Immunological Interventions in Neurodegeneration: A Mechanistic Analysis of BCG and Shingles Vaccines in Reversing Autophagy Failure and Cognitive Decline

1. Introduction: The Immunological Paradigm of Cognitive Decline

The contemporary neuroscientific landscape is currently witnessing a fundamental restructuring of its central tenets regarding the etiology of Alzheimer's disease (AD) and age-related cognitive decline. For decades, the Amyloid Cascade Hypothesis served as the hegemonic framework, positing that the sequential cleavage of the amyloid precursor protein (APP) into neurotoxic amyloid-beta (Aβ) peptides, and their subsequent aggregation into extracellular plaques, was the singular initiating event of neurodegeneration. This model suggested a linear pathology: amyloid accumulation drives tau hyperphosphorylation, which in turn precipitates synaptic loss and neuronal death. However, the consistent and costly failure of amyloid-centric therapeutics—most notably monoclonal antibodies which successfully clear plaques without fundamentally arresting cognitive decline—has precipitated a crisis of confidence in this linear model.[1]

Emerging from this theoretical impasse is a more systemic, integrated paradigm: the Immunological Hypothesis of Neurodegeneration. This framework posits that the central nervous system (CNS) is not an immune-privileged sanctuary isolated from the periphery, but rather an actively regulated tissue dependent on systemic immunological vitality for its homeostatic maintenance. Within this context, the primary driver of neurodegeneration is not merely the production of protein aggregates, but the collapse of the clearance mechanisms responsible for their removal—specifically, the failure of autophagy and phagocytosis in senescent microglia.[4]

This thesis explores a novel and clinically transformative frontier within this paradigm: the observation that specific adult vaccinations—namely the Bacillus Calmette-Guérin (BCG) vaccine against tuberculosis and the recombinant zoster vaccine (RZV, Shingrix) against shingles—confer robust, "off-target" neuroprotective effects. Recent large-scale epidemiological analyses have detected significant reductions in dementia risk, ranging from 20% to nearly 50%, in populations receiving these immunizations.[1] Unlike the elusive mechanism of "healthy user bias" initially proposed to explain these findings, granular

mechanistic data now points to specific biological pathways: the induction of "trained immunity," the epigenetic reprogramming of myeloid cells, and the restoration of autophagic flux via systemic interferon-gamma (IFN-γ) signaling.[8]

Furthermore, this report posits a dual-mechanism model for the efficacy of the shingles vaccine. First, by preventing the reactivation of Varicella Zoster Virus (VZV), the vaccine eliminates a specific neurotropic pathogen known to catalyze amyloid nucleation and inhibit autophagy.[10] Second, the proprietary AS01 adjuvant system used in Shingrix acts as a potent pharmacological restorative of innate immunity, engaging Toll-like Receptor 4 (TLR4) and the NLRP3 inflammasome to reverse microglial senescence.[12]

By synthesizing epidemiological signal detection with deep molecular mechanistics, this document argues that these vaccines function as non-specific immunotherapies. They re-tune the aging immune system, shifting it from a state of chronic, sterile inflammation (inflammaging) to a state of heightened vigilance and metabolic competence, thereby reactivating the brain's intrinsic capacity for repair.

2. The Cellular Crisis: Autophagy Failure and Proteostasis

To understand how a peripheral immunological intervention can rescue a dying neuron, one must first delineate the cellular catastrophe that defines Alzheimer's disease: the failure of the autophagic-lysosomal system. Autophagy is the evolutionarily conserved, lysosome-dependent catabolic process by which cells degrade and recycle cytoplasmic components, including misfolded proteins and damaged organelles. In post-mitotic cells such as neurons, which cannot dilute cellular damage through cell division, the efficiency of autophagy is the primary determinant of longevity.

2.1. The Autophagic Stalemate in Alzheimer's Pathology

In a healthy CNS, macroautophagy (hereafter autophagy) functions as the housekeeper of the proteome. The process begins with the nucleation of a phagophore, driven by the Unc-51-like kinase 1 (ULK1) complex and the Class III PI3K complex (containing Beclin-1 and VPS34). This membrane elongates to engulf cytoplasmic cargo, closing to form a double-membrane autophagosome. Crucially, this vesicle must then traffic along the microtubule network to fuse with an acidic lysosome, forming an autolysosome where hydrolases degrade the cargo.[10]

In Alzheimer's disease, this flux is profoundly disrupted. While the initiation of autophagy often remains intact or is even upregulated as a stress response, the clearance phase—the fusion with the lysosome—is critically stalled. Electron microscopy of AD brains reveals a massive accumulation of immature autophagic vacuoles (AVs) within dystrophic neurites, often described as a "traffic jam" of cellular waste.[9] This stalling is exacerbated by the accumulation of Aβ itself. Intracellular amyloid oligomers have been shown to destabilize lysosomal

membranes, causing the leakage of cathepsins into the cytosol, which triggers NLRP3 inflammasome activation and cell death (pyroptosis) rather than repair.[15]

The failure of autophagy is not merely a consequence of the disease but a primary driver of amyloidogenesis. The amyloid precursor protein (APP) is partially processed within autophagic vesicles. When vesicular maturation fails, these compartments become bioreactors for Aβ production, accumulating high concentrations of APP and secretases (BACE1), which further feed the amyloid cascade.[17]

2.2. Microglial Senescence and the Phagocytic Blockade

The autophagic defect is not limited to neurons; it is perhaps more consequential in microglia, the resident macrophages of the brain. Microglia are tasked with the surveillance of the synaptic landscape and the phagocytosis of extracellular debris, including amyloid plaques. However, in the aging and AD brain, microglia transition into a "senescent" or "dystrophic" phenotype.

