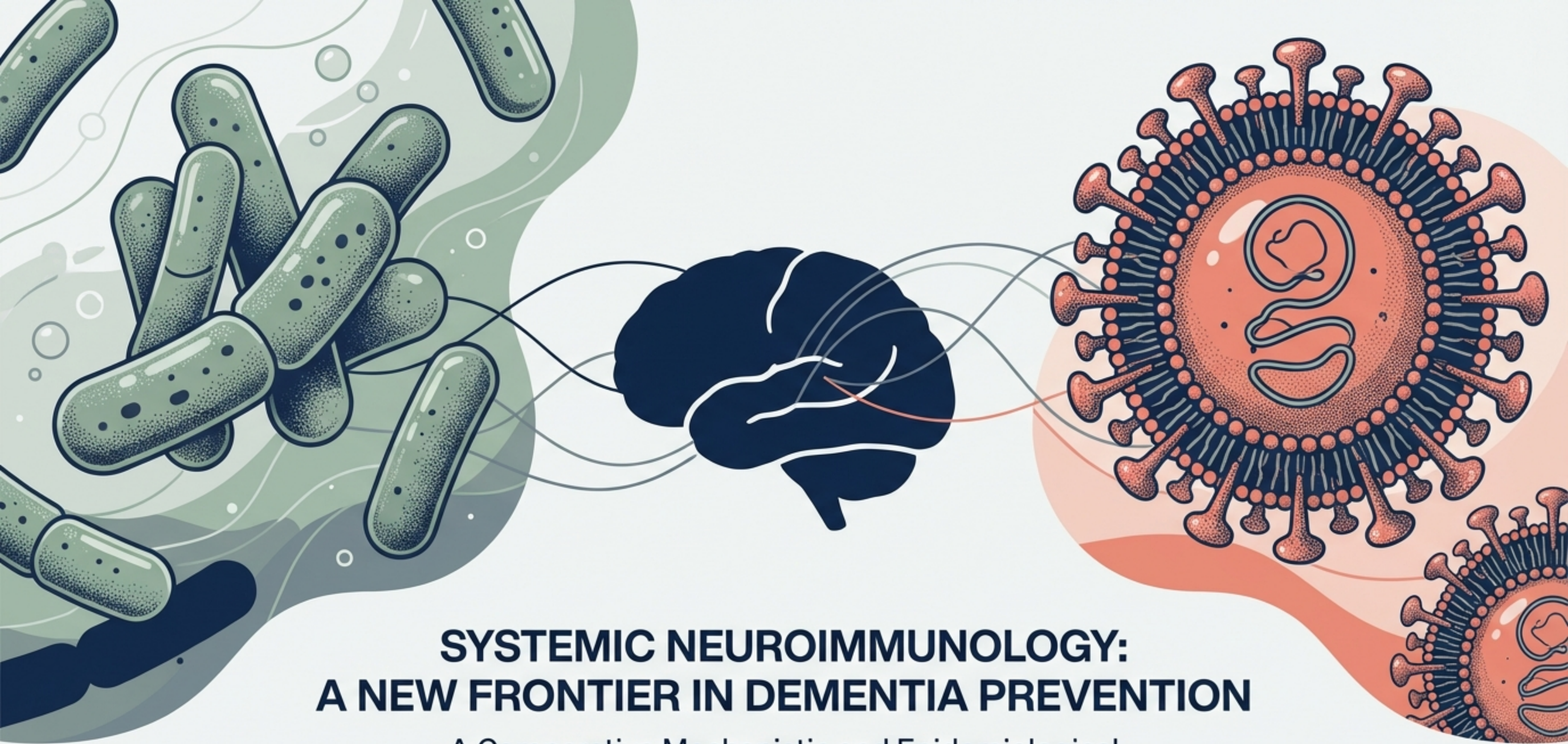


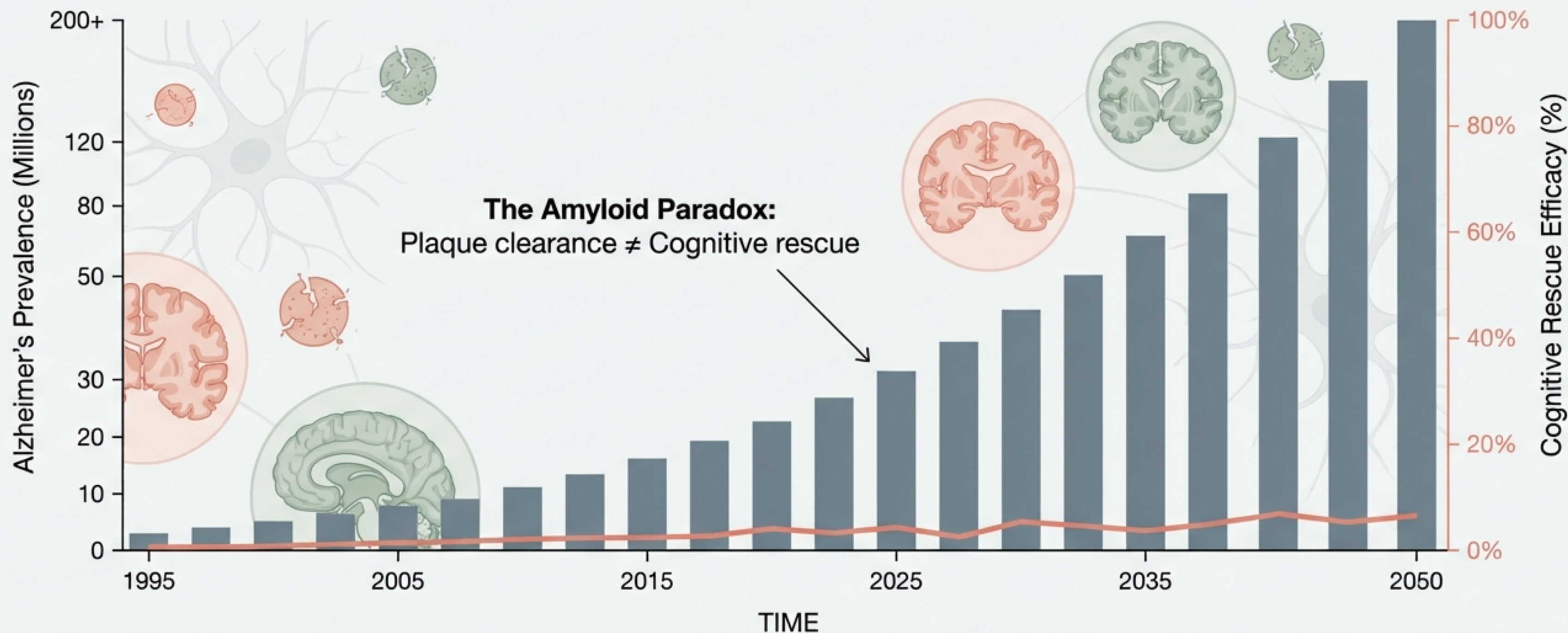


SYSTEMIC NEUROIMMUNOLOGY: A NEW FRONTIER IN DEMENTIA PREVENTION

A Comparative Mechanistic and Epidemiological
Analysis of BCG and Varicella-Zoster Vaccinations

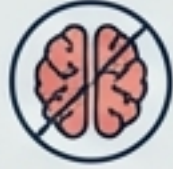
Three Decades of Dogma. Zero Cures.

