Editorial

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# Complement Inhibition Expands the Therapeutic Window of Amyloid-$\beta$ Immunotherapy in Alzheimer's Disease

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Recent advances in Alzheimer's disease immunotherapy highlight the critical importance of both active and passive immunization strategies in promoting the clearance of toxic amyloid-$\beta$ (A$\beta$) aggregates. These immunization approaches induce the production of A$\beta$-specific immunoglobulin G (IgG) antibodies, which bind to A$\beta$ and form immune complexes. These complexes are recognized by activating Fc gamma receptors (Fc$\gamma$Rs) on microglia, facilitating A$\beta$ uptake and removal. However, this beneficial clearance mechanism also triggers the complement cascade, as evidenced by upregulation of complement-related pathways.

Upon Fc$\gamma$R engagement, complement activation results in the generation of potent pro-inflammatory molecules, particularly the anaphylatoxin complement 5a (C5a). The C5a binds to its respective receptor, C5aR1, which is co-expressed with Fc$\gamma$Rs on microglia and potentially other neural cells. This interaction can lead to heightened microglial cell activation and exacerbate neuroinflammation, contributing to neuronal injury and degeneration in Alzheimer's disease.

While active and passive immunotherapies are essential for clearing neurotoxic A$\beta$, they may inadvertently provoke harmful inflammatory responses via the C5a-C5aR1 axis. To address this challenge, a combinatorial therapeutic strategy is recommended, which is pairing A$\beta$-targeting immunotherapies with agents that block C5a-C5aR1 signaling. This integrated approach could preserve the benefits of A$\beta$ clearance while mitigating the risk of complement-mediated neuroinflammation, paving the way for more precise and safer immunotherapeutic interventions in Alzheimer's disease.

## The Role of Microglial Cell Activation at the Intersection of A$\beta$ Clearance and Neuroinflammation in Alzheimer's Disease Immunotherapy

The promise of amyloid-$\beta$ (A$\beta$)-targeted immunotherapy in Alzheimer's disease (AD) is becoming increasingly tangible. Both active and passive immunization strategies have demonstrated consistent reductions in plaque burden, but their clinical benefit remains limited. A recent study by van Olst *et al.* [1] in Nature Medicine brings much-needed clarity to this therapeutic paradox, revealing that A$\beta$ clearance via immunotherapy may be offset by maladaptive neuroinflammatory responses, largely mediated by the complement system.

Leveraging spatial transcriptomics and single-cell RNA sequencing in postmortem AD brains, the study characterizes the immune architecture surrounding A$\beta$ plaques following both active immunization (AN1792) and passive monoclonal antibody therapy (lecanemab) [2–6]. A unifying mechanism suggests that antibody formation between A$\beta$ and IgG antibodies triggers phagocytic microglial responses through immunoglobulin G (IgG) receptor, known as Fc gamma receptors (Fc$\gamma$Rs), marked by transcriptional signatures involving apolipoprotein E (*APOE*), triggering receptor expressed on myeloid cells 2 (*TREM2*), cathepsin B (*CTSB*), lipase A (*LIPA*), lysosomal-associated membrane protein 1 (*LAMP1*), and Niemann-Pick disease, type C2 (*NPC2*) genes, which are all hallmarks of microglia capable of efficient A$\beta$ clearance. This process is associated with varying degrees of plaque clearance, particularly in patients demonstrating extensive cortical A$\beta$ removal. However, clearance alone is not sufficient. Patients with near-complete plaque reduction still progressed clinically and neuropathologically, implicating other pathological mechanisms.

## Divergent Fc$\gamma$R and C5a-C5aR1 Pathways

The immunological architecture of murine and human IgG systems reveals critical interspecies differences that shape immune responses and impact therapeutic strategies. While mouse IgG subclasses (IgG1, IgG2a/c, IgG2b, and IgG3) engage a distinct set of Fc gamma receptors (Fc$\gamma$RI, Fc$\gamma$RIIb, Fc$\gamma$RIII, and Fc$\gamma$RIV), human IgGs (IgG1, IgG2, IgG3, and IgG4) interact with a broader repertoire, including Fc$\gamma$RI, Fc$\gamma$RIIa, Fc$\gamma$RIIb, Fc$\gamma$RIIc, Fc$\gamma$RIIIa, and Fc$\gamma$RIIIb [7,8]. Despite these differences, both species share a common immunological mechanism wherein IgG-

containing immune complexes (ICs) bind to activating Fc$\gamma$Rs, triggering pro-inflammatory signaling cascades, cytokine production, and in some cases, cell death. This activation is counterbalanced by engagement of the inhibitory Fc$\gamma$RIIb receptor, which serves as a critical checkpoint against excessive inflammation [7,9–11].

