

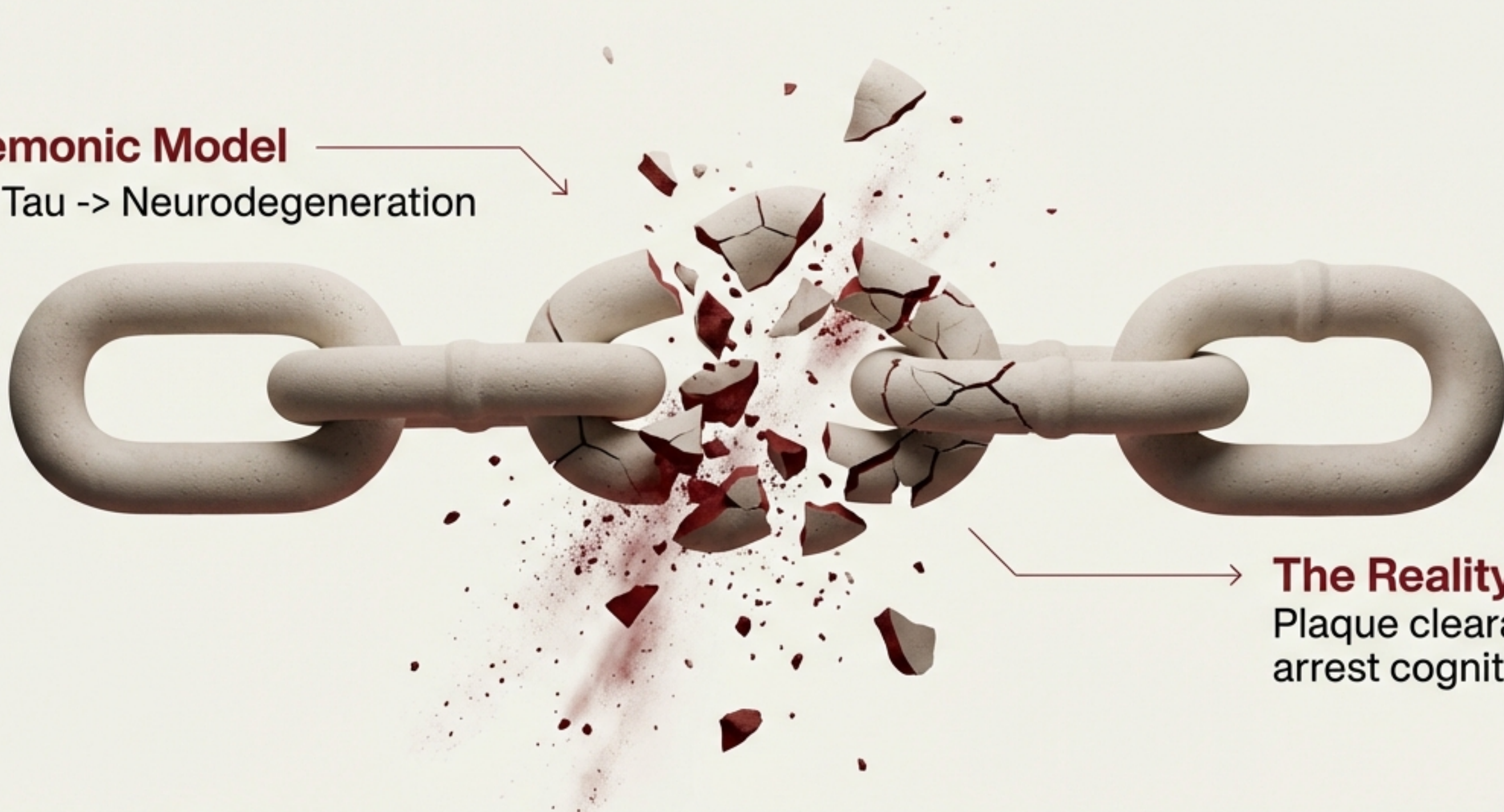
The Immunological Renaissance

Reversing Neurodegeneration via BCG and Shingles Vaccination

The Linear Fallacy & The Stalemate

The Hegemonic Model

Amyloid -> Tau -> Neurodegeneration



The Reality

Plaque clearance fails to arrest cognitive decline.

