New therapeutic drug for Alzheimer's disease without inflammatory side effects

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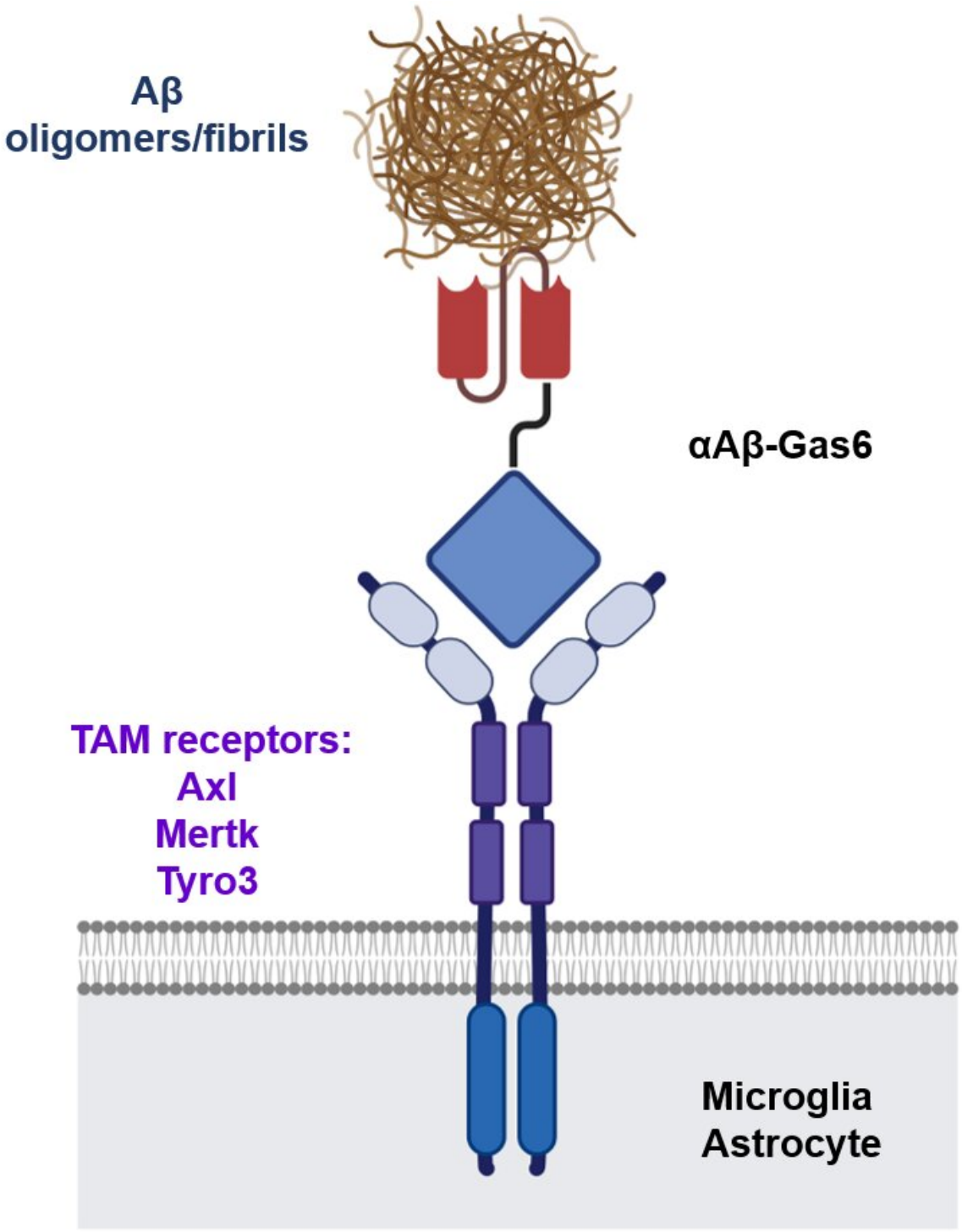


Schematic of a chimeric Gas6 fusion protein. A single chain variable fragment (scFv) of an Amyloid β (Aβ)-targeting monoclonal antibody is fused with a truncated receptor binding domain of Gas6, a bridging molecule for the

clearance of dead cells via TAM (TYRO3, AXL, and MERTK) receptors, which are expressed by microglia and astrocytes. Credit: Gliabiology Lab & Kim Lab of Immunotherapy

