Reduction of β-Amyloid Aggregates and phospho-Tau in Transgenic Mice by a Novel Fusion Protein Bivalent for a General Amyloid Interaction Motif (GAIM)

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**Introduction**

Alzheimer’s disease (AD) is characterized by both Amyloid β (Aβ) plaque deposition and intracellular neurofibrillary tangle formation accompanied by progressive cognitive decline. We have shown that NPT002 (filamentous baculovirus M13) dose-dependently clears Aβ plaques, reduces phospho-Tau and restores normal cognitive performance in aged AD mouse models. Recently, we isolated the protein motif from NPT002 responsible for the amyloid-interacting activity, which we call the general amyloid interacting motif (GAIM). The present studies were conducted to evaluate whether NPT002 (IgG-Fc-GAIM) was also able to alter cognitive and neuropathology endpoints in transgenic Aβ and Tau Alzheimer’s mouse models when administered systemically.

**From Filamentous Phage to Bivalent GAIM Fusion Proteins**

![Image of reduction in amyloid plaques and tau tangles](image1)

**Methods**

Mice. All mice were housed under LD 12:12 and provided access to food and water ad libitum. NPT002 mice were obtained from ‘Genonics’ and individually housed. The initial challenge, Westernc; Reptile (10 mg/kg) was co-administered with 16:18 mg/kg at study start. The dose-response study was performed with 16:18 mg/kg at study start. (Graph): A colony was established from CamHI- and EcoRI-bred mice. Three days prior to study start, mice were individually housed. Mice were 5-3.5 mg/kg at study start. All studies included an Lp dose of anti-CD4 24
drug cocktail to treat infection.

**Behavior.** Strained Observations. Mice were placed into an open field for 5 min and spontaneous behaviors were studied. Behaviors monitored included: ambulations, freezing, rearing, and grooming. Mice were recorded using 2 cameras (1 frame every 200 ms) and analyzed with stereoanalyzer software (Version 7.0).

**Biochemistry.** Mice brains were homogenized in 1/50 of the sample in 0.1 M LiCl/150 mM HEPES buffer with protease and phosphatase inhibitors. Samples were sonicated on ice and spun at 100,000 x g at 4 °C. The supernatant was collected as the soluble fraction. The remaining pellet was homogenized in 70% formic acid to a concentration of 2 mM/mouse tissue. The pellet was sonicated on ice and spun at 100,000 x g at 4 °C. The supernatant was collected as the insoluble fraction. The frozen samples were stored at -80°C.

**Results & Conclusions**

Systemic administration of NPT008 to aged Tg2576 mice resulted in significant:

- Reduction of stereotyped behavioral abnormalities.
- Increases in spatial working memory.
- Reduction of insoluble and soluble Aβ42.
- Reduction of Aβ plaques.
- No adverse events were observed.

These findings indicate that NPT008 is well tolerated and significantly reduces amyloid pathology and improves cognitive function in Aβ and Tau transgenic mouse models when administered systemically. Collectively, these data support the use of NPT008 as a novel therapeutic approach for reducing Aβ plaque and phospho-Tau.