- **The Cost:** High rates of ARIA adverse events vs. negligible clinical benefit.
- **The Conclusion:** Amyloid accumulation is an end-stage marker, not the sole driver.



Old Dogma:

The brain is isolated and immune-privileged.



New Reality:

The Neuroimmunological Hypothesis. Peripheral immune dialogue modifies CNS trajectory.

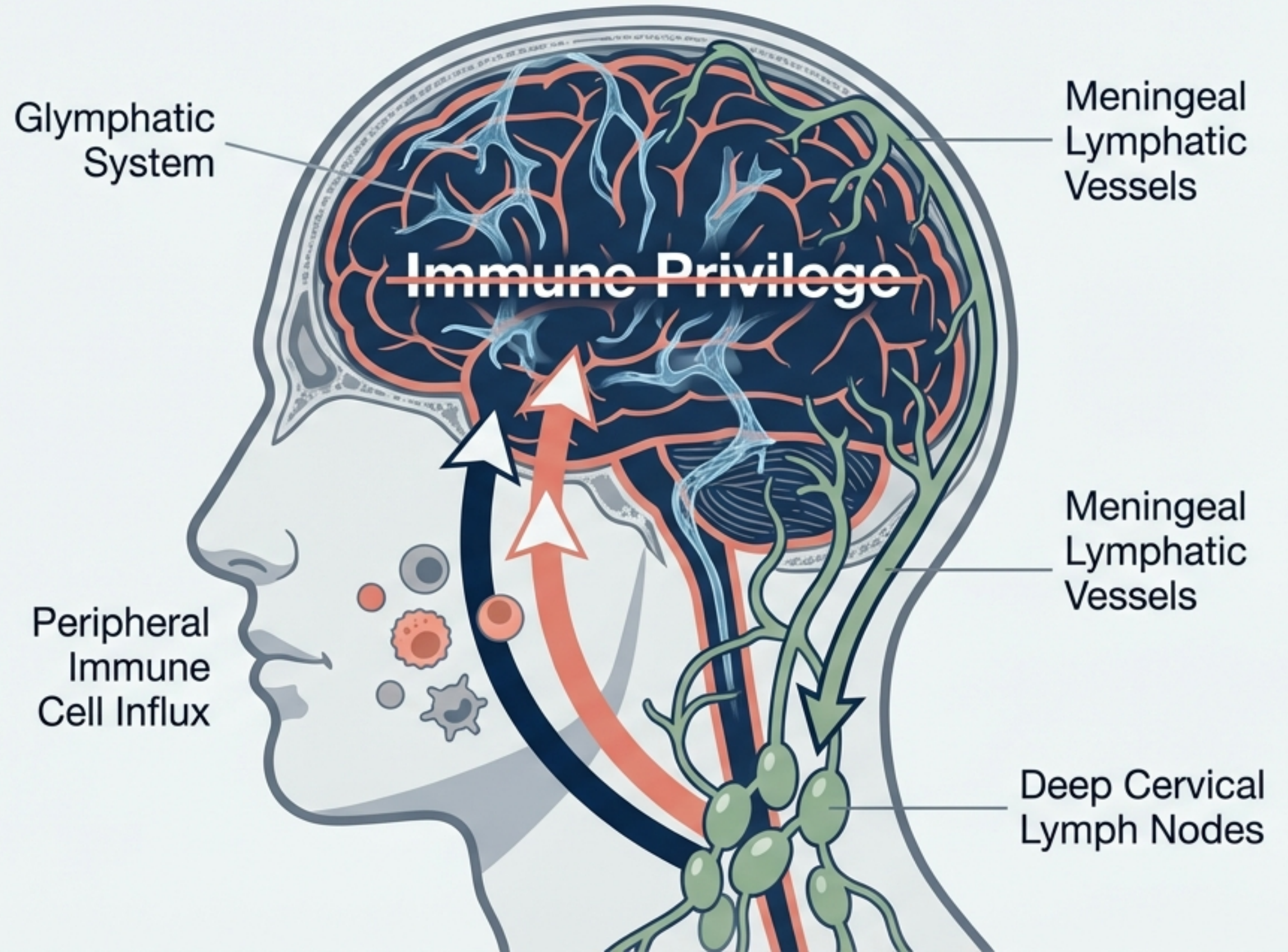


The Opportunity:

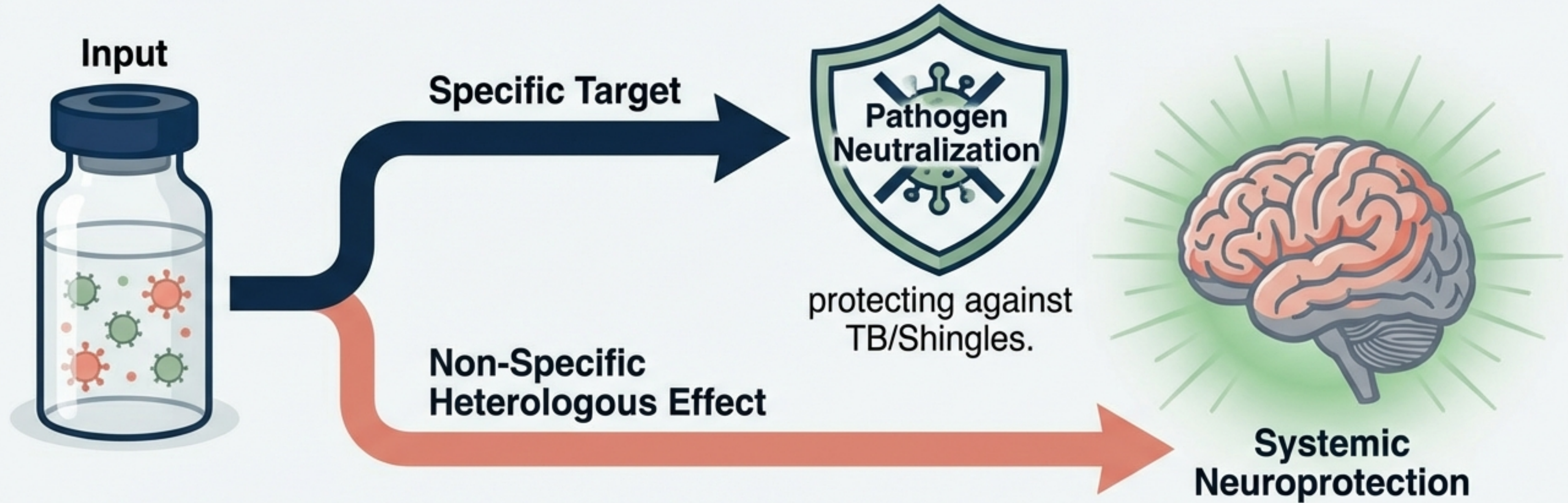
Treating the body to save the brain.



The Brain is Not an Island

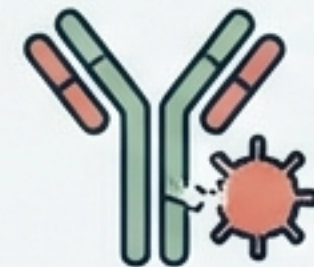


Repurposing the Arsenal: Heterologous Effects



1. Trained Immunity (Innate):

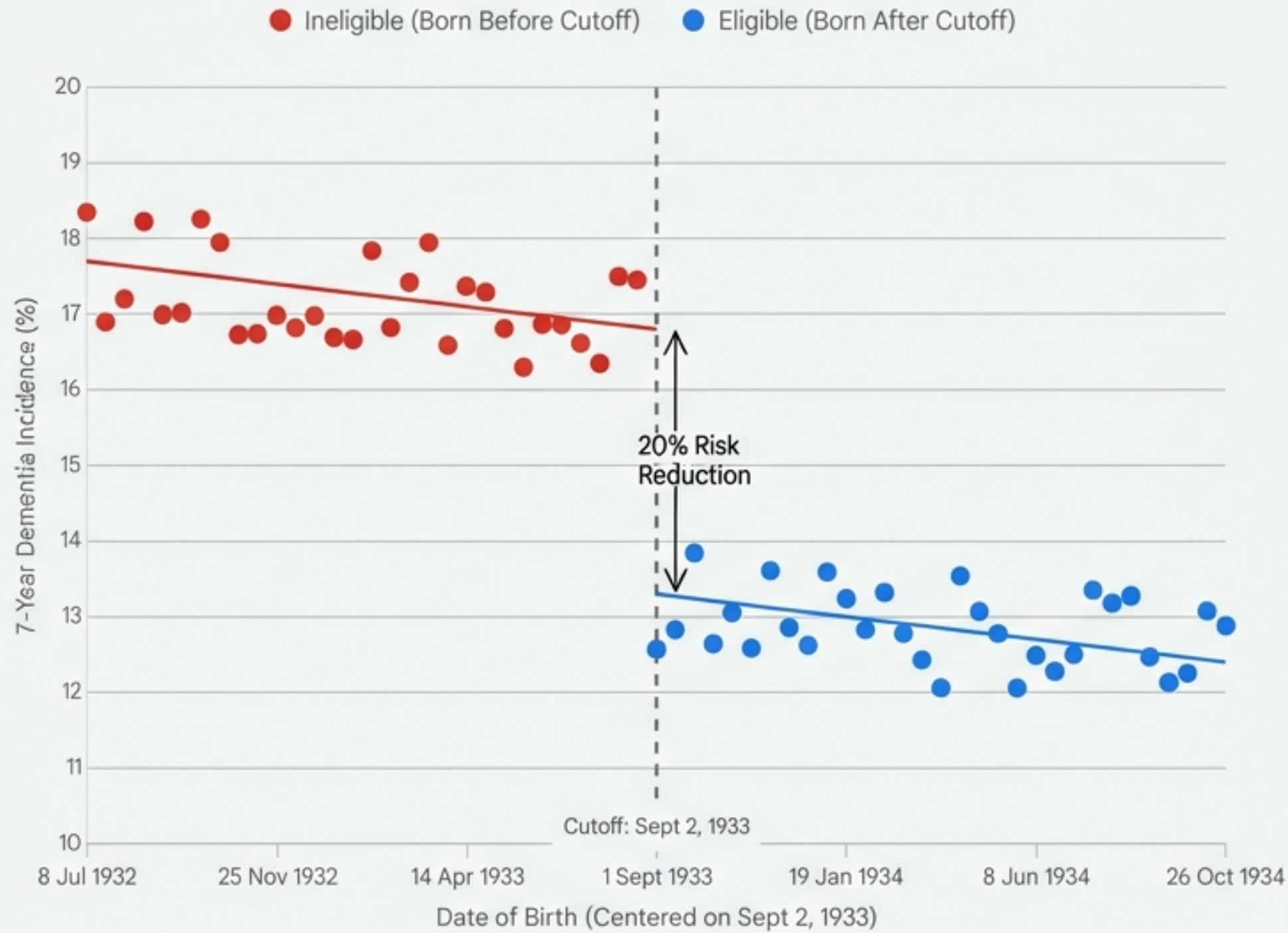
Long-term epigenetic reprogramming of monocytes/macrophages for heightened vigilance (BCG).