**The CNS is not an immune-privileged sanctuary.
It is dependent on systemic vitality.**

The Cellular Crisis: Failure of Clearance

Stalled Autophagy
(Lysosomal failure)

Senescent Microglia
(Downregulated TREM2)

Bioreactor for
 $A\beta$ production

The Signal in the Noise: 'Off-Target' Protection



58%

Risk Reduction (BCG High Dose)

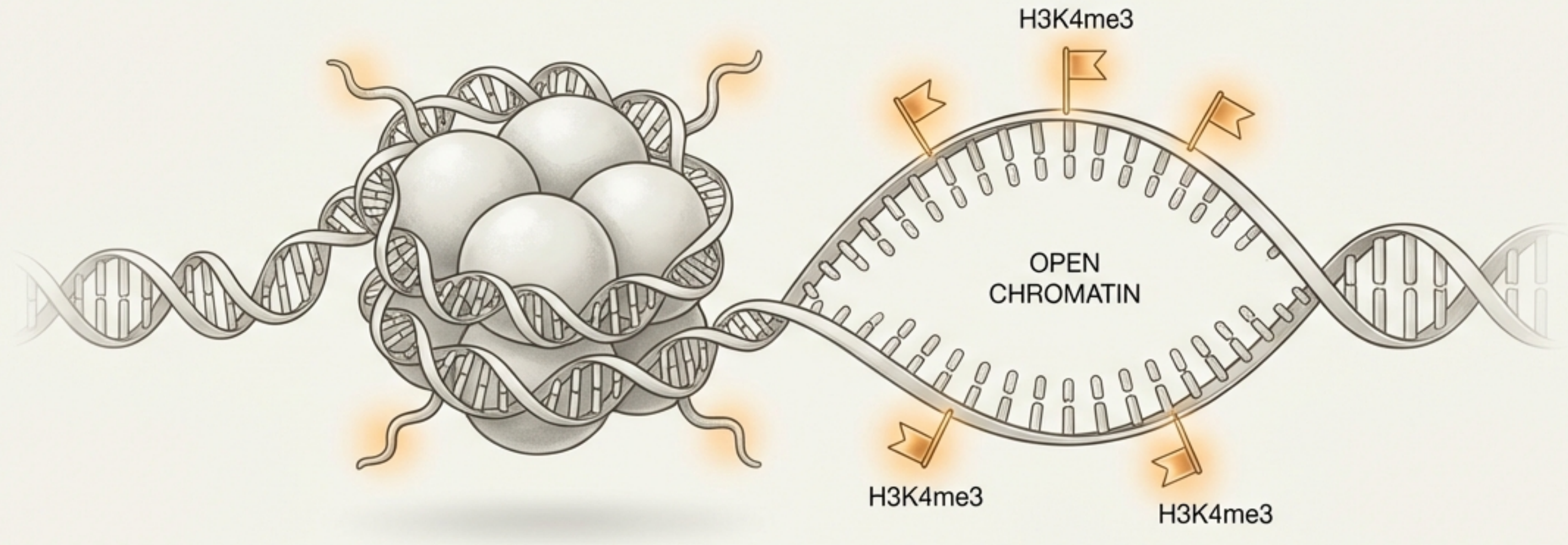


30%

Risk Reduction (Shingrix)

Evidence from bladder cancer cohorts and vaccine rollouts
reveals protection beyond the Healthy User Bias.

Mechanism I: BCG & Epigenetic Reprogramming



Trained Immunity

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Reprogramming innate monocytes, not just adaptive T-cells.

