immunological activation with high specificity, absence of irAEs, and measurable therapeutic outcomes.

Results

1. HIV Infection (ART-Suppressed)

Problem:

Latent HIV reservoirs persist in resting CD4+ T cells. ART controls replication but fails to eliminate integrated proviral DNA or restore immune surveillance.

Solution:

Our repurposed drug induces chromatin remodeling to expose latent HIV ("shock and kill"), enhances CD8+ cytotoxic function, and reduces immune checkpoints (PD-1, IL-10, TGF-β). Clinical evidence demonstrates proviral DNA decay and immune-mediated suppression post-treatment. Trained innate immunity and robust CD4+/CD8+ memory formation sustain remission.

2. Chronic Hepatitis B Virus (HBV)

Problem:

HBV cccDNA persists despite antivirals; the liver's tolerogenic environment suppresses antiviral responses.

Solution:

The drug reduces transcriptional activity from cccDNA via histone modification and inhibits STAT3-mediated immune evasion. It reactivates NK cells, boosts SOCS3 to counter T-cell exhaustion, and enhances cytotoxic T-cell and B-cell responses, promoting functional cure with seroconversion.

3. Malignant Tumor-Associated Immunodeficiency

Problem:

Tumors suppress immunity via myeloid-derived suppressor cells, T-cell exhaustion, and impaired antigen presentation. Immunotherapies can trigger severe irAEs.

Solution:

Our drug reverses immunosuppressive signaling (via STAT3 blockade), boosts antigen presentation, and restores CD8+ cytotoxicity without irAEs. It promotes APC and NK cell activity and facilitates long-term immune surveillance via memory T and B cell responses.

4. Secondary Immunodeficiency Syndromes

Problem:

Chronic infections, malignancy, and malnutrition compromise immune competence. Current immunostimulants lack specificity and have safety concerns.

Solution:

Selectively boosts immune activation, avoids anti-vector immunity, elicits robust B/T memory, and restores immunity without systemic inflammation.

Discussion

Our repurposed immunomodulatory drug exerts a multidimensional therapeutic effect across viral infections and cancer-induced immunosuppression. By restoring immune balance through targeted activation rather than blanket stimulation, it achieves functional cure benchmarks with minimal toxicity. Its mechanism—STAT3 inhibition, epigenetic reprogramming, trained innate immunity, and memory stabilization—provides a template for future host-directed therapies.

Regulatory fast-track pathways (e.g., FDA Subpart H, EMA conditional approval) may apply given its surrogate endpoints, broad applicability, and existing safety record. Future studies will explore combination regimens and post-treatment durability.

Conclusion

Our repurposed drug represents a single-agent, immune-restoring solution to chronic HIV, HBV, and malignancy-induced immunodeficiency. Its selectivity, durability, and absence of irAEs position it as a paradigm-shifting immunotherapeutic platform worthy of accelerated clinical development.

References

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Supplementary Table S1:

Lists markers like PD-1, TOX, IL-7R, CD127, IFN-β, GZMB and their role across exhaustion reversal, $CD8^+$ cytotoxicity, and memory formation.

Supplementary Table S1. Functional roles of key T-cell markers in exhaustion reversal, $CD8^+$ cytotoxicity, and memory formation.

Marker	Primary Function/Description	Role in Exhaustion Reversal	Role in $CD8^+$ Cytotoxicity	Role in Memory Formation
PD-1	Immune checkpoint receptor; up-regulated on chronically stimulated T cells	Blockade (anti-PD-1) reinvigorates exhausted T cells, restoring proliferative capacity and effector function	Enhances degranulation and cytokine secretion when inhibited; increases target killing	Modulates memory precursor differentiation; transient PD-1 marks early memory
TOX	Transcription factor driving the epigenetic programme of exhaustion	High TOX expression enforces exhaustion; its down-regulation is required for phenotypic and functional reversal	Elevated TOX correlates with reduced granzyme B and perforin expression	Persistent TOX impairs memory development; low TOX favours memory commitment

| *IL-7R* | Cytokine receptor α-chain (CD127); critical for T cell survival | IL-7 signalling promotes survival of reinvigorated T cells and supports recovery from dysfunction | IL-7 enhances metabolic fitness, indirectly boosting cytotoxic molecule synthesis | Essential for long-term maintenance and homeostatic proliferation of memory |

| *CD127* | Synonym of IL-7R; marker of memory precursor cells | High CD127 expression identifies cells amenable to functional rescue following checkpoint blockade | $CD127^+$ precursors give rise to potent cytotoxic effectors upon antigen re-encounter | Defines central memory subset; required for durable immune memory |

| *IFN-β* | Type I interferon; modulator of innate and adaptive immunity | Transient IFN-β exposure can reinvigorate T cells by up-regulating effector programs and reducing exhaustion | directly up-regulates granzyme B and perforin; enhances target cell apoptosis | Promotes memory differentiation via STAT1/STAT2 signaling |

| *GZMB* | Granzyme B; serine protease within cytotoxic granules | Levels increase upon functional rescue of exhausted T cells; a read-out of successful reinvigoration | Mediates apoptosis of infected or malignant targets; primary effector molecule | rapidly expressed in early effectors; lower in resting memory but poised for re-expression |

