Title Efferocytosis-Driven Neuroinflammation Reduction by Novel GAS6 Fusion Protein (GAIA) in Anti-Aβ immunotherapies

Background Amyloid-beta (Aβ) immunotherapy has emerged as a promising approach for treating Alzheimer's disease (AD). Recent FDA approvals of antibody therapeutics like Lecanemab and Donanemab have demonstrated significant reductions in Aβ burden and deceleration of cognitive decline, reinforcing Aβ as a viable therapeutic target. However, these therapies are associated with adverse reactions, including antibody-induced inflammation, amyloid-related imaging abnormalities (ARIA), and cerebral microbleeding. The GAIA platform introduces a novel chimeric protein that leverages Tyro3, Axl, and MerTK (TAM) receptors to mediate efferocytosis-driven phagocytosis without triggering inflammatory responses, aiming to address the limitations of current Aβ immunotherapies. This study applies the GAIA platform to Aβ antibodies (GAIA-Aβ) to evaluate their efficacy and pharmacokinetics for therapeutic potential.

Methods We engineered GAIA-Aβ chimeric proteins featuring two functional domains: Aβ-specific fragments fused with an engineered GAS6 domain for TAM receptor binding. Specific binding to oligomeric Aβ (oAβ) and TAM receptors was confirmed using ELISA assays. TAM receptor-mediated phagocytosis and oAβ clearance were assessed using HMC3 (human microglial cells lacking Fcγ receptors). Anti-inflammatory responses were evaluated in induced pluripotent stem cell (iPSC)-derived monocytes. Pharmacokinetic properties and in vivo efficacy of GAIA-Aβ were studied.

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 a reduction in inflammatory cytokines indicated successful efferocytosis-mediated activity. Pharmacokinetic analysis revealed that GAIA-Aβ possesses properties comparable to those of existing monoclonal antibody therapeutics.

Conclusions The GAIA-Aβ chimeric proteins effectively clear amyloid plaques and induce anti-inflammatory responses, with favorable pharmacokinetic profiles similar to monoclonal antibodies. Ongoing in vivo studies aim to further characterize the therapeutic efficacy of GAIA-Aβ. These findings suggest that GAIA-Aβ may offer comparable therapeutic benefits in reducing Aβ burden while improving safety profiles by mitigating issues like vascular damage and ARIA associated with current immunotherapies.