2. Heterologous Adaptive Immunity:

Cross-reactivity and elevated surveillance against endogenous threats (VZV).

Causal Evidence: The Wales Protocol



Design: Regression Discontinuity (RDD). Eligibility determined by birth date, eliminating lifestyle confounding.



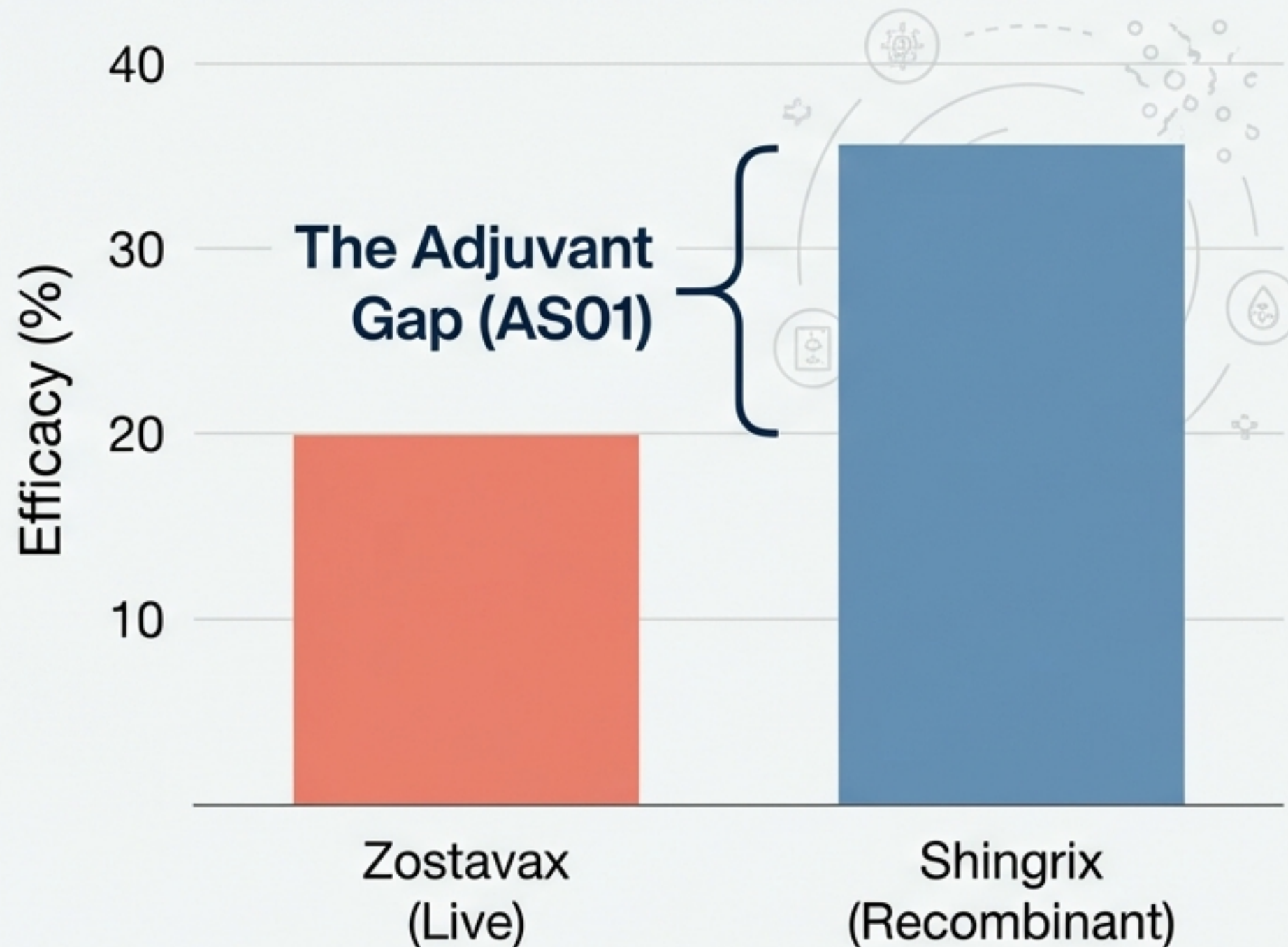
Result: 20% relative reduction in dementia probability.



Significance: Strongest causal evidence to date. Removes “Healthy Vaccinee Bias”.



It's Not Just the Virus. It's the Adjuvant.