Epigenetic Remodeling

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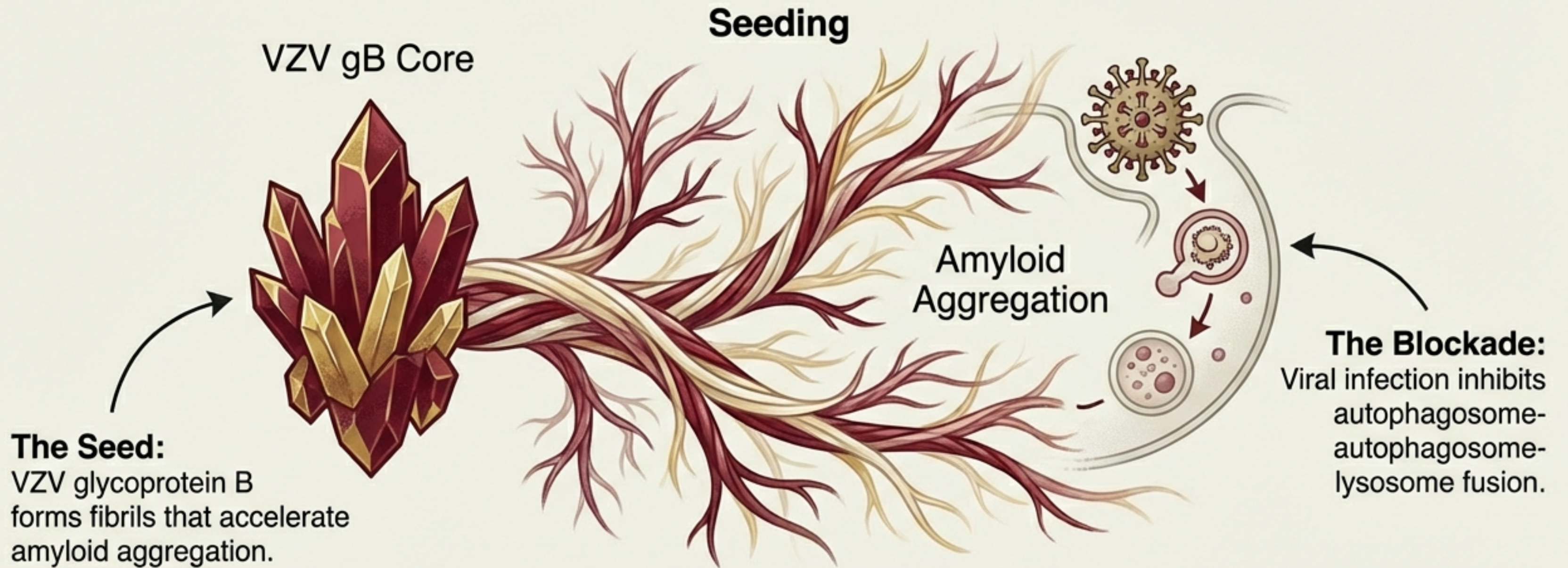
H3K4me3 marks keep chromatin “open” at pro-inflammatory gene promoters.

The Metabolic Switch

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Induction of aerobic glycolysis (Warburg effect) creates high-energy phagocytes.

