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Featured Article

NPT088 reduces both amyloid-β and tau pathologies in transgenic mice

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Abstract

Introduction: Alzheimer's disease (AD) is characterized by appearance of both extracellular senile plaques and intracellular neurofibrillary tangles, comprised of aggregates of misfolded amyloid-β (Aβ) and hyper-phosphorylated tau, respectively. In a previous study, we demonstrated that g3p, a capsid protein from bacteriophage M13, binds to and remodels misfolded aggregates of proteins that assume an amyloid conformation. We engineered a fusion protein ("NPT088") consisting of the active fragment of g3p and human-IgG_1-Fc.

Methods: Aged Tg2576 mice or rTg4510 mice received NPT088 weekly via IP injection. Cognitive and/or functional motor endpoints were monitored during dosing. Pathology was quantified biochemically and immunohistochemically.

Results: NPT088-lowered Aβ plaque and improved cognitive performance of aged Tg2576 mice. Moreover, NPT088 reduced phospho-tau pathology, reduced brain atrophy, and improved cognition in rTg4510 mice.

Discussion: These observations establish NPT088 as a novel therapeutic approach and potential drug class that targets both Aβ and tau, the hallmark pathologies of AD.

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Keywords: GAIM; General amyloid interaction motif; Novel object recognition; Spontaneous alternation; Limb clasping; Thioflavin S; Brain weight; Cerebrospinal fluid; Phospho-tau

1. Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder defined by dementia and the presence of extracellular plaques and intracellular neurofibrillary tangles, which are comprised of aggregates containing misfolded Aβ and tau, respectively [1,2]. Current therapeutic approaches for AD target one of these two protein aggregates. Most clinical trials testing the efficacy of Aβ immunization have not demonstrated significant functional improvements in patients [3–7]. Moreover, compounds targeting tau aggregation are still too early in clinical development to determine whether an approach specifically directed at tau aggregates will be efficacious [8,9].

Based on the clinical failures using Aβ immunization and animal model studies, it is postulated that therapeutic

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strategies for binding and subsequent clearing of Aβ aggregates should ideally exhibit high-affinity binding to aggregated forms of the misfolded proteins (i.e., oligomers, fibers, or plaques) while sparing monomeric or native species [10,11]. In support of this hypothesis, phase I results from the ongoing PRIME clinical trial of aducanumab, a monoclonal antibody (mAb) that specifically targets aggregated Aβ, demonstrated significant reduction of Aβ plaque by PET imaging associated with significant cognitive improvement [12]. Although these results are promising and suggest that treatment with Aβ-directed therapeutics could alter AD progression, the patient population enrolled was specifically selected to exhibit a mild form of the disease, and measurements of changes in tau aggregate loads, which correlate more closely with cognitive function, were not reported. Here, we propose a therapeutic approach for AD that broadly targets aggregates of both Aβ and tau but without affecting their respective monomeric forms.

It was previously reported that the filamentous bacteriophage M13 (M13) improves cognition and decreases Aβ plaque loads in APP-overexpressing transgenic mice after chronic administration [13]. Further research to understand the mechanism of this anti-amyloid activity revealed that M13 binds to and remodels multiple types of misfolded protein aggregates in vitro, including Aβ, tau, and α-synuclein, without binding to monomeric forms of these proteins [14], and that M13 targeting of misfolded protein aggregates is mediated by a two-domain fragment of the phage capsid protein g3p. Therefore, g3p functions as a general amyloid interaction motif (GAIM), targeting multiple misfolded proteins. A fusion protein, NPT088, was engineered that consists of the active fragment of g3p and human-IgG_1-Fc