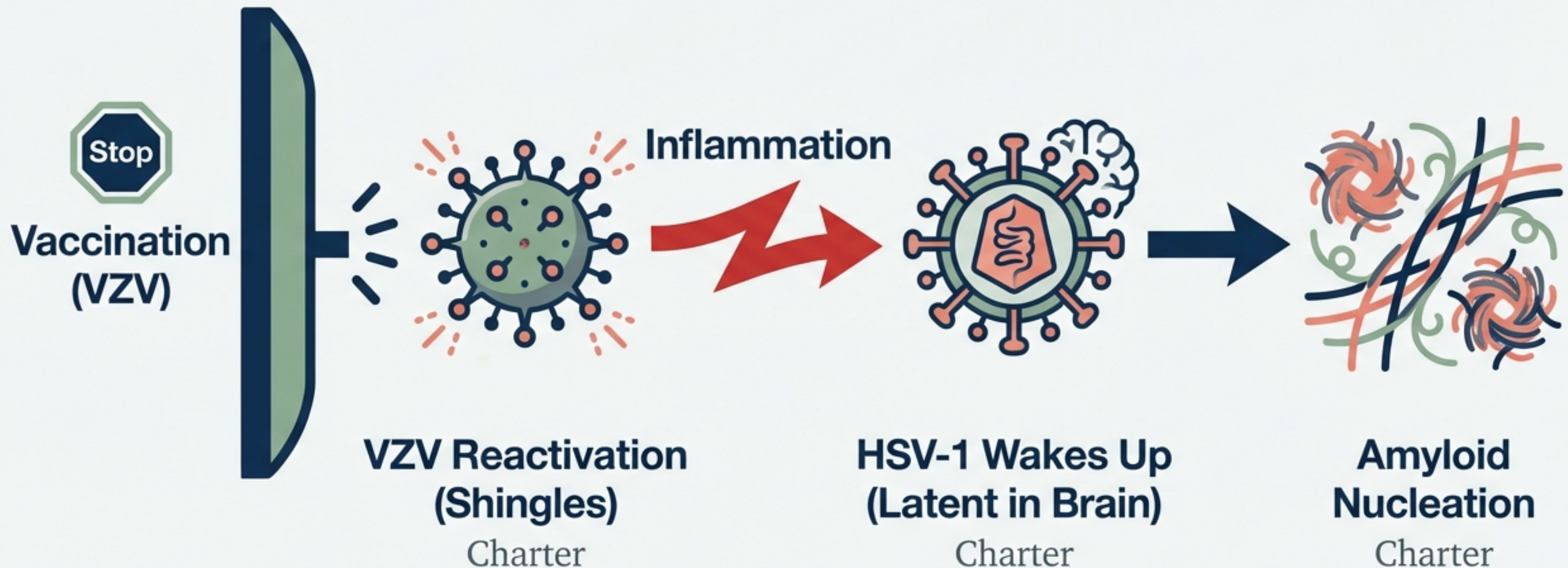
Zostavax: ~20% reduction vs. unvaccinated.

Shingrix: Additional 17-23% reduction over Zostavax.

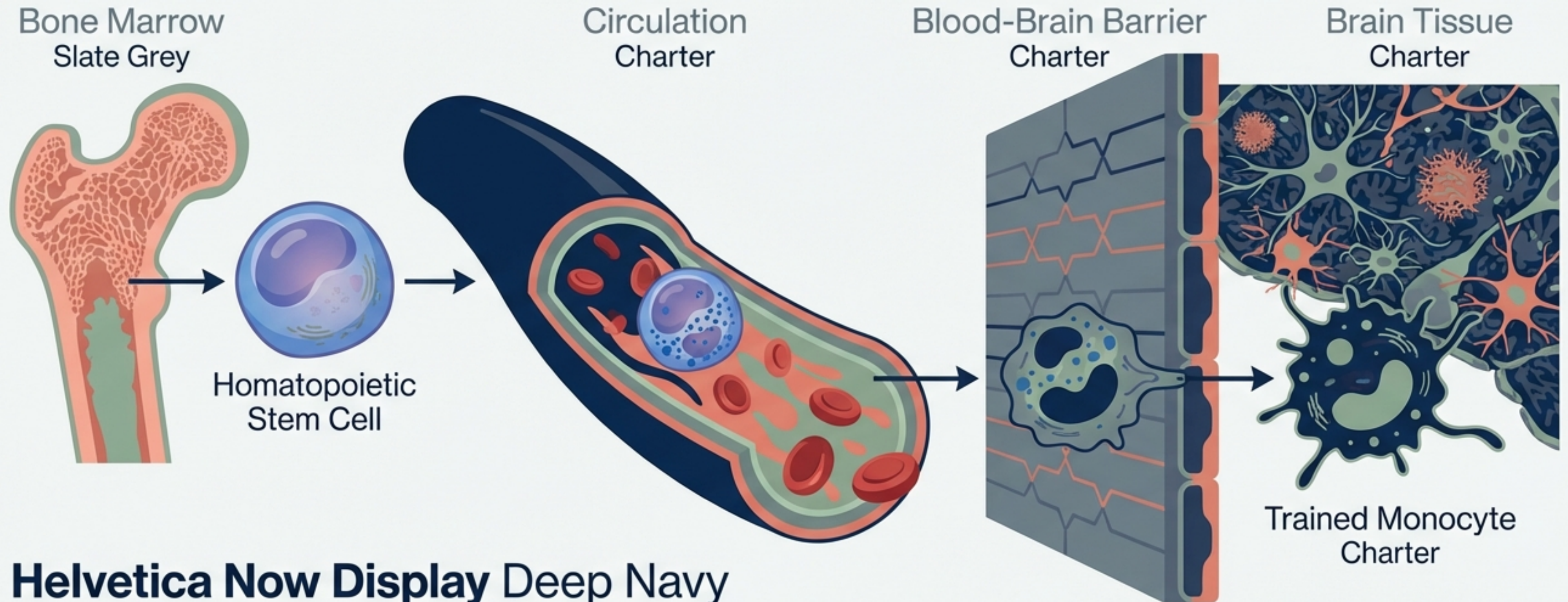
The Driver: AS01 Adjuvant System. Induces potent interferon signature and boosts dendritic cell activity.

The Firewall: Preventing the Spark

VZV reactivation triggers latent HSV-1, which seeds amyloid plaques.
Vaccination keeps the match unlit.