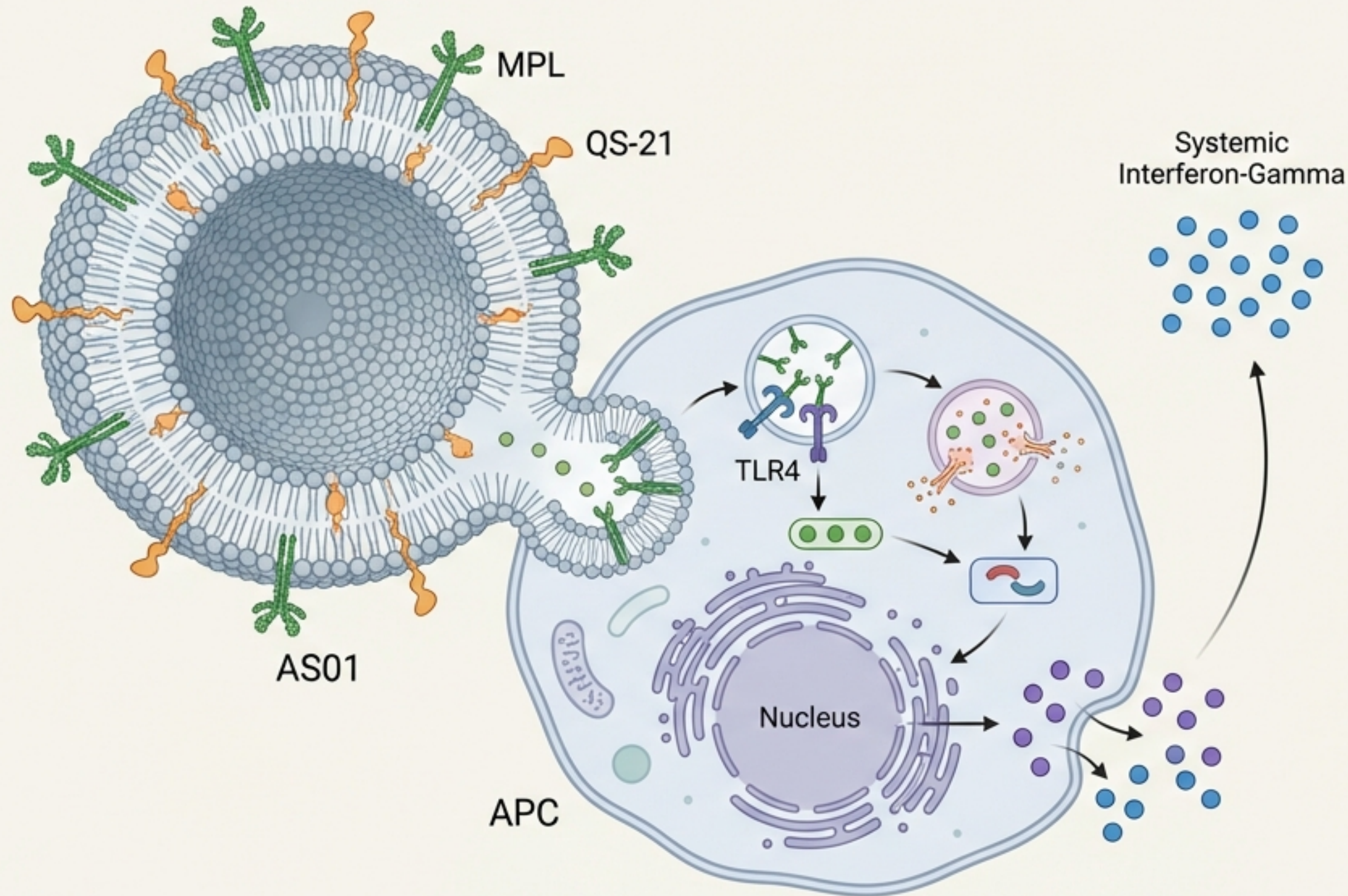
Mechanism II: The VZV Catalyst



The Vaccine Effect: Prevents the "Hit-and-Run" reactivation event.

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Mechanism III: The Adjuvant Advantage (AS01)