This phenotype is characterized by a downregulation of phagocytic receptors (e.g., TREM2), a loss of motility, and a metabolic shift. Healthy, active microglia rely on flexible metabolism to fuel phagocytosis. In AD, these cells often become metabolically rigid, unable to mount the energetic response required to degrade internalized plaque material.[5] Crucially, autophagy is required for the maintenance of the microglial phagocytic machinery. When microglial autophagy is inhibited (e.g., via ATG5 knockdown), these cells lose the capacity to degrade Aβ and instead secrete pro-inflammatory cytokines like IL-1β and TNF-α, which are neurotoxic.[4]

Therefore, the therapeutic goal is not merely to "stimulate" the immune system—which could exacerbate inflammation—but to specifically restore *autophagic flux* and *metabolic competence* in microglia. This restoration allows them to process and degrade the amyloid burden they encounter, rather than becoming overwhelmed by it. As we will explore, this specific restoration is the convergent mechanism of action for both BCG and AS01-adjuvanted vaccines.

2.3. Viral Interference: VZV-Mediated Autophagy Blockade

Recent investigations into the pathophysiology of Varicella Zoster Virus (VZV) have revealed that this neurotropic herpesvirus specifically exploits the autophagic machinery. VZV infection of neural cells has been shown to inhibit autophagosome-lysosome fusion, mirroring the defect seen in AD. The virus expresses immediate-early proteins (such as IE62) and glycoproteins (gB) that manipulate cellular trafficking to prevent the degradation of viral particles.[17]

Visual data from ultrastructural studies confirms that in VZV-infected cells, there is a marked accumulation of autophagic vacuoles that fail to mature into autolysosomes. This viral inhibition creates an environment highly conducive to the aggregation of amyloidogenic

peptides. By blocking the cellular "trash compactor," VZV ensures that any Aβ or amylin produced by the cell accumulates rapidly. This provides a direct mechanistic link between VZV reactivation (shingles) and the acceleration of AD pathology: the virus essentially disables the very machinery the neuron needs to clear misfolded proteins.[10]

3. Varicella Zoster Virus: A Specific Driver of Amyloidogenesis

While the general decline of autophagy is a feature of aging, the epidemiological data linking herpes zoster (shingles) to an increased risk of dementia suggests a specific viral contribution to the disease process. The "Infectious Hypothesis" of Alzheimer's posits that pathogens may act as seeds for protein aggregation or chronic drivers of neuroinflammation. VZV is a particularly compelling candidate due to its unique neurotropism and latency in the dorsal root and cranial nerve ganglia—anatomical sites with direct axonal access to the brainstem and higher cortical centers.[21]

3.1. The Amyloid Seeding Hypothesis

A groundbreaking series of studies has demonstrated that Aβ is not merely a metabolic waste product but acts as an antimicrobial peptide (AMP). Aβ oligomers can entrap viral particles, forming a fibrillar cage that limits viral spread. In the context of Herpes Simplex Virus 1 (HSV-1) and VZV, amyloid plaques may initially form as a protective response to infection.[23] However, in chronic or recurrent infections, this response becomes maladaptive, leading to excessive plaque deposition.

Specifically for VZV, the mechanism is direct and catalytic. Research indicates that VZV infection of primary human spinal astrocytes and brain vascular fibroblasts induces the production of intracellular amylin (Islet Amyloid Polypeptide) and Aβ42. More critically, VZV glycoprotein B (gB) contains sequences that can self-assemble into fibrils. These viral fibrils act as heterologous seeds, catalytically accelerating the aggregation of human amylin and Aβ into toxic oligomers.[11]

This "catalytic seeding" is observed in the cerebrospinal fluid (CSF) of patients with VZV vasculopathy, which shows elevated levels of amylin and amyloid that correlate with anti-VZV antibody titers.[26] The presence of VZV essentially lowers the thermodynamic barrier for amyloid nucleation. Therefore, a reactivation event (shingles) releases a shower of viral particles and glycoproteins that can precipitate widespread amyloidogenesis in a brain already teetering on the edge of proteostatic collapse.

3.2. Viral Synergy: The VZV-HSV Axis

The complexity of the viral contribution to AD is further compounded by interactions between different herpesviruses. It is well-established that HSV-1 is ubiquitous in the human population

and resides latently in the trigeminal ganglia. Recent data suggests that VZV reactivation can trigger the reactivation of quiescent HSV-1 in the brain.

In 3D human brain-like tissue constructs, VZV infection did not always directly lead to Aβ and tau accumulation in every cell type but reliably caused the reactivation of dormant HSV-1. It was the subsequent HSV-1 replication that drove the florid development of AD-like phenotypes, including Aβ plaques and tau hyperphosphorylation.[28] This "hit-and-run" or "trigger" mechanism implies that shingles vaccination may prevent dementia not only by blocking VZV neuropathology but by maintaining the latency of HSV-1, preventing the synergistic viral burden that overwhelms neuronal defenses.