Legend:

This table summarizes the dual and distinct roles of each marker in three critical T-cell processes:

1. *Exhaustion Reversal* – mechanisms by which chronically stimulated, dysfunctional T cells regain effector functions.

2. *$CD8^+$ Cytotoxicity* – direct killing of infected or malignant cells via degranulation and cytolytic enzymes.

3. *Memory Formation* – establishment and maintenance of long-lived T cell populations capable of rapid recall upon re-challenge.

Supplementary Note 1:

Summarizes real-world cohort data:

* *HIV*: $CD8^+$ responses in ART-suppressed individuals (Spinelli et al., JCI Insight 2022)

* *HBV*: EGFR inhibitor evidence of cccDNA suppression

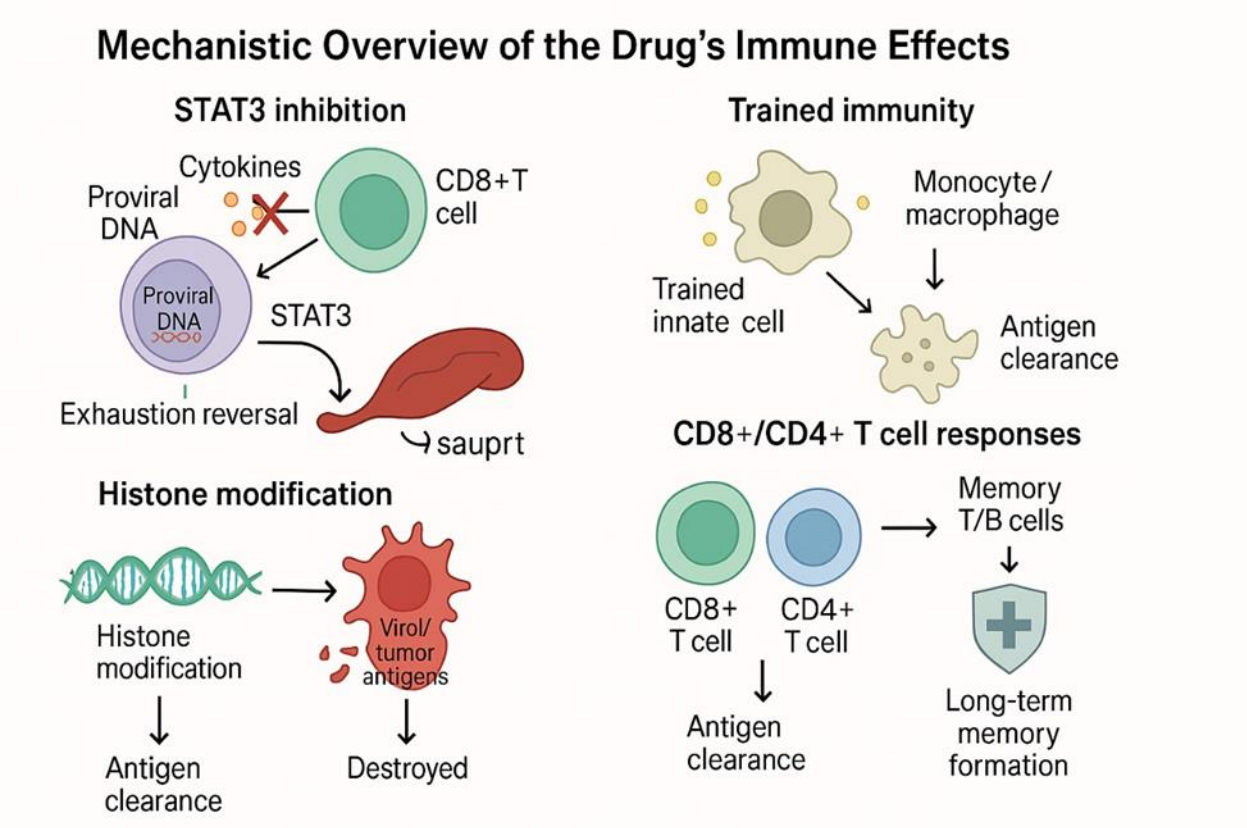
* *Cancer*: Preclinical synergy with checkpoint inhibitors via trained immunity and STAT3 inhibition

Supplementary References:

Includes links to FDA guidelines, PubMed studies, and immunology reviews supporting mechanisms and regulatory feasibility.