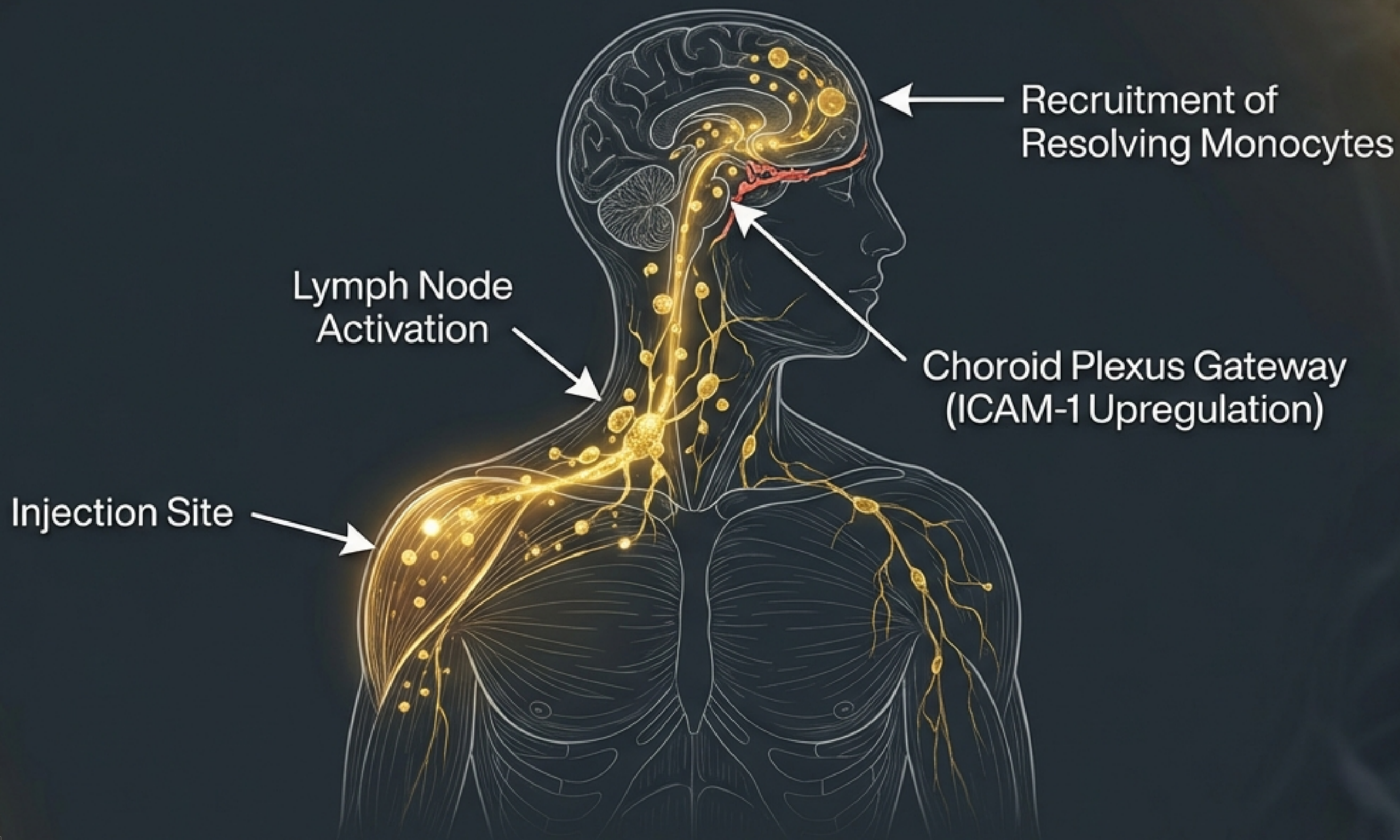


The Synergy: MPL (TLR4 agonist) + QS-21 (Saponin).

The Result: Rapid, potent induction of Systemic Interferon-Gamma.

Shingrix (Recombinant + AS01) outperforms Zostavax (Live Attenuated).