3.3. Prevention vs. Treatment

The implication of this viral mechanism is that the timing of vaccination is critical. Shingrix prevents the *reactivation* of VZV. By stopping the virus from leaving the ganglia and entering the CNS or circulation, the vaccine prevents the "seeding events" described above. This explains the robust protective effect seen in epidemiological studies: by eliminating the trigger (VZV reactivation), the cascade of amyloid seeding and autophagy inhibition is never initiated. This contrasts with amyloid-clearing antibodies, which attempt to clean up the mess after the damage is done.

4. Bacillus Calmette-Guérin (BCG) and Trained Immunity

Moving beyond specific viral pathogens, the BCG vaccine presents a different but equally powerful paradigm: the non-specific boosting of the innate immune system. BCG, an attenuated strain of *Mycobacterium bovis*, is the standard immunotherapy for non-muscle-invasive bladder cancer (NMIBC). It is in this clinical population—patients receiving intravesical BCG—that the most striking data regarding dementia protection has emerged.

4.1. Epidemiological Evidence from Bladder Cancer Cohorts

The association between BCG and reduced AD risk was identified through retrospective cohort studies comparing bladder cancer patients treated with BCG against those treated with surgery or chemotherapy (e.g., mitomycin C). These studies provide a unique natural experiment, controlling for the "healthy user bias" to some extent, as all subjects are cancer patients within a medical system.

The data reveals a consistent and significant protective effect. A seminal study of over 13,000 patients found that BCG exposure was associated with a 20% to nearly 60% reduction in the risk of developing Alzheimer’s disease and related dementias (ADRD).[1] The variation in risk reduction often correlates with the "dose"—patients receiving maintenance therapy (multiple

instillations over years) show greater protection than those receiving only an induction course.

To rigorously present this data, the following table summarizes key epidemiological findings from the provided research materials, highlighting the magnitude of the effect and relevant subgroups.

Study Characteristic	Comparator Group	Risk Reduction (Hazard Ratio / %)	Key Findings & Subgroup Analysis	Source
General Cohort	Non-BCG treated NMIBC patients	**~20% - 58% Reduction** (HR 0.42 - 0.80)	Significant reduction in AD risk across multiple studies. Efficacy correlates with age, showing stronger protection in patients >70 years.	30
Dose-Response	Induction vs. Maintenance Therapy	**~27% (Any) vs. 46% (High Dose)**	Patients receiving ≥12 doses showed a 46% risk reduction, compared to 27% for any exposure, supporting biological causality.	31
Mental Health	Patients with Mental Health Disorders	**14.7% Reduced Risk**	Significant heterogeneity; robust protection in	6

			those with pre-existing mental health conditions, suggesting immune modulation of neuro-psychiatric pathways.	
Average Treatment Effect (ML)	Propensity-matched controls	**6.9% Average Reduction**	When utilizing rigorous machine learning to control for all confounders, a conservative but statistically significant causal effect remains.	[6]
Age Stratification	Patients aged ≤ 65 vs. > 65	**Variable Aβ42/40 Ratio**	Younger patients showed a significant increase in plasma Aβ42/40 ratio post-vaccination, indicating improved clearance/turnover.	[32]

4.2. Mechanisms of Trained Immunity

The mechanism underlying BCG's broad protection is "trained immunity." Unlike adaptive immunity, which relies on antigen-specific T and B cell memory, trained immunity involves the functional reprogramming of innate immune cells (monocytes, macrophages, NK cells) to respond more vigorously to subsequent, unrelated stimuli.

Epigenetic Reprogramming: Upon administration, BCG components (such as peptidoglycans) bind to NOD2 receptors on hematopoietic stem cells (HSCs) in the bone marrow and circulating monocytes. This signaling cascade triggers epigenetic remodeling. Specifically, it induces the enrichment of activating histone marks, such as the trimethylation of histone H3 at lysine 4 (**H3K4me3**), at the promoters of pro-inflammatory genes (e.g., *TNF*, *IL6*, *IL1B*) and metabolic genes.[8] This keeps the chromatin in an "open" state, allowing for rapid gene transcription upon future challenge.

Metabolic Shift (The Warburg Effect): Concurrently, BCG induces a metabolic switch in these cells from oxidative phosphorylation to aerobic glycolysis, mediated by the Akt/mTOR pathway.[8] This shift mimics the Warburg effect seen in tumors but serves a functional purpose in immunity: glycolysis provides the rapid energy and biosynthetic intermediates required for phagocytosis and cytokine production. In the context of the aging brain, where microglia often suffer from metabolic insufficiency and bioenergetic failure, the recruitment of these metabolically "supercharged" monocytes offers a significant functional upgrade.[35]

4.3. The Neuro-Immune Axis: Trafficking to the CNS

How does a bladder or skin vaccination affect the brain? The link is systemic cytokine signaling and cellular trafficking. BCG vaccination induces a systemic Th1 immune response, characterized by elevated levels of Interferon-gamma (IFN-γ).

Research in APP/PS1 mouse models has demonstrated that BCG vaccination leads to the recruitment of resolving monocytes to the brain's borders—specifically the choroid plexus and the meninges.[35] These sites act as the "immune gateway" to the CNS. The systemic IFN-γ signal increases the expression of trafficking molecules (ICAM-1, VCAM-1) at the choroid plexus, facilitating the entry of immune cells.

