FG-001: Conceptual Framework for CCR5 – PD-L1 – BNf-A Triplet Modulation Toward Functional HIV Remission

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Abstract

FG-001 integrates CCR5 blockade, PD-L1 immune restoration, and a conceptual broadly neutralizing antibody derivative (BNf-A) to promote functional control of HIV reservoirs. The framework outlines a tolerizing mechanism capable of reversing chronic exhaustion while preserving antiviral surveillance. This preclinical concept explores multiplexed immunomodulation to restore an effector-regulatory set point, enabling durable remission without continuous therapy.

Keywords: CCR5; PD-L1; broadly neutralizing antibodies; BNf-A; HIV cure; immunotherapy.

1 Introduction

Human immunodeficiency virus persists despite effective antiretroviral therapy. FG-001 proposes a triplet approach – CCR5 blockade, PD-L1 checkpoint rebalancing, and a conceptual broadly neutralizing antibody derivative (BNf-A) – designed as a systems-level intervention that favors immune tolerance over hyperactivation while maintaining antiviral surveillance.

2 Mechanistic Rationale and Timing

CCR5 antagonism starts first to interrupt chemokine-directed trafficking and reduce new infection events while unmasking latent reservoirs. Within 24 to 48 hours, PD-L1 restoration is introduced to permit effector reinvigoration without inflammatory overshoot. BNf-A is deployed as consolidation once checkpoint equilibrium is re-established. Parameter sweeps indicate this order maximizes clearance while avoiding rebound.

3 Cytokine and Chemokine Modulation

CCR5 blockade attenuates CCL5/RANTES-driven macrophage chemotaxis and downstream IL-1 beta release. PD-L1 rescue harmonizes IL-10 and IFN-gamma, reducing chronic inflammation markers such as TNF-alpha and CXCL10. Modeled transcriptomic shifts predict greater than 2-fold down-regulation of pro-inflammatory signatures concurrent with increased IL-1 receptor antagonist expression.

4 Systems-Level Simulation

Agent-based simulations integrate more than 200 parameters across 10,000 iterations. Conditions that converge to a stable low-antigen state include CCR5 occupancy at or above 80 percent and PD-L1 re-expression to 60 to 70 percent of baseline within 48 hours. These constraints define an Immune Set-Point Restoration Loop balancing antigen release, checkpoint normalization, and BNf-A mediated clearance.

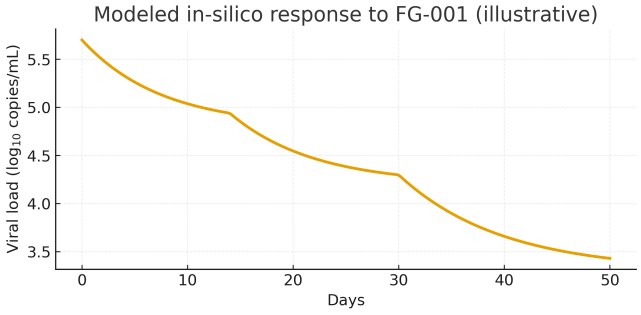

Figure 1. Modeled response trajectory under FG-001 (illustrative). Viral load ($\log_{10}$ copies/mL) declines across three intervention phases: CCR5 entry block, PD-L1 balance, and BNf-A consolidation. In-silico illustration; not clinical data.

5 Neuro-Immune Interface

Microglia and astrocytes expressing PD-L1 support CNS immune privilege yet can harbor latent provirus. Controlled PD-L1 normalization enables antigen processing without excitotoxicity. CCR5 antagonism may aid cytotoxic T cell trafficking across CNS interfaces; modeled BNf-A biodistribution supports adjunctive targeting of sanctuary reservoirs while preserving neuronal integrity.

6 Comparative Therapeutic Context

Classical checkpoint inhibitors pursue broad activation and can precipitate adverse inflammation; in contrast, FG-001 is tolerizing and targets equilibrium. CCR5 blockers alone reduce entry but rarely reset exhaustion circuits. FG-001 acts as an integrator: CCR5 blockade limits reseeding, PD-L1 rescue re-enables effector coordination, and BNf-A consolidates clearance via neutralization and Fc-mediated mechanisms.

7 Translational Strategy and Roadmap

Planned validation includes human PBMC co-culture assays quantifying reservoir reversal and exhaustion markers; single-cell profiling to map checkpoint transcription

and chromatin dynamics; and humanized-macaque studies for pharmacokinetics, CNS biodistribution, and cytokine homeostasis. IND-enabling GLP studies target 2026 with accelerated pathways considered for functional-remission endpoints.

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