Figures:-

Figure 1: Mechanistic Overview of the Drug's Immune Effects



This diagram illustrates the global mechanism of action of the repurposed immunomodulatory drug. Key processes include:

* STAT3 pathway inhibition (suppressing immune exhaustion)

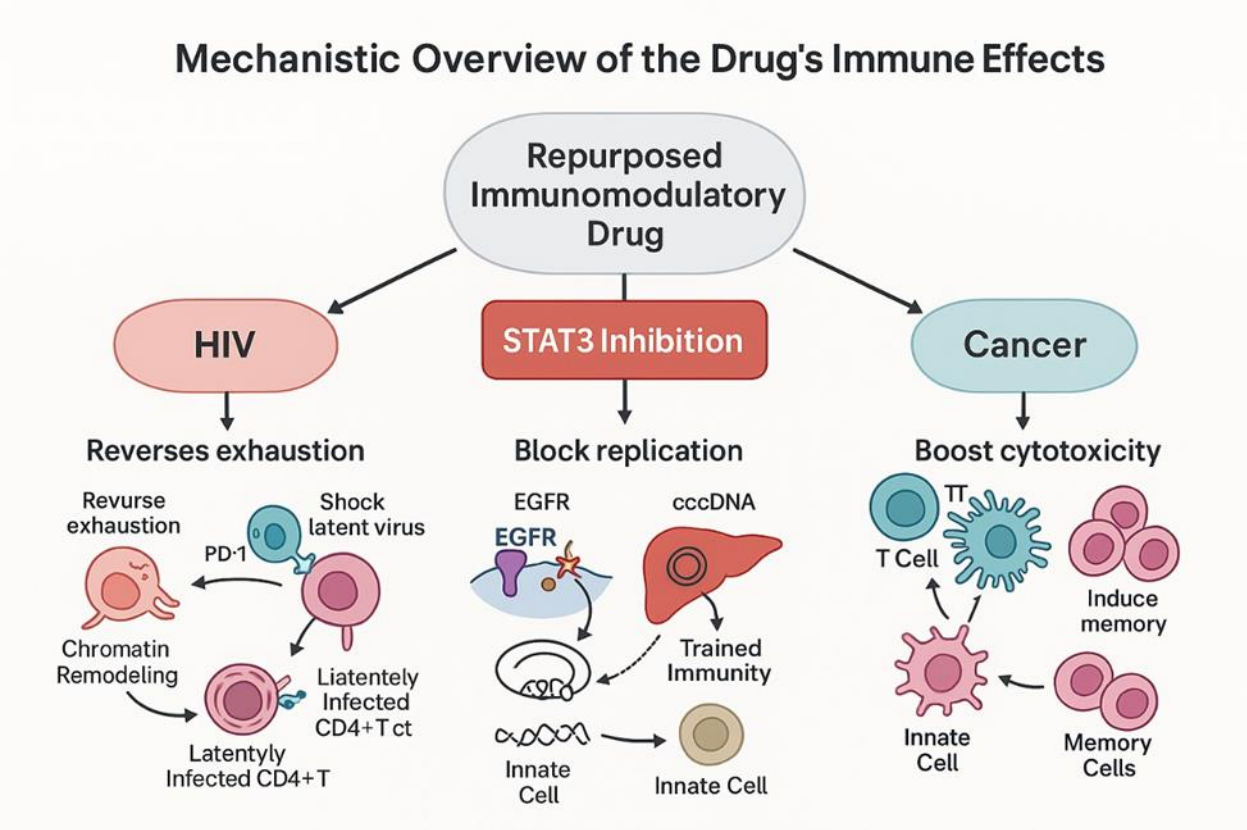
* Chromatin remodeling (reactivating latent virus or tumor antigen expression)

* Trained innate immunity (reprogramming macrophages and NK cells)

* Enhanced adaptive responses ($CD8^+$ cytotoxicity, $CD4^+$ T cell help, and memory B/T cell formation)