Once at the meninges, these BCG-trained cells do not necessarily need to infiltrate the parenchyma to have an effect. They secrete anti-inflammatory cytokines (IL-10) and, crucially, neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) and Insulin-Like Growth Factor-1 (IGF-1).[37] These factors diffuse across the brain barriers, acting on resident microglia to shift them from a pro-inflammatory (M1) to a neuroprotective/phagocytic (M2) phenotype. This "remote control" of the CNS microenvironment by peripheral immunity restores hippocampal neurogenesis and improves cognitive function, as evidenced by improved spatial learning in vaccinated mice.[37]

5. The Shingles Vaccine and the AS01 Adjuvant System

While BCG provides a general boost, the Recombinant Zoster Vaccine (Shingrix) represents a highly engineered immunological intervention. Its superior efficacy over the live-attenuated Zostavax in preventing dementia points to the critical role of its unique adjuvant system: **AS01**.

5.1. Shingrix vs. Zostavax: The Adjuvant Advantage

Epidemiological studies comparing Shingrix (recombinant glycoprotein E + AS01 adjuvant) to Zostavax (live attenuated virus) have revealed a startling trend: Shingrix is associated with a significantly greater reduction in dementia risk. While Zostavax offers some protection (likely via VZV prevention), Shingrix has been linked to a 20-30% reduction in dementia diagnosis compared to Zostavax and other vaccines like Tdap or Influenza.[7]

Recent "natural experiments," such as the vaccine rollout in Wales, have utilized regression discontinuity designs to isolate the effect of the vaccine from confounding factors. These studies confirm that eligibility for the shingles vaccine is causally linked to a nearly 20% reduction in dementia incidence over a 7-year follow-up.[42] The fact that Shingrix (with AS01) outperforms the live vaccine suggests that the adjuvant itself contributes an independent neuroprotective effect.

5.2. AS01 Chemistry: MPL and QS-21 Synergy

The AS01 adjuvant system is a liposomal formulation containing two key immunostimulants:

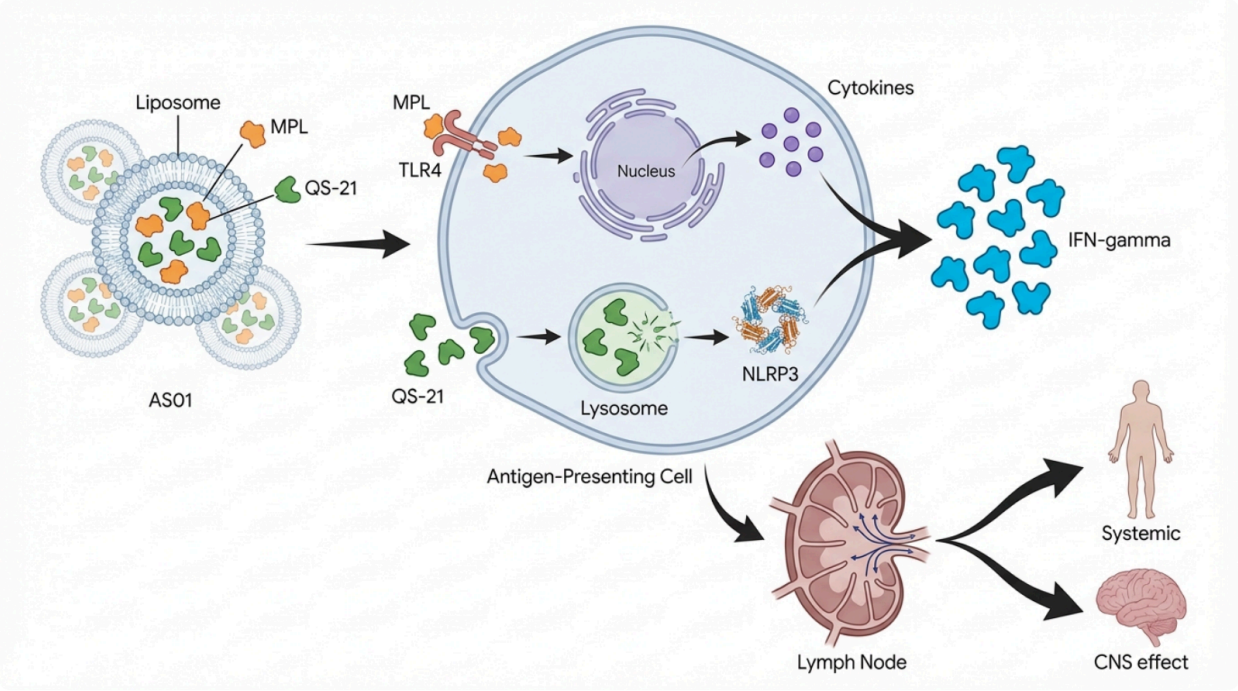
1. **3-O-desacyl-4'-monophosphoryl lipid A (MPL):** A non-toxic derivative of lipopolysaccharide (LPS) from *Salmonella minnesota*. MPL is a specific agonist of **Toll-like Receptor 4 (TLR4)**.
2. **QS-21:** A triterpene glycoside saponin purified from the bark of the *Quillaja saponaria* tree.[43]

These two components act synergistically. MPL stimulates TLR4 on antigen-presenting cells (APCs), activating the NF-κB pathway and inducing cytokine production. However, unlike toxic LPS, MPL biases the signaling towards a less inflammatory, more phagocytic profile. Independently, MPL has been shown to reduce Alzheimer's pathology in mice by stimulating microglial phagocytosis of Aβ.[2]

QS-21 adds a unique dimension. Saponins like QS-21 possess amphipathic properties that allow them to interact with cell membranes. Mechanisms suggest that QS-21 can destabilize endosomal/lysosomal membranes within APCs, triggering the **NLRP3 inflammasome**.[45] This activation promotes the release of IL-1β and IL-18, and enhances antigen cross-presentation.