A central node linking antibody-mediated immunity to broader inflammatory pathways is the complement system, particularly through the activation of complement component 3 (C3). Once cleaved, C3b decorates damaged tissue and immune complexes, promoting opsonization and immune cell recruitment. Importantly, C3b also nucleates the assembly of the C5 convertase, culminating in the generation of C5a, which is a potent anaphylatoxin and chemoattractant [7,10,12–18]. In the central nervous system (CNS), C5a interacts with its receptor, C5aR1, which is highly expressed on microglia and other resident immune cells. This axis not only amplifies chemotaxis and cytokine secretion but also upregulates activating Fc$\gamma$Rs while suppressing inhibitory Fc$\gamma$Rs, creating a self-perpetuating loop of inflammation and neurotoxicity [7,19–24].

## The IgG-Fc$\gamma$R-C5aR1 Axis in Alzheimer's Disease

In the context of AD, both the Fc$\gamma$R-IgG axis and complement activation, particularly via the C5a-C5aR1 pathway, have been implicated in disease pathophysiology [25–37]. Although complement activation may initially facilitate the clearance of amyloid-$\beta$ (A$\beta$) plaques, chronic or excessive generation of C5a can lead to sustained microglial activation, synaptic pruning, and neuronal injury [30,38–41]. Recent work by van Olst *et al.* [1] provides compelling evidence supporting this dual role, in which elevated expression of Fc gamma receptor IIIA (FCGR3A), complement C1q subcomponent subunit C (C1qc), and C3 was observed in immunized AD patients, while increased C5aR1 expression was noted in non-immunized individuals with AD. These findings suggest that A$\beta$-IgG immune complexes formed following passive or active immunization can initiate classical complement activation through C1q binding, resulting in downstream cleavage of C3 and C5. While surface-bound C3b enhances A$\beta$ clearance by microglia, it also drives C5a production and the subsequent engagement of C5aR1, which further amplifies Fc$\gamma$R signaling and lowers the threshold for microglial cell activation. This convergence of Fc$\gamma$R and complement pathways fosters a neuroinflammatory environment that may undermine the therapeutic benefit of A$\beta$ immunotherapy. Thus, C3 activation in this context emerges as a double-edged sword contributing both to immunotherapeutic clearance of A$\beta$ and to C5a-C5aR1-mediated neuroinflammation that may accelerate neurodegeneration (Fig. 1).

This finding is further refined through transcriptomic comparison of brains with limited (iAD-lim, incomplete Alzheimer's disease-limited plaque clearance) versus extensive (iAD-ext, incomplete Alzheimer's disease – extensive plaque clearance) plaque clearance. The iAD-lim group displayed a distinct pro-inflammatory profile within A$\beta$-rich niches, including upregulation of alpha-2-macroglobulin (A2M), cluster of differentiation 74 (CD74), myristoylated alanine-rich C-kinase substrate (MARCKS), and genes associated with interleukin-2-signal transducer and activator of transcription 5 (IL-2-STAT5) and nuclear factor kappa B (NF-$\kappa$B) signaling. Complement genes such as *C1qc* and *C3* were significantly enriched in areas with A$\beta$ deposition and showed nonlinear expression patterns that tracked with plaque density. Conversely, iAD-ext brains exhibited microglial cells states more akin to homeostasis, with decreased expression of stress response genes and increased phagocytic gene programs. Passive immunotherapy exhibited similar duality. The lecanemab-treated patient showed regional A$\beta$ clearance accompanied by activation of microglial cell states enriched for lysosomal (CTSB, cathepsin B), interferon (IFI6, interferon alpha-inducible protein 6), and stress-response (*CHI3L1*, chitinase-3-like protein 1; *SPP1*, secreted phosphoprotein 1) genes. Notably, co-localization of ionized calcium-binding adapter molecule 1 (IBA1), cluster of differentiation 68 (CD68), and apolipoprotein C1 (APOC1) suggested ongoing innate immune activation despite apparent therapeutic engagement.