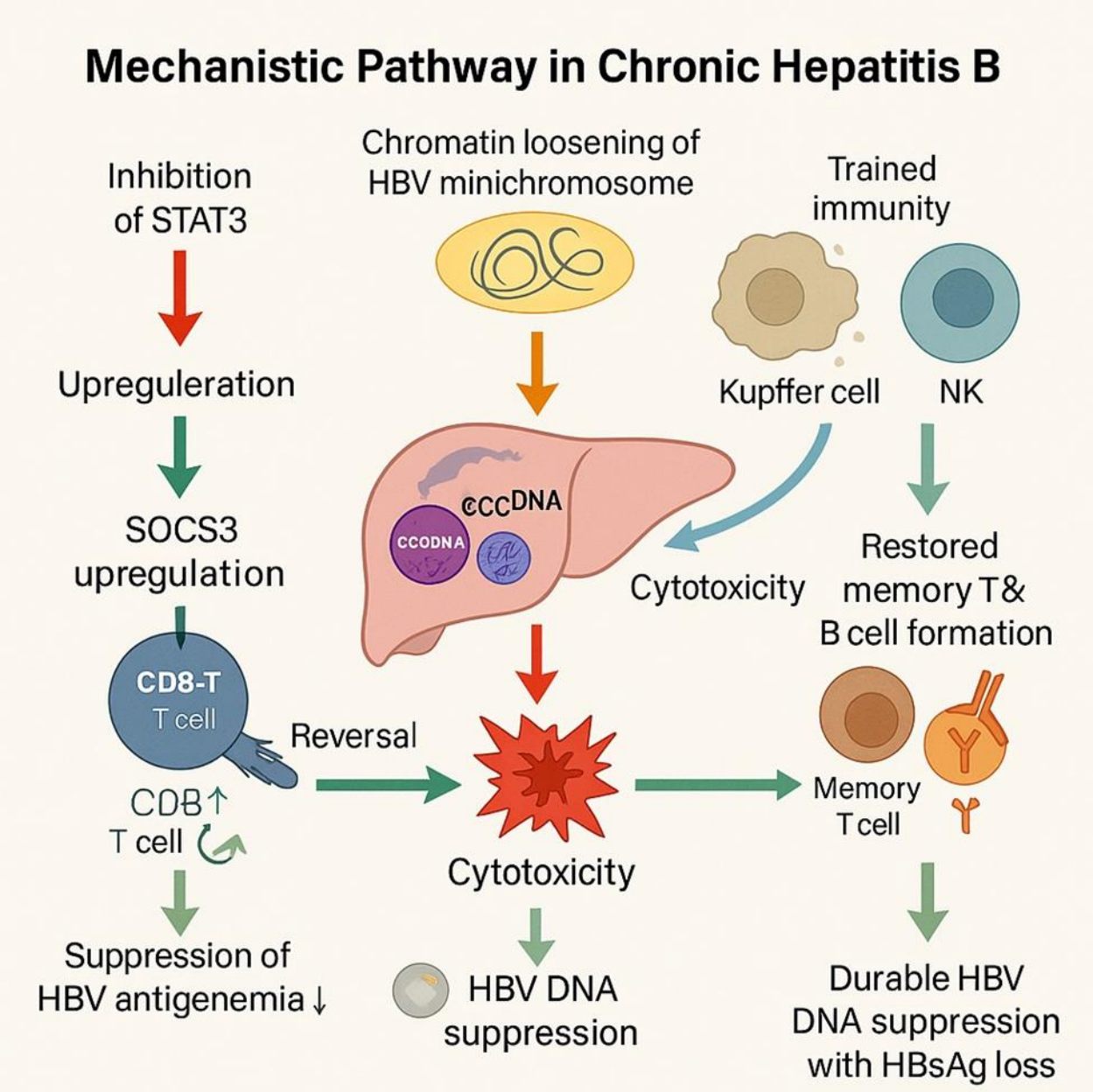
These effects synergize to disrupt immune evasion and establish long-term immune surveillance across HIV, HBV, and cancer.

Figure 2: HIV-Specific Mechanism of Action



The figure details how STAT3 inhibition reduces PD-1^{+} T cell exhaustion in ART-suppressed patients. Chromatin remodeling reactivates the latent provirus, while CTL activity eliminates infected cells. Memory cells ensure post-ART viral control.