The combination of MPL and QS-21 in the AS01 liposome results in a rapid and potent induction of **Interferon-gamma (IFN-γ)** from draining lymph nodes.[13] This synergistic surge of IFN-γ is far greater than that induced by either component alone. As established in the BCG section, systemic IFN-γ is a master regulator of CNS immune surveillance. By inducing this potent Th1-biased cytokine profile, AS01 effectively "wakes up" the CNS innate immune system, enhancing the clearance of amyloid and tau aggregates.

Molecular Mechanism of the AS01 Adjuvant System: From Injection to Neuroprotection



Synergistic activation of the immune response by AS01. The adjuvant combines MPL (a TLR4 agonist) and QS-21 (a saponin) within a liposomal formulation. MPL stimulates NF-kB pathways in antigen-presenting cells (APCs), while QS-21 activates the NLRP3 inflammasome and promotes antigen cross-presentation. This synergy results in a potent, rapid production of IFN-gamma and the generation of high-quality, long-lived cellular immunity that may confer cross-protection to the CNS.

5.3. Safety and Toxicity Profiles

One critical consideration with potent adjuvants is toxicity. QS-21 alone can be hemolytic and cytotoxic. However, the AS01 formulation mitigates this by quenching the saponin in cholesterol-containing liposomes.[45] This maintains the immunostimulatory properties while preventing widespread membrane lysis. Clinical data from millions of Shingrix doses confirms an acceptable safety profile, with transient local reactions (pain, swelling) being common but serious neuroinflammatory events (like the meningoencephalitis seen with the AN-1792 vaccine) being rare.[49] This safety profile is paramount if AS01 is to be repurposed as a standalone neuroprotective agent.

6. Systemic-Central Crosstalk: Restoring Autophagic Flux

The convergence of BCG (trained immunity) and Shingrix (AS01 adjuvant) on the production of systemic IFN-γ leads us to the central mechanistic node of this thesis: **The Systemic Restoration of Microglial Autophagy.**

6.1. The Interferon-Gamma Bridge

How does a systemic cytokine clear a brain plaque? The answer lies in the specific receptors expressed by microglia. Microglia constitutively express IFN-γ receptors (IFNGR). In the AD brain, microglia are often locked in a state of "tolerance" or "exhaustion"—they surround plaques but do not degrade them.

Systemic administration of IFN-γ, or its induction via vaccination, provides the necessary signal to break this tolerance. IFN-γ binding activates the JAK/STAT1 signaling pathway in microglia. This cascade has two critical outcomes:

1. **Upregulation of MHC-II:** Promoting antigen presentation and interaction with T cells.
2. **Induction of Autophagy Genes:** Crucially, IFN-γ upregulates the transcription of core autophagy genes, including *Atg5*, *Atg7*, and *Beclin-1*.[9]

Simultaneously, IFN-γ suppresses the Akt/mTOR pathway. Since mTOR is the master *inhibitor* of autophagy, its suppression releases the "brake" on the system. This allows the stalled autophagic vacuoles within microglia to finally mature and fuse with lysosomes. Studies utilizing intravital two-photon microscopy have shown that following systemic IFN-γ treatment, microglia rapidly extend processes toward amyloid deposits and engage in active phagocytosis and degradation.[4]

6.2. Monocyte Engraftment vs. Signaling

A debate persists in the field regarding whether peripheral monocytes physically enter the brain to replace microglia or merely signal to them.

- **The Engraftment Model:** Some evidence suggests that in the context of neuroinflammation or blood-brain barrier (BBB) breakdown, "trained" peripheral monocytes (CCR2+) can cross the BBB and differentiate into macrophage-like cells that actively clear amyloid. These cells are often more phagocytically efficient than the senescent resident microglia.[52]
- **The Signaling Model:** Other studies argue that frank infiltration is limited in AD. Instead, peripheral cells populate the perivascular spaces and the meninges (Border-Associated Macrophages, BAMs). From these vantage points, they regulate the clearance of amyloid via the glymphatic system and secrete soluble factors (cytokines, trophic factors) that diffuse into the parenchyma to rejuvenate resident microglia.[54]

Regardless of the precise spatial dynamics, the functional outcome is the same: the presence of a "trained" peripheral immune system relieves the burden on the CNS, facilitating the

clearance of proteopathic waste.