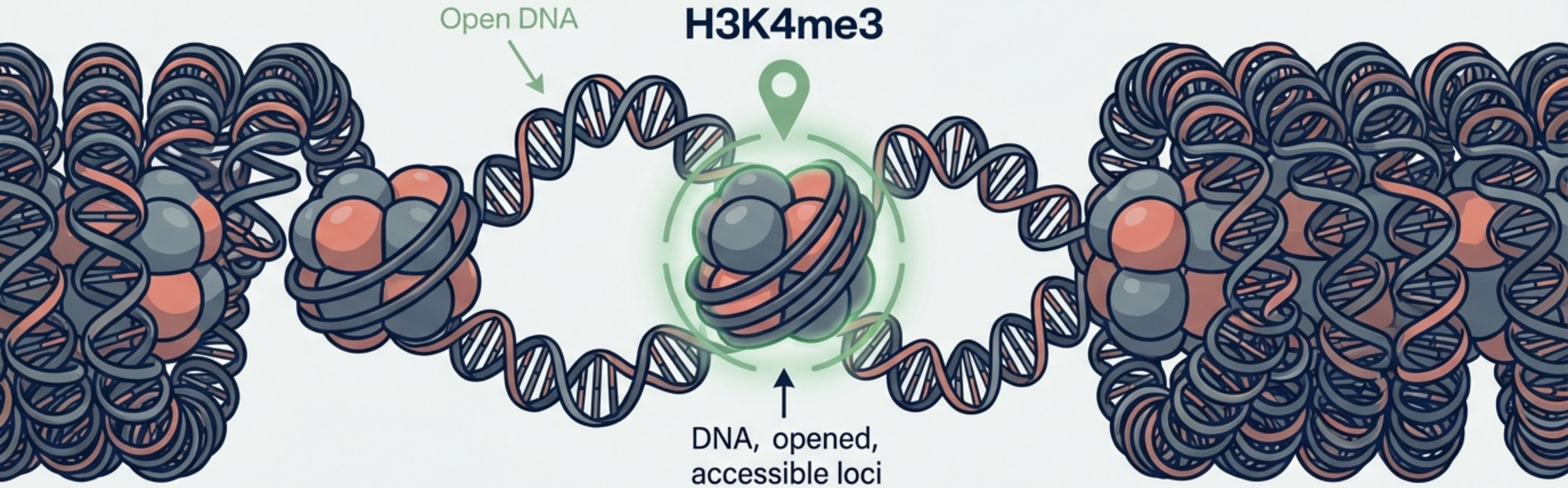
Trained Immunity: The Biological Bootcamp



Helvetica Now Display Deep Navy

- **Origin:** BCG stimulates Hematopoietic Stem Cells via NOD2.
- **Result:** Production of "Trained" monocytes (Ly6C-high).
- **Destination:** Crossing the BBB to rescue failing microglia.

Rewiring the Hardware: Epigenetic Reprogramming

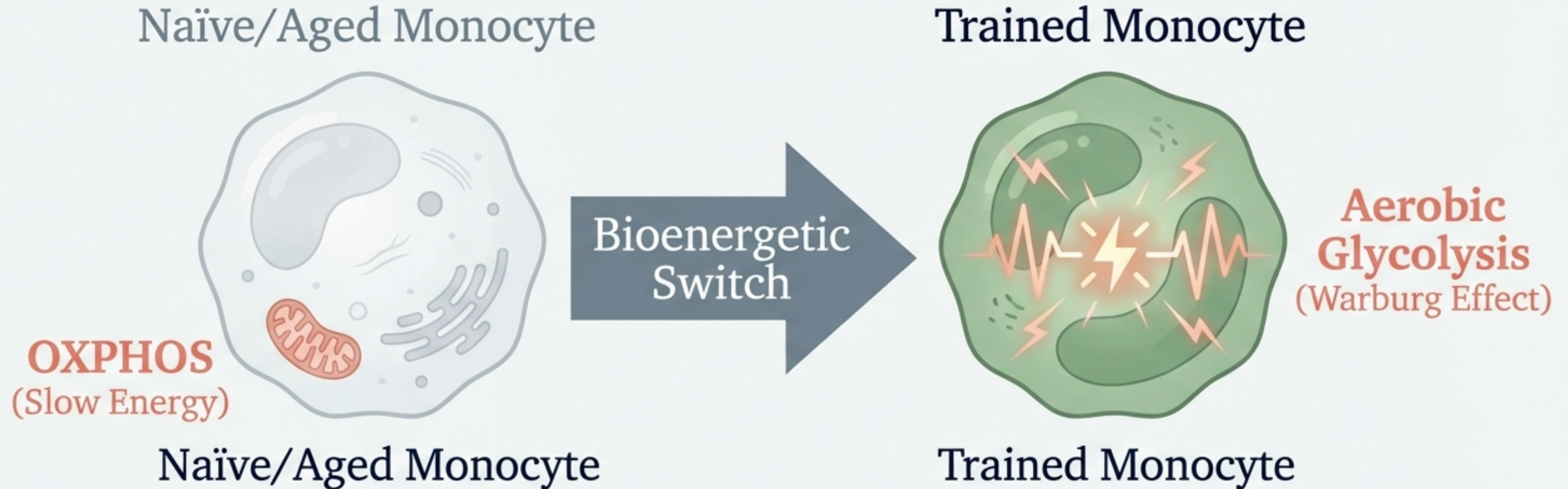


- **The Mechanism:** Trimethylation of histone H3 at lysine 4 (H3K4me3).

- **The Effect:** Chromatin remains 'open' at inflammatory loci.