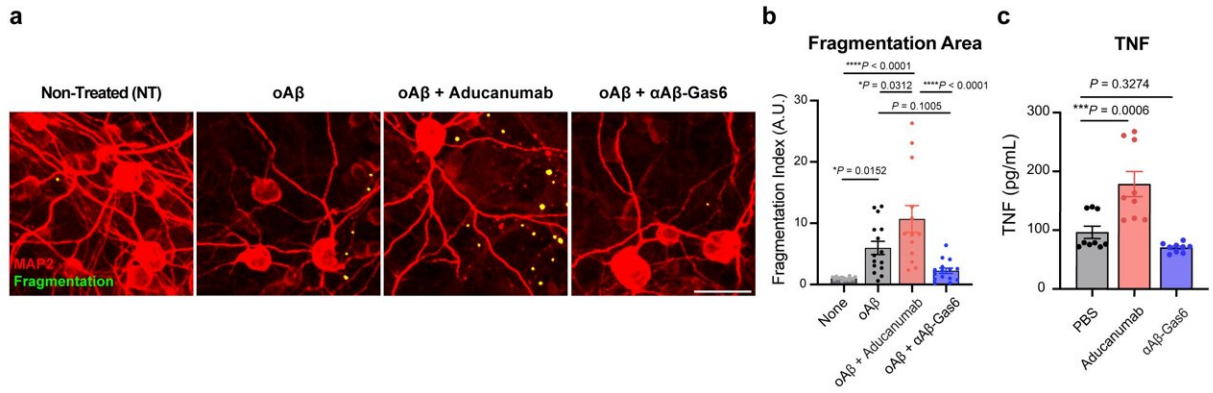
Although Aduhelm, a monoclonal antibody targeting amyloid beta (Aβ), recently became the first US FDA approved drug for Alzheimer's disease (AD) based on its ability to decrease Aβ plaque burden in AD patients, its effect on cognitive improvement is still controversial. Moreover, about 40% of the patients treated with this antibody experienced serious side effects including cerebral edemas (ARIA-E) and hemorrhages (ARIA-H) that are likely related to inflammatory responses in the brain when the Aβ antibody binds Fc receptors (FCR) of immune cells such as microglia and macrophages. These inflammatory side effects can cause neuronal cell death and synapse elimination by activated microglia, and even have the potential to exacerbate cognitive impairment in AD patients. Thus, current Aβ antibody-based immunotherapy holds the inherent risk of doing more harm than good due to their inflammatory side effects.

To overcome these problems, a team of researchers at KAIST in South Korea has developed a novel fusion protein drug, αAβ-Gas6, which efficiently eliminates Aβ via an entirely different mechanism than Aβ antibody-based immunotherapy. In a mouse model of AD, αAβ-Gas6 not only removed Aβ with higher potency, but also circumvented the neurotoxic inflammatory side effects associated with conventional antibody treatments.

Their findings were published on August 4 in *Nature Medicine*.

"FcR activation by Aβ targeting antibodies induces microglia-mediated Aβ phagocytosis, but it also produces inflammatory signals, inevitably

damaging brain tissues," said paper authors Chan Hyuk Kim and Won-Suk Chung, associate professors in the Department of Biological Sciences at KAIST.