These findings point out an urgent need to recalibrate our therapeutic strategies for AD. The promise of A$\beta$ immunotherapy is undeniable, yet its full potential is undermined by unintended immune activation that may exacerbate neuroinflammation. The benefits of A$\beta$ clearance must therefore be carefully balanced against its immunological liabilities. Among the most promising avenues for mitigating this trade-off is targeted modulation of the complement cascade, particularly the C5a-C5aR1 axis. This axis plays a pivotal role in linking antibody-mediated responses to chronic microglial cell activation and tissue injury. By selectively disrupting this pathway, it may be possible to preserve beneficial microglial cell phagocytosis of A$\beta$ while dampening the pro-inflammatory signals that drive neurotoxicity. Preclinical studies and emerging clinical data provide compelling support for this approach. Agents such as anti-C5 monoclonal antibodies (e.g. eculizumab and ravulizumab) [42–58], anti-C5a therapies (e.g., vilobelimab) [59–65], and C5aR1 antagonists (e.g., avacopan) [66–70] offer clinically tractable tools to uncouple immunotherapy from inflammatory adverse events, including amyloid-related imaging abnormalities, while preserving therapeutic efficacy. These insights demand a new therapeutic paradigm, one in which A$\beta$-targeting antibodies are not used in isolation but are paired with precision immunomodulators to optimize safety, efficacy, and long-term benefit.