6.3. Addressing the Healthy User Bias

Skeptics of the vaccination-dementia link often cite the "Healthy User Bias"—the notion that people who seek vaccinations are generally healthier, wealthier, and more active, and thus less likely to develop dementia regardless of the shot. While this bias undoubtedly exists, several lines of evidence suggest it cannot explain the full magnitude of the effect:

1. **Active Comparators:** The Shingles vaccine shows superior protection compared to the Flu or Tdap vaccines in the *same* populations. If it were purely behavioral, all elective vaccines should show similar benefit.[40]
2. **Specific Biological Plausibility:** The connection to VZV prevention and the specific adjuvants (AS01 vs. Alum) provides a mechanistic basis that aligns with animal models.
3. **Dose-Response:** The observation that more doses of BCG confer greater protection (HR 0.54 for maintenance vs 0.73 for induction) strongly supports a biological pharmacological effect.[31]

7. Conclusion and Future Directions

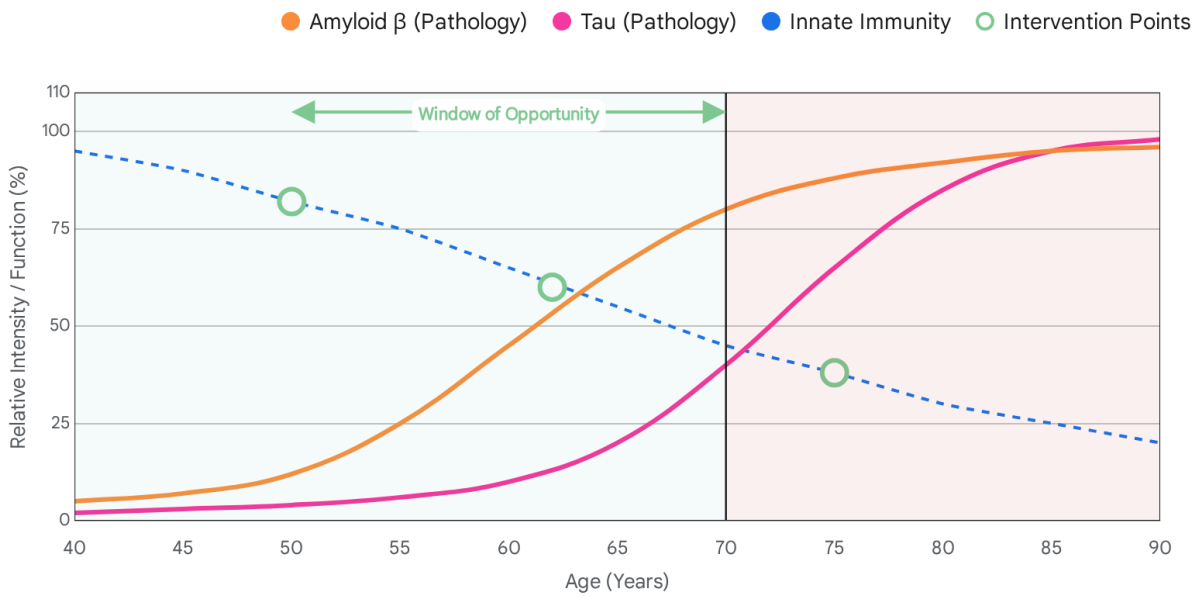
The data presented in this thesis supports a paradigm shift in the prevention of Alzheimer's disease. The prevailing strategy of targeting amyloid directly with antibodies has yielded marginal clinical benefits. In contrast, the "off-target" effects of existing vaccines—specifically BCG and Shingrix—appear to address the upstream cellular failure: the collapse of autophagic flux and immune surveillance.

The mechanism is elegant in its duality. First, the Shingrix vaccine prevents the reactivation of VZV, removing a specific viral catalyst of amyloid seeding and autophagy inhibition. Second, both BCG and the AS01 adjuvant system act as potent "immune trainers." They reprogram the innate immune system via epigenetic and metabolic modifications, generating a systemic IFN-γ signal that crosses the brain barriers. This signal reactivates the dormant autophagic machinery in microglia, allowing for the clearance of protein aggregates and the restoration of cognitive function.

7.1. Clinical and Therapeutic Implications

The "Window of Opportunity" for these interventions is critical. As illustrated in the timeline below, vaccination is most effective when administered during the "prodromal" phase of immunosenescence—typically ages 50 to 70—before the amyloid burden becomes irreversible and the immune system becomes completely anergic.

Temporal Window of Immunological Intervention in Alzheimer's Progression



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.

Data sources: PubMed, IDSociety, Frontiers in Aging Neuroscience, ClinicalTrials.gov

Current clinical trials, such as the PRIME study [58], are now testing BCG specifically for Alzheimer's. If successful, these trials could validate the repurposing of century-old vaccines as primary neuroprotective agents. Furthermore, the isolation of the AS01 adjuvant suggests a path toward "adjuvant-only" immunotherapies—drugs that boost microglial competence without the need for viral antigens.

In conclusion, the cure for Alzheimer's may not lie in a new, high-tech molecule, but in the revitalization of the body's oldest defense system. By understanding and harnessing the mechanisms of trained immunity and autophagic restoration, we may finally be able to turn the tide against the epidemic of dementia.

Works cited

1. Bacillus Calmette-Guerin (BCG) Vaccine Impact on Dementia Risk in Bladder Cancer Patients: A Systematic Review and Meta-Analysis - PubMed, accessed