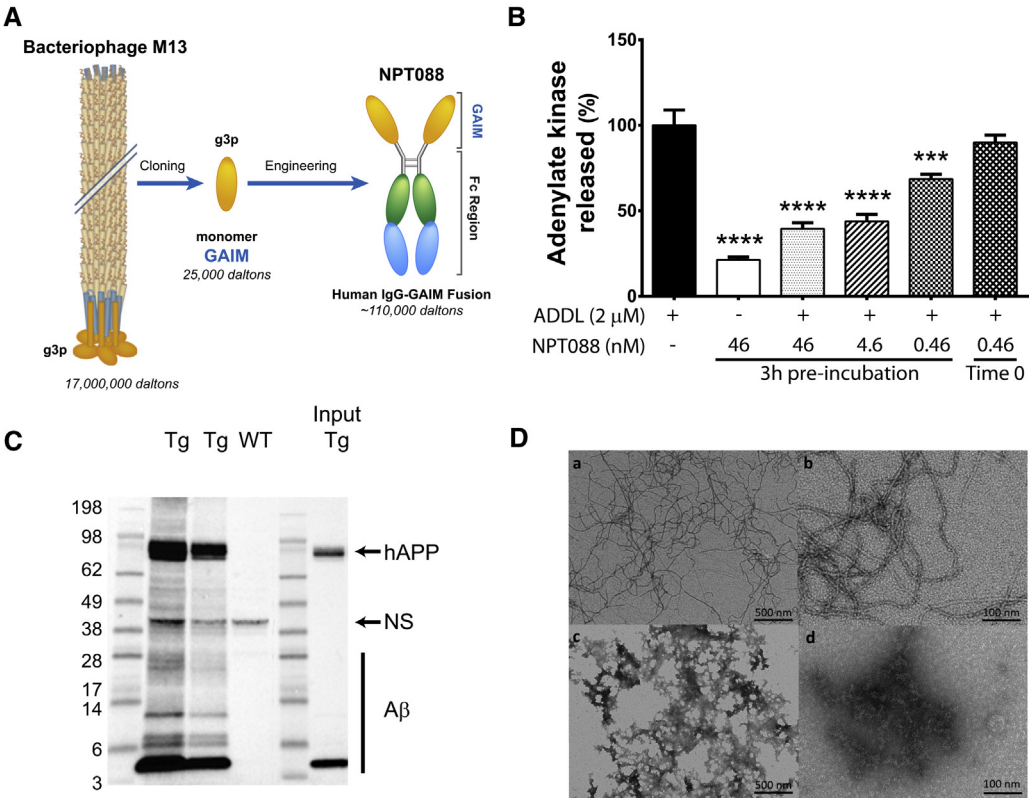

Fig. 1. Generation and in vitro characterization of NPT088, an immunoglobulin-GAIM fusion protein. (A) Native bacteriophage M13 potently and broadly binds to and disrupts a variety of misfolded protein assemblies, including Aβ, tau, α-synuclein, and yeast prion Sup35. M13, owing to its large size (17 MDa), represents a significant hurdle for effective CNS drug delivery. Subsequent characterization of amyloid fiber binding and remodeling of M13 revealed that the minor capsid protein, gene 3 protein (g3p), is critical for this activity and, furthermore, that the two N-terminal domains of g3p facilitate binding and disruption of amyloids as a general amyloid interaction motif (GAIM). The engineered fusion protein, NPT088 (NPT088), consists of the active fragment of g3p and human-IgG_1-Fc. (B) Incubation of differentiated N2a cells with 2 μM (9 μg/mL) $Aβ_{42}$ ADDLs for 24-hour-induced robust cytotoxicity. Preincubation of ADDLs with NPT088 for 3 hours significantly inhibited cytotoxicity. Co-application of ADDL and NPT088 (Time 0 control) had no effect on induction of cytotoxicity. Asterisks indicate significant difference from ADDL alone (Dunnett's test, $^{***}P < .001$, $^{****}P < .0001$). (C) NPT088 was used to precipitate Aβ from formic acid lysates of aged Tg2576 brain. Precipitates were resolved on SDS-PAGE and western blots probed with a monoclonal anti-Aβ antibody (6E10). NPT088 precipitated Aβ from formic acid extracts of brain prepared from two different Tg2576 mice (Tg). No Aβ was extracted from lysates prepared from WT mice. NS indicates nonspecific band that is present in formic acid extracts from WT brains and is recognized by 6E10. hAPP represents human amyloid precursor protein. Note the enrichment of all species of Aβ in the immunoprecipitated lanes relative to the Input material lane. (D) Transmission electron microscopy images of $Aβ_{42}$ fiber preparations incubated for 7 days and stained with 1% uranyl acetate. (a–b) Examples of Aβ fiber structure after incubation for 7 days in buffer alone. (c–d) Examples of $Aβ_{42}$ fiber structure after incubation with NPT088 (0.25 μM) for 7 days. Note the dramatic loss of fiber structure.

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