Figure (3)



This panel shows:

* STAT3 inhibition suppresses HBV DNA/cccDNA transcription

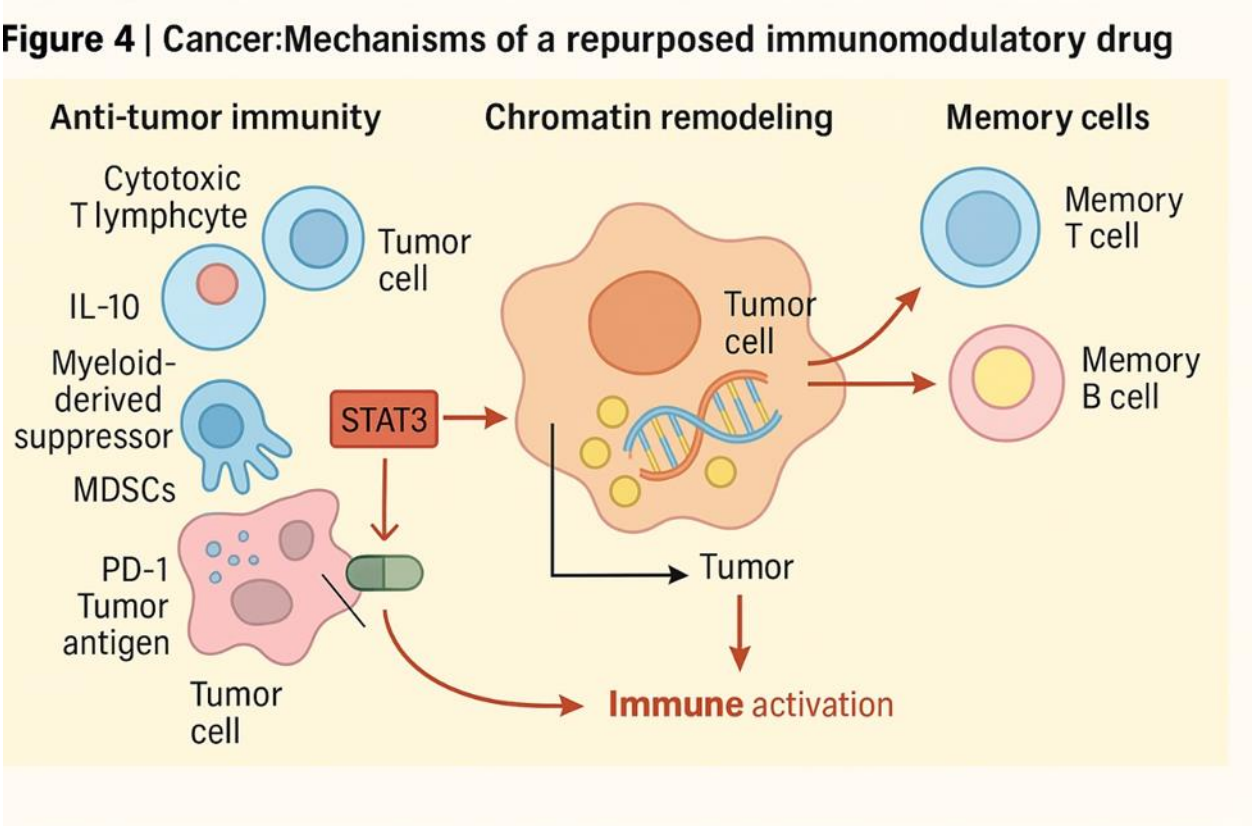
* SOCS3 upregulation and immune exhaustion reversal

* Chromatin remodeling of HBV minichromosomes

* Trained immunity via liver-resident Kupffer and NK cells

* Restored CTL/B cell responses resulting in HBsAg loss and durable HBV DNA suppression

Figure 4: Cancer Immunotherapy Synergy



STAT3 blockade in tumors decreases IL-10 and myeloid suppressor cells. The figure illustrates improved dendritic cell activation, enhanced CTL/NK cytotoxicity, and antigen presentation. Memory formation contributes to long-term tumor surveillance.

Figure Legends

PROBLEM:

Immunodeficiency complications of malignant tumors

Tumor-Induced Immune Suppression

Tumors create an immunosuppressive environment that inlibits immune responses

Limited T-Cell Function

Dysfunctional or deJ.eted T-cells

Toxicity & Side Effects

Severe autoimmune or toxic effects

SOLUTION:

Our repurposced drug counteractact immune suppression:

Attracts APCs, T cells, and other leukocytes

Cytokine/chemokine release

Enhances dendritic cell and macrophage antigen presentation

Promotes helper (CD4+) and cytotoxic (CD8+) T-cell activation

and memory formaton

Drives B-cell affinity maturation

(IgM +high-affinity IgG

PROBLEM:

Immunodeficiency complications of infectious diseases

Pathogen Persistence

Chronic infections over time detune immune function

Exhausted T-Cells

T-cells reduceal antiviral activity

Global Immunosup-pression

Increased susceptibility to viral reactivattion or reinfection

SOLUTION:

Our repurposed drug counteractact immue supproaanches

Enhances clearing of pathogens

Restores functional impairments

Reduces risk of co-infections

by other pathogens

Promotes protective host responses against reinfection

T-cell and antibody activation

Overcoming Immunodeficiency in Malignant Tumors

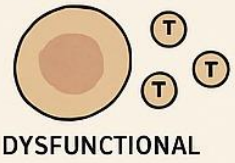
Problem

Tumor-Induced Immune Suppression

Immunosuppressive molecules inhibit immune responses

Limited T-Cell Function

Dysfunctional or depleted T-cells reduce therapy efficacy



Toxicity and Side Effects

Autoimmune reactions and other toxicities pose risks

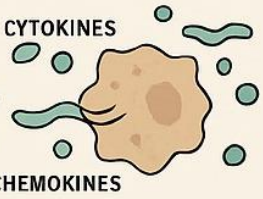
Enhanced Antibody I Production

and AffinityMaturation

Solution

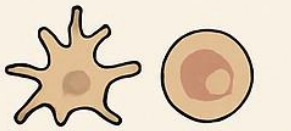
Attracting Immune Cells to the Tumor Site

Cytokines and chemokines cause local infiammation



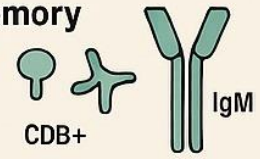
Boosting Antigen Presentation

Enhanced activity of dendritic cells and macrophages



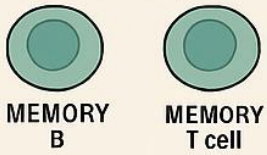
Strengthening T Cell Activation and Memory

Enhanced Antibody Production and Affinity Maturation



Long-Term Immune Memory

Memory B and T cells help reduce recurenc risk



REACTIVATING & CLEARING HIV RESERVOIRS

PROBLEM

Latent Reservoirs

HIV persists in dormant cells, making it difficult for treatments to eradicate the virus

Immune Evasion

HIV mutates rapidly, enabling it to escape immune responses and antiviral drugs

Incomplete Immune Restoration

ART does not fully restore immune function, leaving residual inflammation and immune dysfunction

Side Effects & Adherence

Long-term ART can cause side effects, and adherence is crubal to prevent viral rebound

SOLUTION

Histone Modification

Reactivates latent HIV by altering chromatin structure

STAT3 Inhibition

Suppresses immune evosion genes (eg. PD-1, IL-10, TGF-β)

Core Protein Modulation

Disrupts viral persistence by tageting the HIV core profem

CD8+ Activation

Kills infected cells and reduces antigen burden

CD4+ Activation

Supports CDB+ activity and promotes memory

Immune Memory

Maintains long-term

Reactivating & Clearing HIV Reservoirs

PROBLEM

Latent Reservoirs
HIV persists in dormant cells, making it difficult for treatments to eradicate the virus.

Immune Evasion
HIV mutates rapidly, enabling it to escape immune responses and antiviral drugs.

Incomplete Immune Restoration
ART does not fully restore immune function, leaving residual inflammation and immune dysfunction.

Side Effects and Adherence
Long-ferm ART can cause side effects, and adherence is crucial to prevent viral rebound

Side Eflares and Adherence
Carefully manages immune response to prevent harmful fares

SOLUTION

Histone Modification
Reactivates latent HIV by opening up chromatin

STAT3 Inhibition
Biocks franscription factors involved in imrune evasion

Modulation of Core Protein
Destabilizes HIV reservois. by targeting cccDNA maintenance

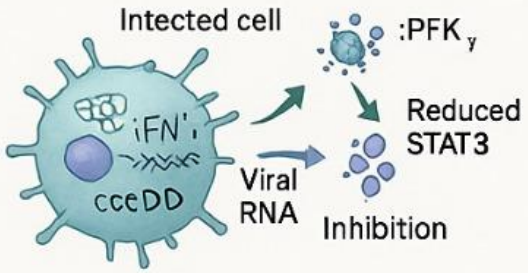
CD8+ T Cell Activation
Increases cyrotoxicity to clear HIV-infected cells

CD4+ T Cell Activation
Enhances helper function to support CD8+ and B cells

Long-Term Immune Memune
Forms memory B and T cells to maintain immunity

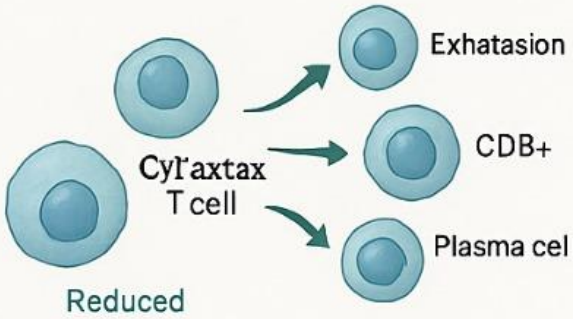
Problem 1

Persistent HBV Repplication and Latent Reservors (cccNDA)