December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/39350381/
2. Toll-like receptor 4 stimulation with the detoxified ligand monophosphoryl lipid A improves Alzheimer's disease-related pathology | PNAS, accessed December 15, 2025, https://www.pnas.org/doi/10.1073/pnas.1215165110
3. Two Phase 2 Multiple Ascending-Dose Studies of Vanutide Cridificar (ACC-001) and QS-21 Adjuvant in Mild-to-Moderate Alzheimer's Disease - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/26967206/
4. Intraperitoneal injection of IFN-γ restores microglial autophagy, promotes amyloid-β clearance and improves cognition in APP/PS1 mice - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/32514180/
5. Peripheral monocyte–derived cells counter amyloid plaque pathogenesis in a mouse model of Alzheimer's disease - JCI, accessed December 15, 2025, https://www.jci.org/articles/view/152565
6. Heterogeneous treatment effects of BCG vaccine on Alzheimer's disease risk - PMC, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11864241/
7. Shingles Vaccine Lowers Risk of Dementia, Major Cardiovascular Events - IDSA, accessed December 15, 2025, https://www.idsociety.org/news--publications-new/articles/2025/shingles-vaccine-lowers-risk-of-dementia-major-cardiovascular-events/
8. BCG-induced trained immunity: history, mechanisms and potential applications, accessed December 15, 2025, https://www.springermedizin.de/bcg-induced-trained-immunity-history-mechanisms-and-potential-ap/24015732
9. (PDF) Intraperitoneal injection of IFN-γ restores microglial autophagy, promotes amyloid-β clearance and improves cognition in APP/PS1 mice - ResearchGate, accessed December 15, 2025, https://www.researchgate.net/publication/342020089_Intraperitoneal_injection_of_IFN-g_restores_microglial_autophagy_promotes_amyloid-b_clearance_and_improves_cognition_in_APPPS1_mice/download
10. Varicella zoster virus-induced autophagy in human neuronal and hematopoietic cells exerts antiviral activity - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/38804180/
11. Varicella-Zoster Virus Infection of Primary Human Spinal Astrocytes Produces Intracellular Amylin, Amyloid-β, and an Amyloidogenic Extracellular Environment - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/31665341/
12. Adjuvant system AS01: from mode of action to effective vaccines - MalariaWorld, accessed December 15, 2025, https://www.malariaworld.org/scientific-articles/adjuvant-system-as-01-from-mode-of-action-to-effective-vaccines
13. Lower risk of dementia with AS01-adjuvanted vaccination against shingles and respiratory syncytial virus infections - NIH, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC12198376/
14. Autophagy Controls BCG-Induced Trained Immunity and the Response to

Intravesical BCG Therapy for Bladder Cancer | PLOS Pathogens - Research journals, accessed December 15, 2025, https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004485
15. Interactions of Autophagy and the Immune System in Health and Diseases - PMC, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10327624/
16. Molecular Regulation Mechanism of Microglial Autophagy in the Pathology of Alzheimer's Disease - Semantic Scholar, accessed December 15, 2025, https://pdfs.semanticscholar.org/4052/0246c159f4948dc26fd4c422179a699c4f13.pdf
17. Autophagosome formation during varicella-zoster virus infection following endoplasmic reticulum stress and the unfolded protein response - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/21752906/
18. Neuroimmune Crosstalk Between the Peripheral and the Central Immune System in Amyotrophic Lateral Sclerosis - Frontiers, accessed December 15, 2025, https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2022.890958/full
19. Varicella-Zoster Virus Infection Induces Autophagy in both Cultured Cells and Human Skin Vesicles - ASM Journals, accessed December 15, 2025, https://journals.asm.org/doi/10.1128/jvi.02670-08
20. Autophagosome Formation during Varicella-Zoster Virus Infection following Endoplasmic Reticulum Stress and the Unfolded Protein Response - PubMed Central, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC3165774/
21. The Role of Autophagy in Varicella Zoster Virus Infection - MDPI, accessed December 15, 2025, https://www.mdpi.com/1999-4915/13/6/1053
22. The elusive role of herpesviruses in Alzheimer's disease: current evidence and future directions - PubMed Central, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10474380/
23. Amyloid-β and p-Tau Anti-Threat Response to Herpes Simplex Virus 1 Infection in Primary Adult Murine Hippocampal Neurons | Journal of Virology, accessed December 15, 2025, https://journals.asm.org/doi/10.1128/jvi.01874-19
24. Alzheimer's Disease-Associated β-Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/30001512/
25. Mechanisms by which varicella zoster virus contributes to Alzheimer's disease pathologies, accessed December 15, 2025, https://alz.confex.com/alz/2024/meetingapp.cgi/Paper/90837
26. Amyloid Potentially Involved in VZV Vasculopathy - Pharmacy Times, accessed December 15, 2025, https://www.pharmacytimes.com/view/amyloid-potentially-involved-in-vzv-vasculopathy
27. Amylin, Aβ42, and Amyloid in Varicella Zoster Virus Vasculopathy Cerebrospinal Fluid and Infected Vascular Cells - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/32809013/