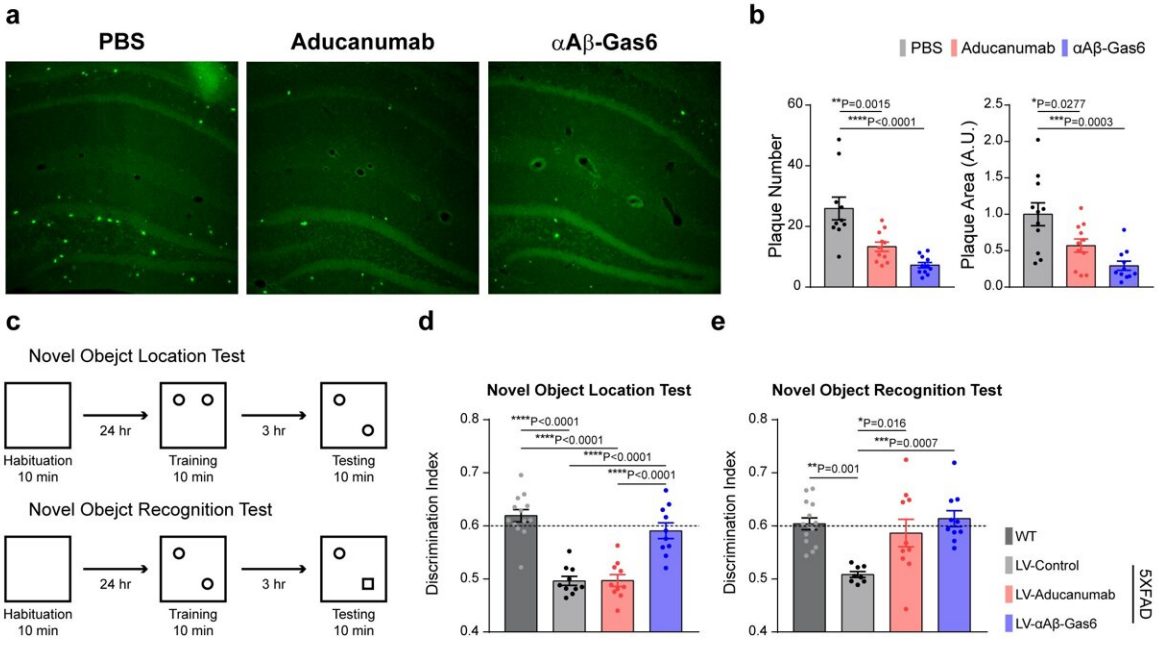


The resulting αAβ-Gas6 clears Aβ oligomers and fibrils without causing neurotoxicity (a-b, neurons: red, and fragmented axons: yellow) and proinflammatory responses (c, TNF release), which are conversely exacerbated by the treatment of an Aβ-targeting monoclonal antibody (Aducanumab). Credit: Gliabiology Lab & Kim Lab of Immunotherapy

"Therefore, we utilized efferocytosis, a cellular process by which dead cells are removed by phagocytes as an alternative pathway for the clearance of Aβ in the brain," Prof. Kim and Chung said. "Efferocytosis is accompanied by anti-inflammatory responses to maintain tissue homeostasis. To exploit this process, we engineered Gas6, a soluble adaptor protein that mediates efferocytosis via TAM phagocytic receptors in such a way that its target specificity was redirected from dead cells to Aβ plaques."

The professors and their team demonstrated that the resulting αAβ-Gas6

induced Aβ engulfment by activating not only microglial but also astrocytic phagocytosis since TAM phagocytic receptors are highly expressed by these two major phagocytes in the brain. Importantly, αAβ-Gas6 promoted the robust uptake of Aβ without showing any signs of inflammation and neurotoxicity, which contrasts sharply with the treatment using an Aβ monoclonal antibody. Moreover, they showed that αAβ-Gas6 substantially reduced excessive synapse elimination by microglia, consequently leading to better behavioral rescues in AD model mice.



The number and total area of Aβ plaques (Thioflavin-T, green) were significantly reduced in αAβ-Gas6-treated AD mouse brains compared to Aducanumab-treated ones (a, b). The cognitive functions of AD model mice were significantly rescued by αAβ-Gas6 treatment, whereas Aducanumab-treated AD mice showed a partial rescue in these cognitive tests (c-e). Credit: Gliabiology Lab & Kim Lab of Immunotherapy

"By using a mouse model of cerebral amyloid angiopathy (CAA), a cerebrovascular disorder caused by the deposition of Aβ within the walls of the brain's blood vessels, we also showed that the intrathecal administration of Gas6 fusion protein significantly eliminated cerebrovascular amyloids, along with a reduction of microhemorrhages. These data demonstrate that aAb-Gas6 is a potent therapeutic agent in eliminating Aβ without exacerbating CAA-related microhemorrhages."

Professors Kim and Chung noted, "We believe our approach can be a breakthrough in treating AD without causing inflammatory side effects and synapse loss. Our approach holds promise as a novel therapeutic platform that is applicable to more than AD. By modifying the target-specificity of the fusion protein, the Gas6-fusion protein can be applied to various neurological disorders as well as autoimmune diseases affected by toxic molecules that should be removed without causing inflammatory responses."

More information: Won-Suk Chung, Anti-inflammatory clearance of amyloid-β by a chimeric Gas6 fusion protein, *Nature Medicine* (2022). DOI: 10.1038/s41591-022-01926-9.
www.nature.com/articles/s41591-022-01926-9

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