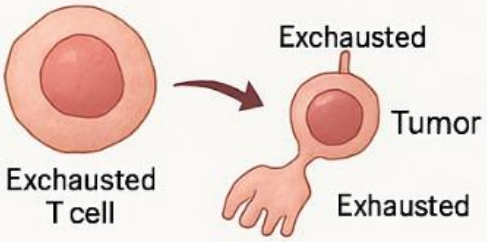
Solution

Enhanced Cytototic Tël˙Activation



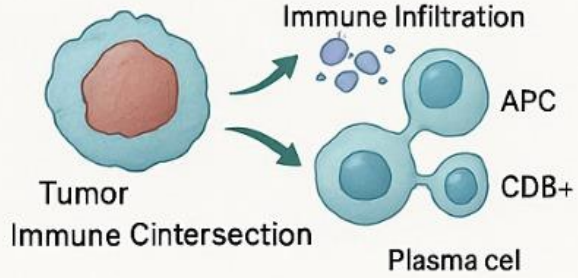
Problem 2

Immune Tolerance and T-cell Exchustion in Chronic HBV



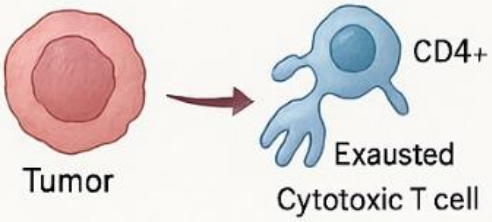
Solution

Immune Infiltration and Activation



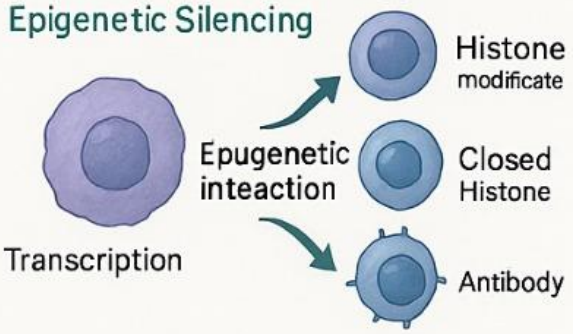
Problem 3

Tumor Microemironment Suppression of Immune Sureillance



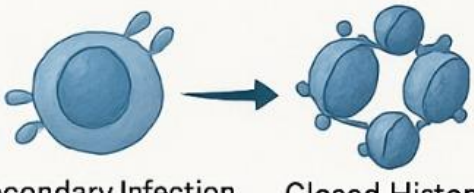
Solution

Epigenetic Silencing



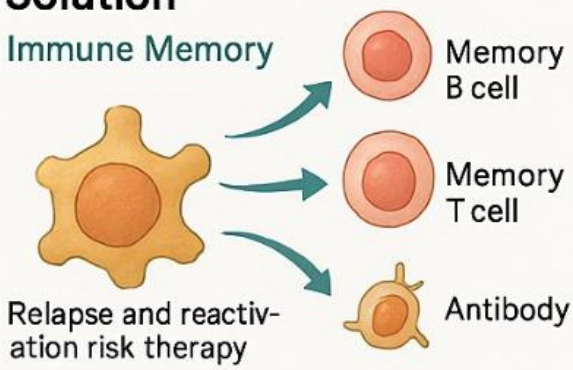
Problem 4

Transcriptional Activity of HBV cccDNA



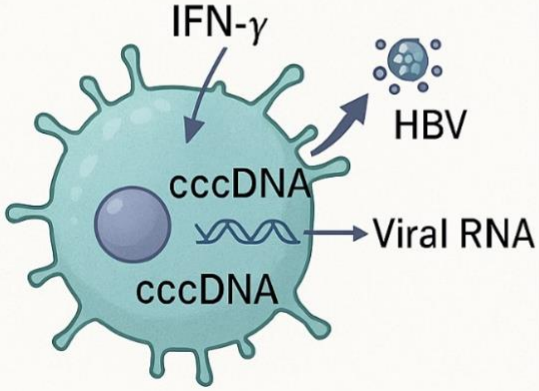
Solution

Immune Memory



Problem 1

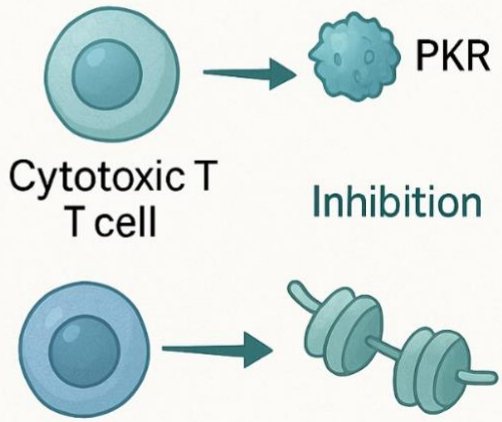
Persistent HBV Replication and Latent Reservors (cccDNA)