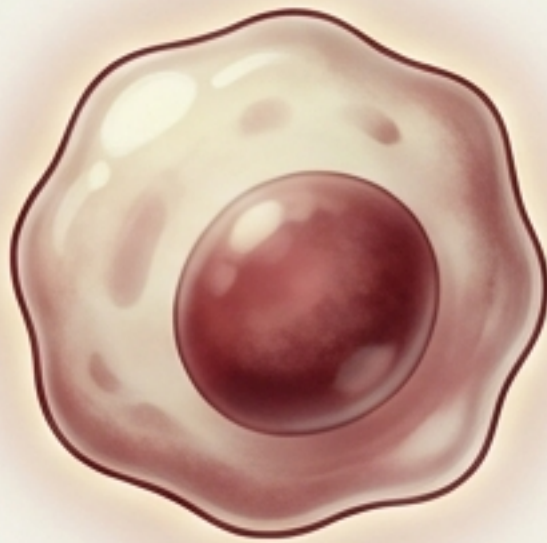
The Bridge: Systemic Interferon-Gamma



Breaking Tolerance & Restoring Flux

Tolerance

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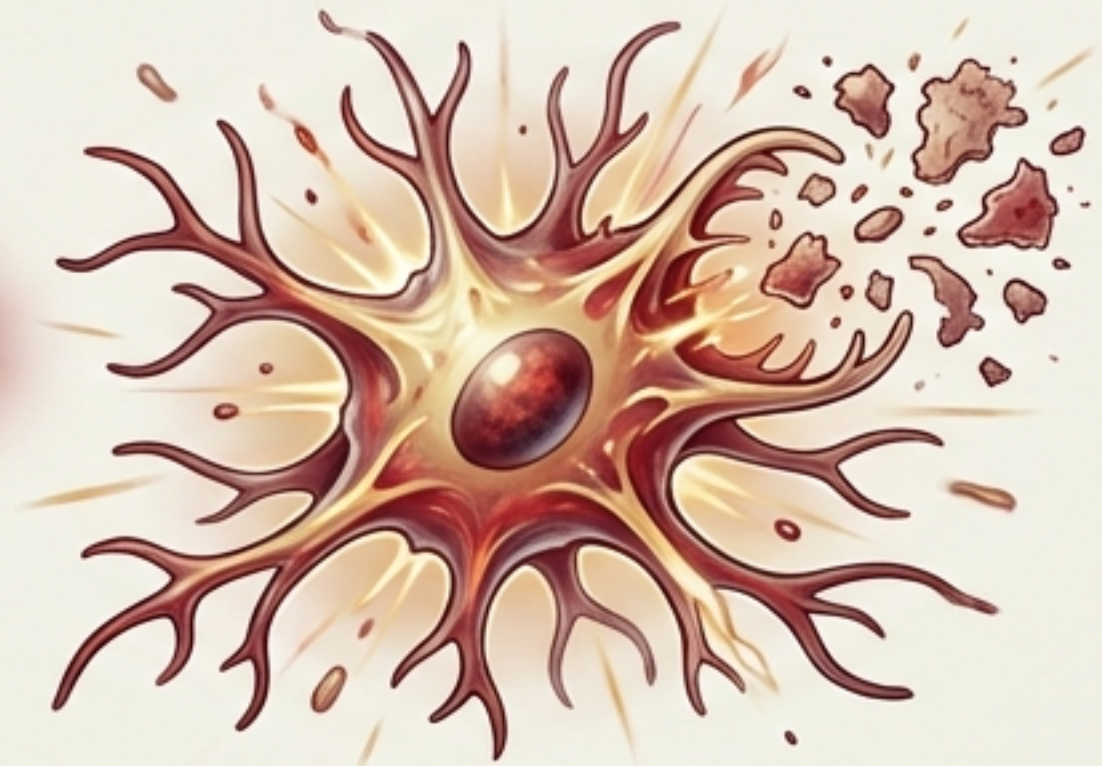


mTOR Active
(Brake On)



