Gene therapy targeting neuroinflammation in AD

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Alzheimer's Disease (AD) is a devastating and incurable disorder that poses one of the greatest economic and societal challenges to humanity, as the burden on healthcare systems is becoming unsustainable. For decades, AD research primarily focused on developing compounds targeting classical neuropathological hallmarks, such as Amyloid β (Aβ). However, the only EMA-recommended medication has shown only marginal effects on disease progression and is associated with concerning side effects. Currently, AD research has shifted towards the neuroinflammation hypothesis, driven by strong epidemiological associations with key inflammatory risk factors, including common genetic variants, aging, trauma, infections, and midlife obesity. Among the inflammatory mediators implicated in initiating and propagating AD pathology is the common adaptor inflammasome protein ASC (Apoptosis-associated speck-like protein containing a CARD). ASC levels are elevated in the early stages of AD before cognitive decline becomes apparent. Moreover, ASC co-seeds and co-aggregates with Aβ plaques. Notably, its genetic removal or intracortical treatment with neutralizing ASC antibodies has been shown to ameliorate AD pathology. Therefore, ASC is hypothesized to be a promising molecular target for therapeutic intervention in AD.

Our project aims to develop a systemic gene therapy using Adeno-Associated Viral Vectors (AAV) targeting ASC, thereby modulating neuroinflammation and protein aggregation in AD. The primary objective is to optimize AAV vectors for efficient transduction of brain tissue. This strategy will enable us to tackle chronic neuroinflammation and protein aggregation associated with AD. This innovative approach integrates cutting-edge advancements in AAV-based gene therapy with a novel molecular target in AD pathology, offering the potential for a groundbreaking treatment for this devastating neurodegenerative disease.