Infected Cell

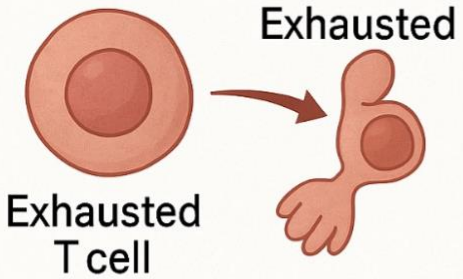
Solution

Enhanced Cytotoxic T cell



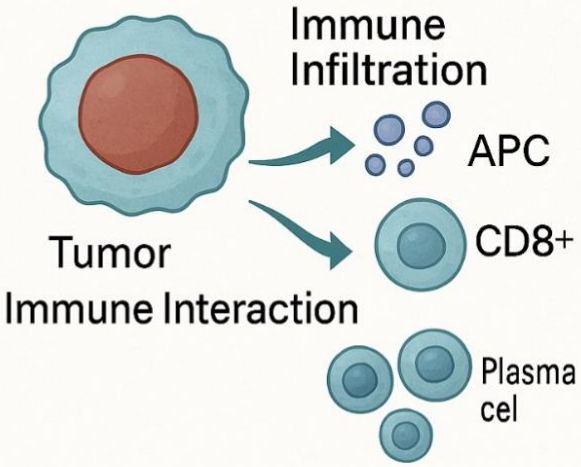
Problem 2

Immune Tolerance and T-cell Exhaustion in Chronic HBV



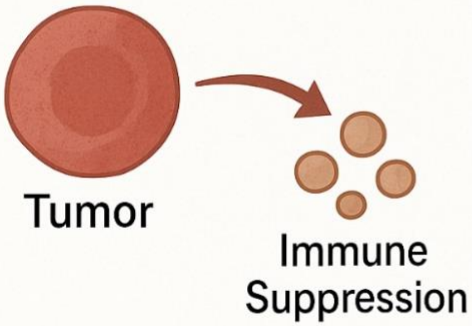
Solution

Immune-Boostting Strategy



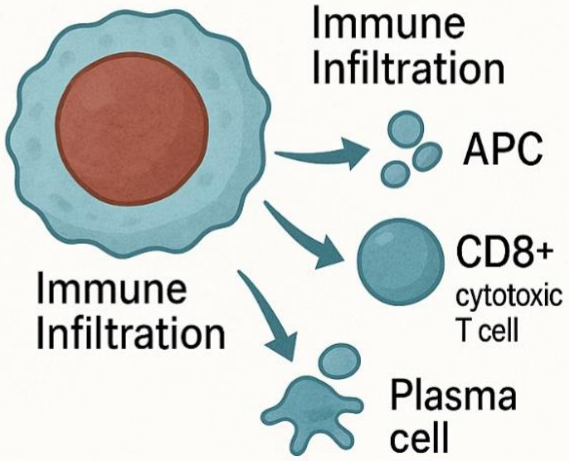
Problem 3

Tumor Microenvironment Suppresses Immune Surveillance



Solution

Immune-Boosting Strategy



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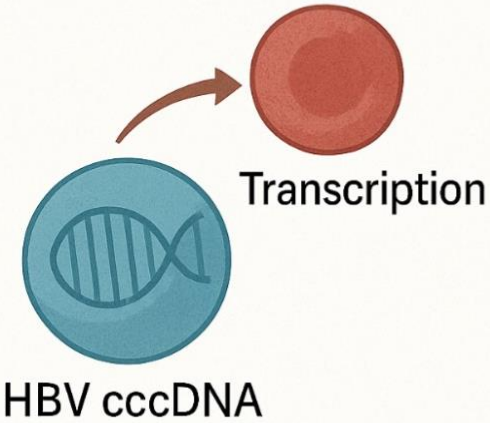
Transcriptional Activity of HBV cccDNA



Solution

Epigenetic Silencing of cccDNA