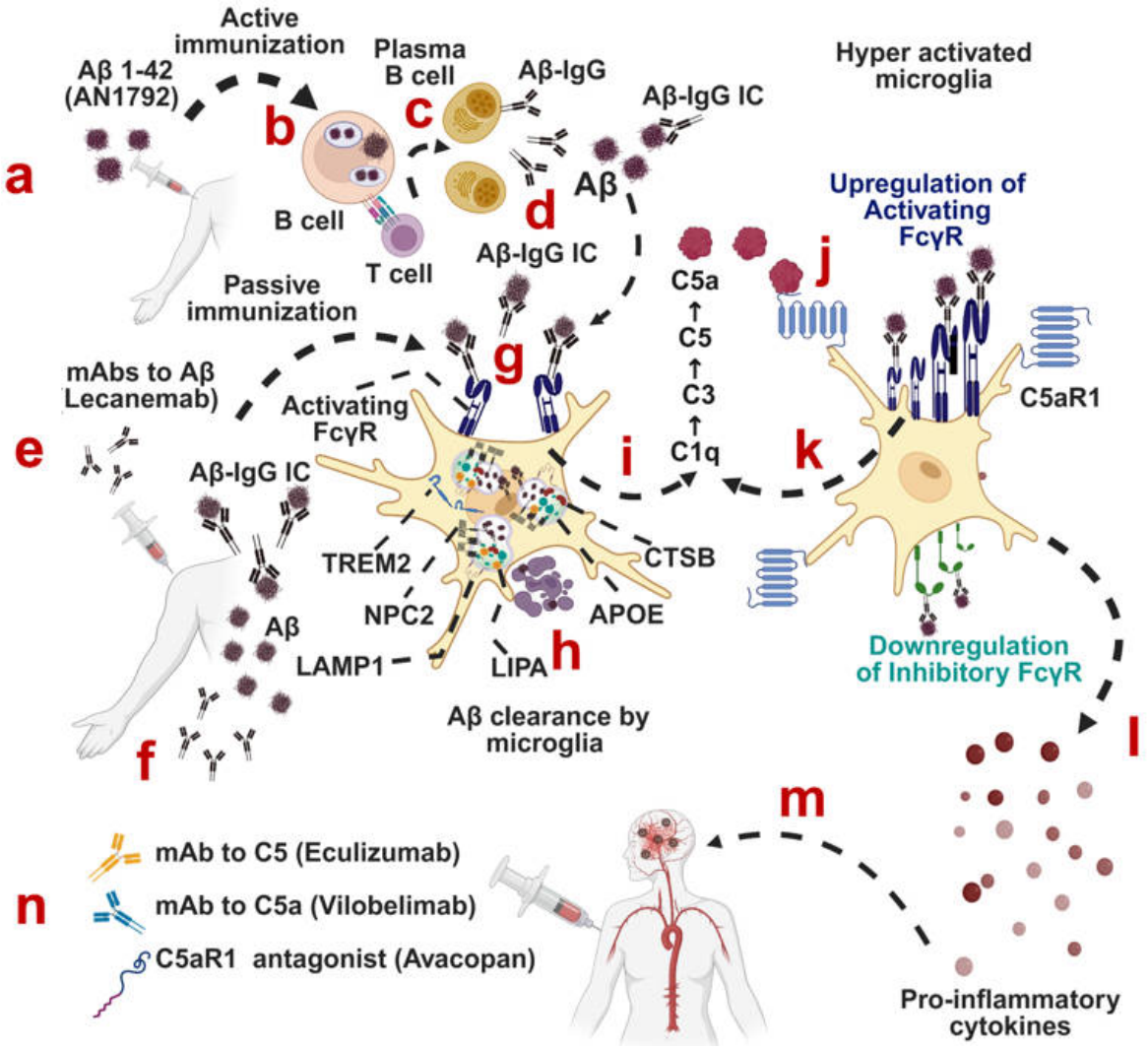


**Fig. 1. Dual role of amyloid-$\beta$ (A$\beta$) Immunotherapy: Fc gamma receptors (Fc$\gamma$Rs)-mediated clearance vs. complement-driven neuroinflammation and the potential for complement-targeted modulation in Alzheimer's disease.** This schematic illustrates the mechanisms underlying both active and passive A$\beta$ immunotherapy in Alzheimer's disease (AD) and highlights potential intervention points within the complement cascade to mitigate treatment-associated neuroinflammation. (a–d) In active immunotherapy, administration of $A\beta_{1-42}$ peptide (e.g., AN1792) leads to recognition and uptake by B cells, which present processed antigen to T helper cells. This interaction drives B cell differentiation into plasma cells that secrete A$\beta$-specific immunoglobulin G (IgG) antibodies. These antibodies bind aggregated A$\beta$, resulting in the formation of A$\beta$-IgG immune complexes (A$\beta$-IgG ICs). (e,f) In passive immunotherapy, exogenously administered monoclonal antibodies targeting A$\beta$ (e.g., lecanemab) directly bind to A$\beta$ plaques, also generating A$\beta$-IgG ICs. (g,h) These immune complexes are recognized by microglial cells, activating Fc$\gamma$Rs, leading to activation of microglia and promotion of A$\beta$ phagocytosis, a potentially beneficial outcome. (i) Simultaneously, A$\beta$-IgG ICs activate the classical complement pathway by activating C1q, C3, resulting in the cleavage of complement component C5 and the release of complement 5a (C5a), a potent anaphylatoxin. (j) C5a binds to C5a receptor 1 (C5aR1) on microglia, promoting the upregulation of activating Fc$\gamma$Rs and suppression of inhibitory Fc$\gamma$Rs. This signaling increases microglial cell sensitivity to immune complexes. (k) The resulting shift in Fc$\gamma$R balance lowers the activation threshold, amplifying microglial cell responses to A$\beta$-IgG ICs and further fueling complement activation and C5a generation. (l,m) This self-reinforcing loop drives sustained microglial cell activation and excessive production of pro-inflammatory cytokines, contributing to neuronal injury, tau hyperphosphorylation, and cognitive decline even in the context of successful A$\beta$ plaque removal. (n) The potential therapeutic targets within the complement cascade, specifically C5, C5a, and C5aR1, that may offer a strategy to suppress harmful neuroinflammation while preserving Fc$\gamma$R-mediated A$\beta$ clearance. The figure was created using BioRender (www.biorender.com).

## Conclusion

A$\beta$ immunotherapy marks a major advance in Alzheimer's disease treatment by promoting microglial cell-mediated clearance of plaques through Fc$\gamma$R engagement and the upregulation of neuroprotective and phagocytic genes such as *APOE*, *TREM2*, *NPC2*, *LAMP*, *LIPA*, and *CTSB*. However, these same immune complexes can activate the classical complement cascade, generating C5a, which, through C5aR1 signaling, promotes sustained microglial cell inflammation, pro-inflammatory Fc$\gamma$R expression, and potentially worsens tau pathology. This feedback loop may persist even after plaque removal, raising safety concerns. As shown in Fig. 1, regional transcriptomic differences emphasize the need to balance clearance with immune restraint. Targeting complement components such as C5, C5a, or C5aR1 alongside A$\beta$ antibodies offers a promising path to preserve beneficial microglial cell functions while curbing neuroinflammation. This combined strategy could extend the therapeutic window, limit adverse effects, and improve cognitive outcomes for patients with Alzheimer's disease.

## Availability of Data and Materials

Not applicable.

## Author Contributions

MP is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the preparation of the manuscript; and for being accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

Manoj Kumar Pandey serves as one of the editorial board members of this journal. We declare that Manoj Kumar Pandey had no involvement in the review of this article and has no access to information regarding its review. Fig. 1 was created using BioRender. The author has no financial or personal relationship with BioRender, and the use of this tool does not imply any endorsement.

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