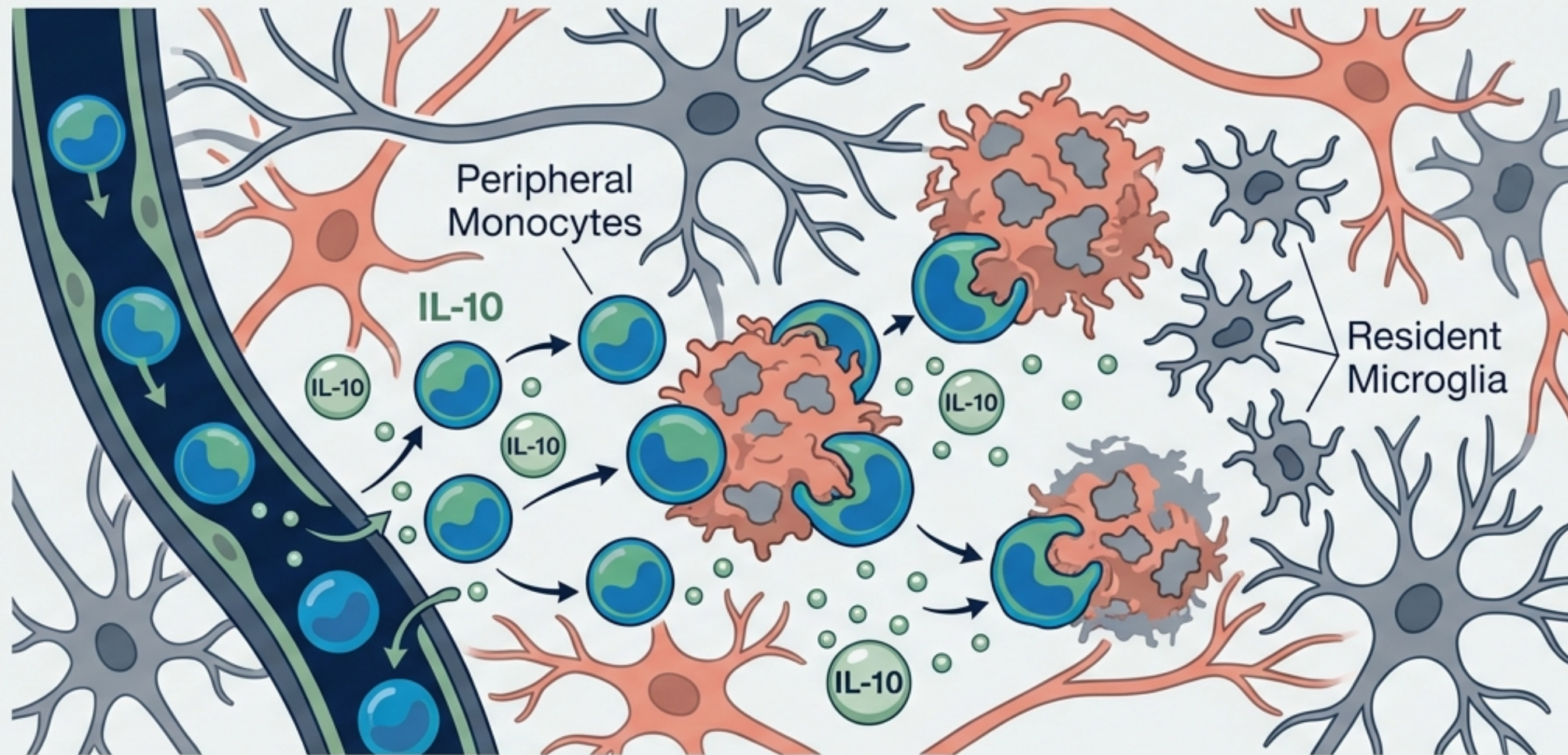
- **The Result:** Cells are 'poised' to react faster and stronger to secondary challenges like Amyloid-beta.

Fueling the Cleanup Crew: The Warburg Effect



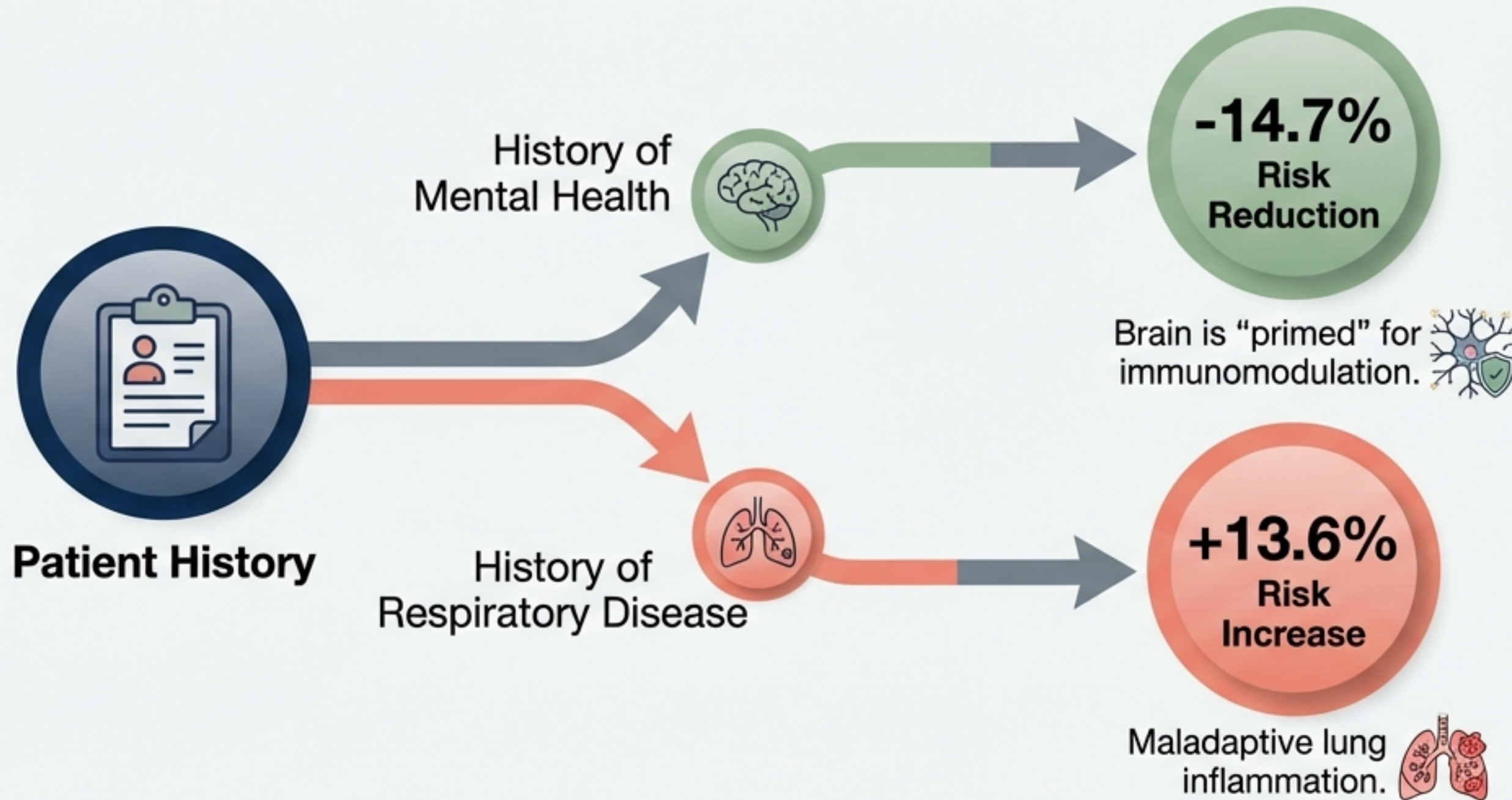
- Reverses bioenergetic failure in aged myeloid cells.
- Provides rapid ATP for phagocytosis (plaque eating).
- Mediated by Akt/mTOR/HIF-1 α pathways.

