Title Efferocytosis-Driven Reduction of Neuroinflammation and Amyloid Beta Burden via Novel GAS6 Fusion Protein (GAIA): A Promising Therapeutic Approach in Alzheimer's Disease

Background Amyloid-beta (Aβ) accumulation is a hallmark of Alzheimer's disease (AD), and reducing Aβ burden is a key therapeutic strategy. Recent FDA-approved anti-Aβ antibodies, such as Lecanemab and Donanemab, have demonstrated significant reductions in Aβ burden and deceleration of cognitive decline. However, these therapies are associated with adverse events, including antibody-induced neuroinflammation and amyloid-related imaging abnormalities (ARIA). The GAIA platform leverages TAM receptors—Tyro3, Axl and MerTK—to facilitate efferocytosis-driven Aβ clearance without triggering inflammatory responses, addressing limitations of current anti-Aβ immunotherapies. This study evaluates the pharmacokinetic properties and therapeutic efficacy of GAIA-Aβ.

Methods GAIA-Aβ was engineered with dual functional domains, a GAS6 domain for TAM receptor binding and Aβ-targeting moiety. Specific binding to oligomeric Aβ (oAβ) and TAM receptors was confirmed using ELISA. TAM receptor-driven phagocytosis and oAβ clearance were evaluated using HMC3, human microglial cell line. Additionally, anti-inflammatory responses were assessed in induced pluripotent stem cell (iPSC)-derived monocytes. Pharmacokinetic properties of GAIA-Aβ were analyzed to determine serum exposure and brain-to-serum ratio. To evaluate the in vivo efficacy, GAIA-Aβ was intravenously administered to 5xFAD mice once weekly (QW) for 8 weeks, and Aβ plaque burden and glial phagocytic activity were assessed using immunohistochemistry.

Results GAIA-Aβ exhibited specific binding to oAβ and activated TAM receptors in a dose-dependent manner. Phagocytosis assays demonstrated effective clearance of oAβ while reducing inflammatory cytokines, indicating successful efferocytosis-mediated activity. Pharmacokinetic analysis revealed that GAIA-Aβ possesses properties comparable to conventional monoclonal antibodies. In 5xFAD mice, GAIA-Aβ treatment led to significant reductions in Aβ plaques and enhanced glial-mediated clearance, particularly via astrocyte engagement.

Conclusions GAIA-Aβ effectively reduces Aβ burden while mitigating neuroinflammation, presenting a favorable safety profile compared to existing anti-Aβ antibodies. These findings highlight the potential of GAIA-Aβ as an improved therapeutic approach for Alzheimer's disease, addressing the limitations of current anti-Aβ immunotherapies.