28. VZV infection reactivates quiescent HSV-1 to induce amyloid-β and P-Tau... - ResearchGate, accessed December 15, 2025, https://www.researchgate.net/figure/VZV-infection-reactivates-quiescent-HSV-1-to-induce-amyloid-b-and-P-Tau-accumulation-in_fig6_361467667
29. HSV-1 infection induces brain cofilin hyperphosphorylation in the 5xFAD Alzheimer's Disease mouse model - bioRxiv, accessed December 15, 2025, https://www.biorxiv.org/content/10.1101/2025.08.10.669568.full.pdf
30. BCG Vaccines May Provide Protective Effect Against Alzheimers Disease - The ASCO Post, accessed December 15, 2025, https://ascopost.com/news/may-2023/bcg-vaccines-may-provide-protective-effect-against-alzheimers-disease/
31. Bacillus Calmette–Guérin in Immuno-Regulation of Alzheimer's Disease - Frontiers, accessed December 15, 2025, https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2022.861956/full
32. Evaluation of BCG Vaccination and Plasma Amyloid: A Prospective, Pilot Study with Implications for Alzheimer's Disease - PMC - NIH, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC8880735/
33. Microglial immune regulation by epigenetic reprogramming through histone H3K27 acetylation in neuroinflammation - Frontiers, accessed December 15, 2025, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1052925/full
34. BCG-induced trained immunity: history, mechanisms and potential applications - PMC, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9913021/
35. Immunization with Bacillus Calmette-Guérin (BCG) alleviates neuroinflammation and cognitive deficits in APP/PS1 mice via the recruitment of inflammation-resolving monocytes to the brain | Request PDF - ResearchGate, accessed December 15, 2025, https://www.researchgate.net/publication/313536165_Immunization_with_Bacillus_Calmette-Guerin_BCG_alleviates_neuroinflammation_and_cognitive_deficits_in_APPPS1_mice_via_the_recruitment_of_inflammation-resolving_monocytes_to_the_brain
36. Immunization with Bacillus Calmette-Guérin (BCG) alleviates neuroinflammation and cognitive deficits in APP/PS1 mice via the recruitment of inflammation-resolving monocytes to the brain - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/28189498/
37. Combined effect of BCG vaccination and enriched environment ..., accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5301319/
38. Neonatal BCG Vaccination of Mice Improves Neurogenesis and Behavior in Early Life, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/26536170/
39. Combined effect of BCG vaccination and enriched environment promote neurogenesis and spatial cognition via a shift in meningeal macrophage M2 polarization - R Discovery, accessed December 15, 2025,

https://discovery.researcher.life/article/combined-effect-of-bcg-vaccination-and-enriched-environment-promote-neurogenesis-and-spatial-cognition-via-a-shift-in-meningeal-macrophage-m2-polarization/e03be4e11b5f3d05b1fb569c42bc378e
40. Shingles vaccine tied to significant reductions in risk of dementia, heart disease, and death, accessed December 15, 2025, https://www.cidrap.umn.edu/adult-non-flu-vaccines/shingles-vaccine-tied-significant-reductions-risk-dementia-heart-disease-and
41. A routine shingles shot may offer powerful defense against dementia - ScienceDaily, accessed December 15, 2025, https://www.sciencedaily.com/releases/2025/12/251203004721.htm
42. For those living with dementia, new study suggests shingles vaccine could slow the disease, accessed December 15, 2025, https://med.stanford.edu/news/all-news/2025/03/shingles-vaccination-dementia.html
43. GSK presents new data at the Alzheimer's Association International Conference 2024, accessed December 15, 2025, https://www.gsk.com/en-gb/media/press-releases/gsk-presents-new-data-at-the-alzheimers-association-international-conference-2024/
44. QS-21: A Potent Vaccine Adjuvant - PMC - NIH, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC4874334/
45. Updated insights into the mechanism of action and clinical profile of the immunoadjuvant QS-21: A review, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC7127804/
46. An Overview of Vaccine Adjuvants: Current Evidence and Future Perspectives - MDPI, accessed December 15, 2025, https://www.mdpi.com/2076-393X/10/5/819
47. Innate immune cell activation by adjuvant AS01 in human lymph node explants is age independent - PubMed Central, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11563676/
48. QS-21 INFINITYTM - SPI Pharma, accessed December 15, 2025, https://www.spipharma.com/media/4221/qs-21-infinity_0303-human-vaccine.pdf
49. Safety of RTS,S with AS01 and AS02 Adjuvant Systems | CPAA - Dove Medical Press, accessed December 15, 2025, https://www.dovepress.com/systematic-review-of-safety-of-rtss-with-as01-and-as02-adjuvant-system-peer-reviewed-fulltext-article-CPAA
50. Safety assessment of adjuvanted vaccines: Methodological considerations - PMC - NIH, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC4514270/
51. Intraperitoneal injection of IFN-γ restores microglial autophagy, promotes amyloid-β clearance and improves cognition in APP/PS1 mice - PubMed Central, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC7280212/
52. Epigenetic Adaptation Drives Monocyte Differentiation into Microglia-Like Cells Upon Engraftment into the Central Nervous System - eLife, accessed December 15, 2025, https://elifesciences.org/reviewed-preprints/108641
53. Monocytes can efficiently replace all brain macrophages and fetal liver

monocytes can generate bona fide SALL1+ microglia - PubMed Central, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC12094688/
54. Border-associated macrophages in the central nervous system - PMC, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10938757/
55. Border-associated macrophages in the central nervous system - PubMed, accessed December 15, 2025, https://pubmed.ncbi.nlm.nih.gov/38316202/
56. Plaque-associated myeloid cells derive from resident microglia in an Alzheimer's disease model | Journal of Experimental Medicine | Rockefeller University Press, accessed December 15, 2025, https://rupress.org/jem/article/217/4/e20191374/133630/Plaque-associated-myeloid-cells-derive-from
57. The association of herpes zoster and influenza vaccinations with the risk of developing dementia: a population-based cohort study within the UK Clinical Practice Research Datalink - PMC - NIH, accessed December 15, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10546661/
58. Study Details | NCT06078891 | Does BCG Vaccination Reduce Biomarkers of Alzheimer's Disease? | ClinicalTrials.gov, accessed December 15, 2025, https://www.clinicaltrials.gov/study/NCT06078891?term=AREA%5BConditionSearch%5D(%22Late%20Onset%20Disorders%22)&rank=2