Restoration

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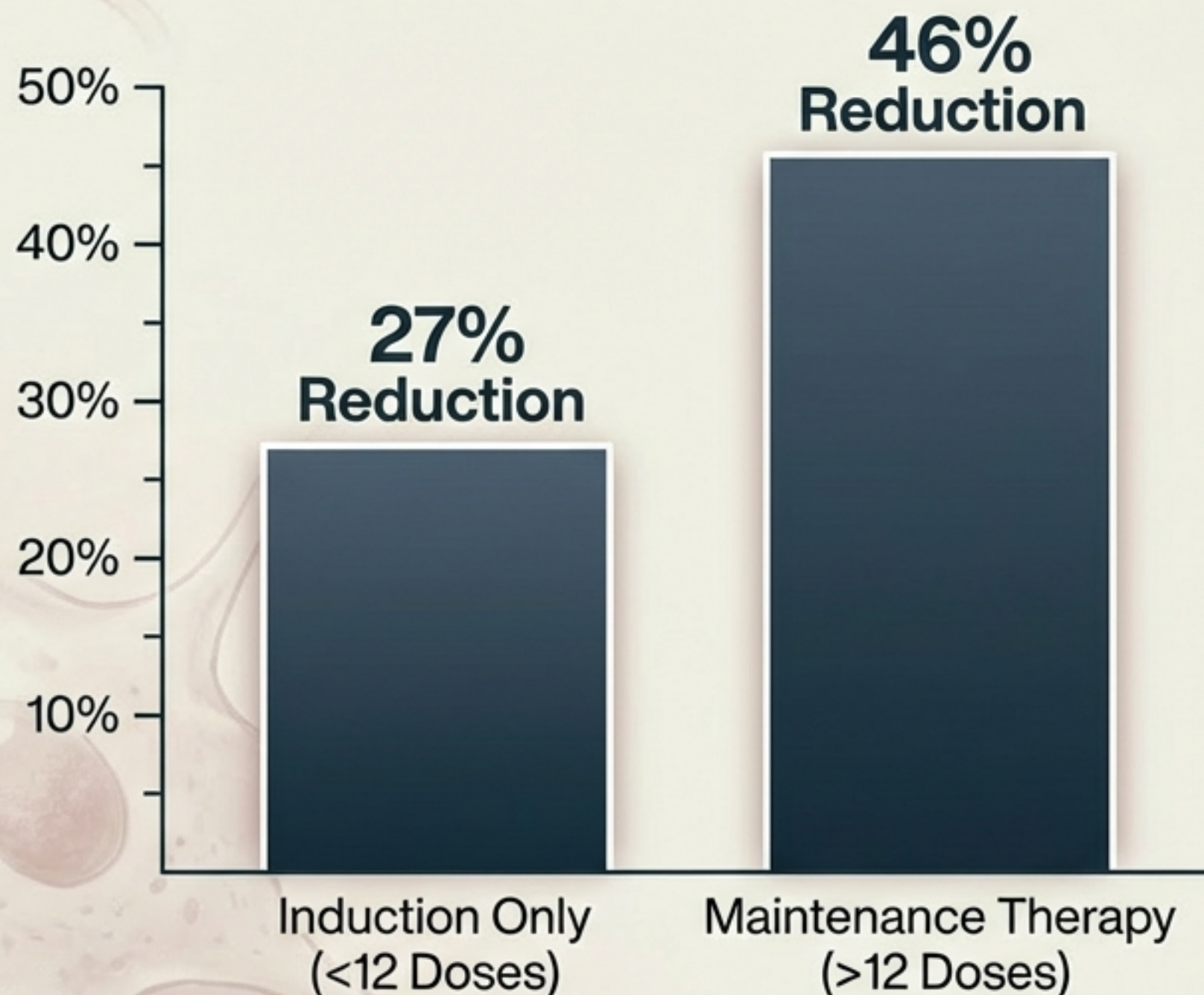
IFN-γ Stimulated
(Brake Released)

Interferon-gamma unlocks the autophagic brake, allowing
Microglia to resume clearing the amyloid traffic jam.