Peripheral Reinforcements Rescue the Brain



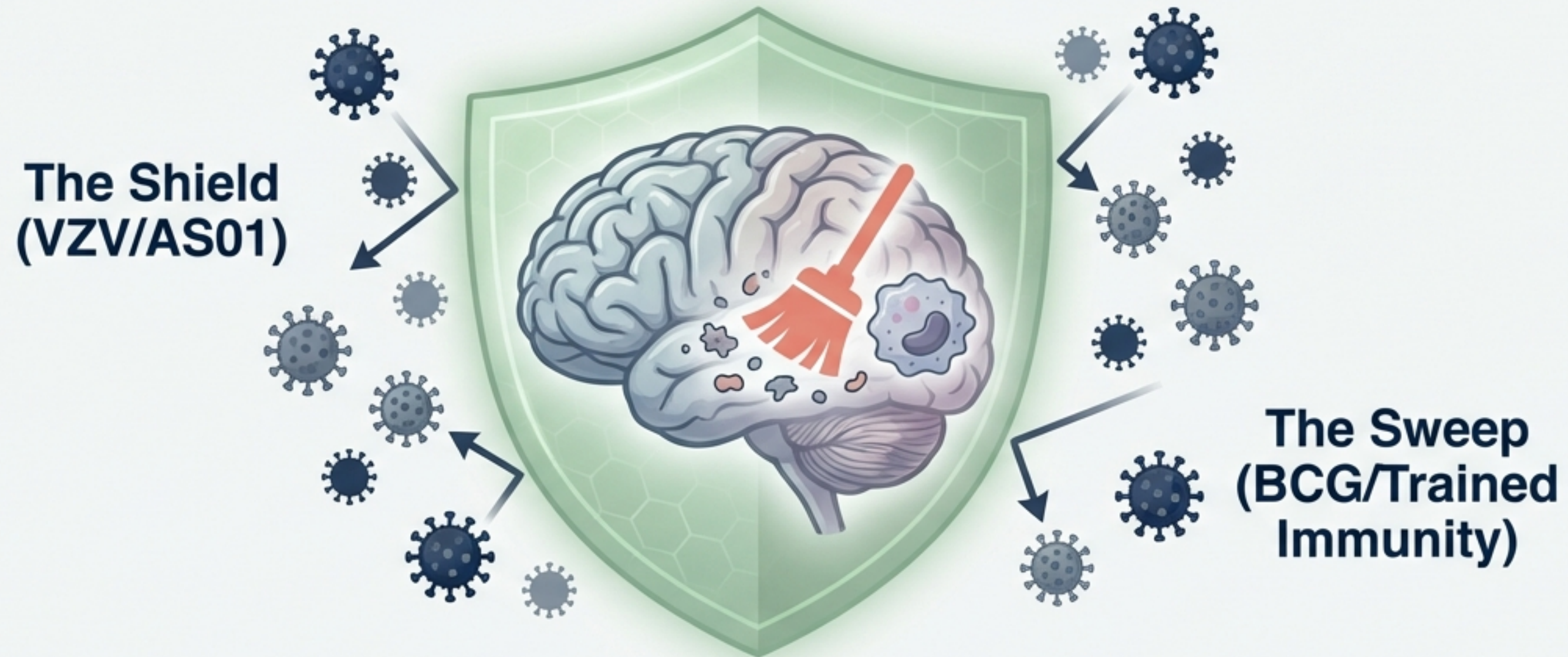
- **Phagocytosis:**
Efficient clearance of $A\beta$ plaques.
- **Anti-Inflammatory:**
Secretion of IL-10 dampens neuroinflammation.
- **Vascular Protection:**
Clears amyloid without damaging vessel walls.

Precision Immunology: One Size Does Not Fit All



BCG effects are heterogeneous. Indiscriminate application is dangerous; targeted application is powerful.

A Unified Model: Shield and Sweep



● **The Shield:** Prevents viral triggers (HSV-1) and maintains surveillance.

● **The Sweep:** Remodels bone marrow to produce cells that clear debris.

● **Strategy:** Combine viral suppression with periodic immunomodulation.

Future Directions: Vaccines Without Antigens



**Immunomodulator
Only (AS01)**

- 🧠 Can we use AS01 alone to maintain brain health without a viral target?
- 🌿 Can we correlate vaccine response with biomarkers like p-tau217?
- 🩸 Can trained monocytes synergize with monoclonal antibodies to reduce dosage?

A Systemic Solution to a Global Crisis

30%

Potential Risk Reduction

- **The Shift:** From organ-specific proteinopathy to systemic immunological failure.
- **The Goal:** Repurposing scalable tools to delay onset.
- **The Promise:** A viable strategy to redefine aging.