in Martina Plantin

Beyond the 'Healthy User' Bias

Dose-Dependent Protection

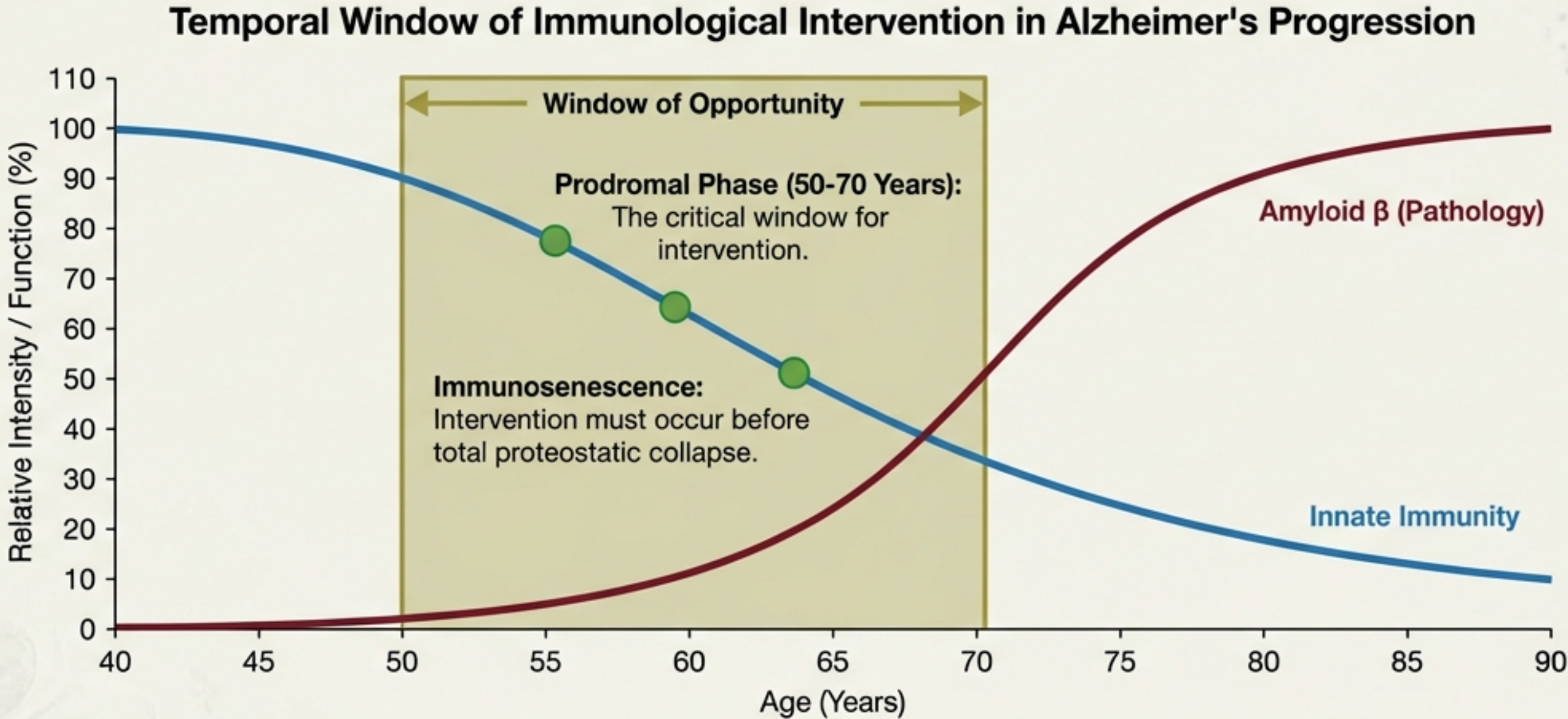


Biologically Plausible:
Protection scales with dose frequency.

Active Comparator:
Shingrix outperforms Flu/Tdap vaccines in the same populations.

Animal Models:
Causality confirmed in APP/PS1 mice.

The Window of Opportunity



Proposed temporal interaction between disease progression and immunological intervention. Alzheimer's pathology (Amyloid/Tau accumulation) begins decades before symptoms. Immunosenescence (blue line) accelerates in the 6th and 7th decades, coinciding with the inflection point of pathology. BCG and Shingles vaccinations (green markers) administered in this window may boost innate immunity, potentially restoring clearance mechanisms before irreversible neurodegeneration occurs.

The Future of Neuroprotective Immunotherapy

Adjuvant-Only Therapies

Isolating AS01 (MPL + QS-21) to boost microglial competence without viral antigens.

Repurposing

Clinical trials (e.g., PRIME) repositioning BCG as a primary Alzheimer's therapeutic.

The Dual Model

Viral Prevention (Stopping the Seed) + Immune Training (Restoring Clearance).

Revitalizing the Oldest Defense

The cure may not lie in a novel molecule, but in re-tuning the body's ancient, intrinsic capacity for repair.

From sterile inflammation to heightened vigilance.



References & Data Sources

PubMed: BCG Vaccine Impact on Dementia Risk (2025)

PNAS: TLR4 stimulation with MPL (2025)

JCI: Peripheral monocyte-derived cells (2025)

Frontiers in Aging Neuroscience: BCG in Immuno-Regulation (2022)

ClinicalTrials.gov: NCT06078891 (PRIME Study)

Nature Aging: VZV and Amyloid Seeding (2024)

The Lancet Healthy Longevity: Shingrix vs Zostavax (2024)