

**NOT ALL AMYLOID-BETA THERAPEUTICS ARE CREATED EQUAL: PROMIS NEUROSCIENCES
LEAD PRODUCT CANDIDATE FOR ALZHEIMER'S DISEASE SHOWS IMPROVED THERAPEUTIC
POTENCY VERSUS OTHER AMYLOID BETA-DIRECTED ANTIBODIES**

***Humanized PMN310 Shows Significantly Greater Binding to the Toxic Oligomer Fraction from
Alzheimer's Disease Brain Extract Compared to Aducanumab***

Low molecular weight toxic A β oligomers are the "true pathogen" in Alzheimer's disease

Strong genetic and experimental evidence implicates amyloid-beta (A β) in the pathogenesis of Alzheimer's disease (AD). However, views on the nature of the A β species responsible for progressive neurodegeneration have evolved considerably along with a greater understanding of AD disease biology. A β plaque is a hallmark of AD and was initially believed to be responsible for neuronal cell death. But a mounting body of experimental and clinical data has shown that soluble toxic oligomers propagating in a prion-like manner, rather than insoluble plaque, are actually the primary drivers of neuronal loss and cognitive decline in AD patients.^{1,2} Plaque burden correlates poorly with memory impairment^{3,4} and A β insoluble fibrils show little or no demonstrable toxicity in vitro or in vivo.^{5,6} In contrast, a significant correlation exists between disease severity and levels of soluble A β in the central nervous system⁴, in line with the high degree of neurotoxicity and induction of cognitive impairment demonstrated with soluble A β oligomers.⁵⁻⁹

Examination of soluble A β species in AD brain extracts by several investigators has further indicated that the neurotoxic activity resides primarily in the low molecular weight (LMW; <70kDa) fraction of A β oligomers as opposed to A β monomers or high molecular weight (HMW; >70kDa) aggregates of A β . Overall, analysis of soluble human AD brain extracts by various methodologies, including size-exclusion chromatography (SEC), ultracentrifugation and immunoprecipitation, shows the presence of a range of different sized aggregates of A β dominated by HMW species and less abundant smaller oligomeric species consisting of dimers, trimers, tetramers and dodecamers.^{7,10-12} In a variety of assays, the LMW A β oligomers, but not A β monomers, exhibited potent neuronal toxicity causing neurite degeneration, disruption of cytoskeleton microtubules and decreased synaptic function in vitro, and memory impairment when injected into the brain of rodents in vivo.⁵⁻¹⁰ By comparison, HMW A β aggregates were largely inert although they reportedly can dissociate into LMW species and act as a reservoir for toxic oligomers.¹⁰

Clinical activity of A β -directed antibodies correlates with their ability to target LMW toxic oligomers

These critical insights into the nature of the "true pathogen" in AD provide an explanation for the disappointing clinical results obtained with approaches that fail to effectively target LMW toxic oligomers. For example, solanezumab (Eli Lilly) and the BACE inhibitor verubecestat

(Merck) designed to bind A β monomers or prevent their generation, respectively, were found to be safe but lacked efficacy in large Phase III trials. This failure is consistent with the expected inability of these agents to neutralize the ongoing prion-like propagation of pre-existing A β toxic oligomers. Bapineuzumab (Pfizer, J&J) which binds all forms of A β , was also found to lack efficacy and encountered safety issues attributable to the engagement of A β plaque and vascular A β deposits associated with an increased risk of brain edema (ARIA-E).^{13,14} To date, aducanumab (Biogen) is the only antibody shown to provide a cognitive benefit in AD patients.¹⁵ This success is in agreement with the ability of aducanumab to bind A β oligomers without unproductive binding to A β monomers. However, binding of aducanumab to A β plaque has resulted in the occurrence of dose-limiting ARIA-E.¹⁵

SEC fractionation studies of soluble human AD brain extracts were conducted in the laboratory of ProMIS' Chief Scientific Officer, Dr. Neil Cashman, to compare the binding activity of our PMN310 lead candidate to other A β -directed antibodies. Fractionation of soluble extracts from 8 confirmed AD brains gave rise to a reproducible pattern with LMW peaks consistent with the presence of reportedly toxic dimers, tetramers and dodecamers (fig. 1). Binding of humanized (hu)PMN310, aducanumab and bapineuzumab to SEC fractions was assessed by surface plasmon resonance (SPR). The test antibodies and a negative control antibody (huIgG1) were immobilized on sensor chips and the LMW fraction of brain extract was flowed over the chips to assess the degree of binding by each antibody. The results showed greater binding of aducanumab to the toxic oligomer-enriched LMW fraction compared to bapineuzumab (fig. 2), in line with the greater therapeutic activity of aducanumab. Humanized PMN310 showed even greater binding (~1.5-2 fold) compared to aducanumab providing important validation for the ability of ProMIS' computational platform to identify disease-associated conformational epitopes that arise upon misfolding of normal proteins into toxic oligomeric forms.

The ability of huPMN310 to target LMW toxic oligomers without binding A β monomers (reduced efficacy) or plaque (increased risk of ARIA-E) supports the potential for safe administration of higher effective doses and greater therapeutic potency. Humanized PMN310 is currently undergoing affinity maturation which could lead to an even greater advantage.

Figure 1 – SEC fractionation profile of AD soluble brain extract

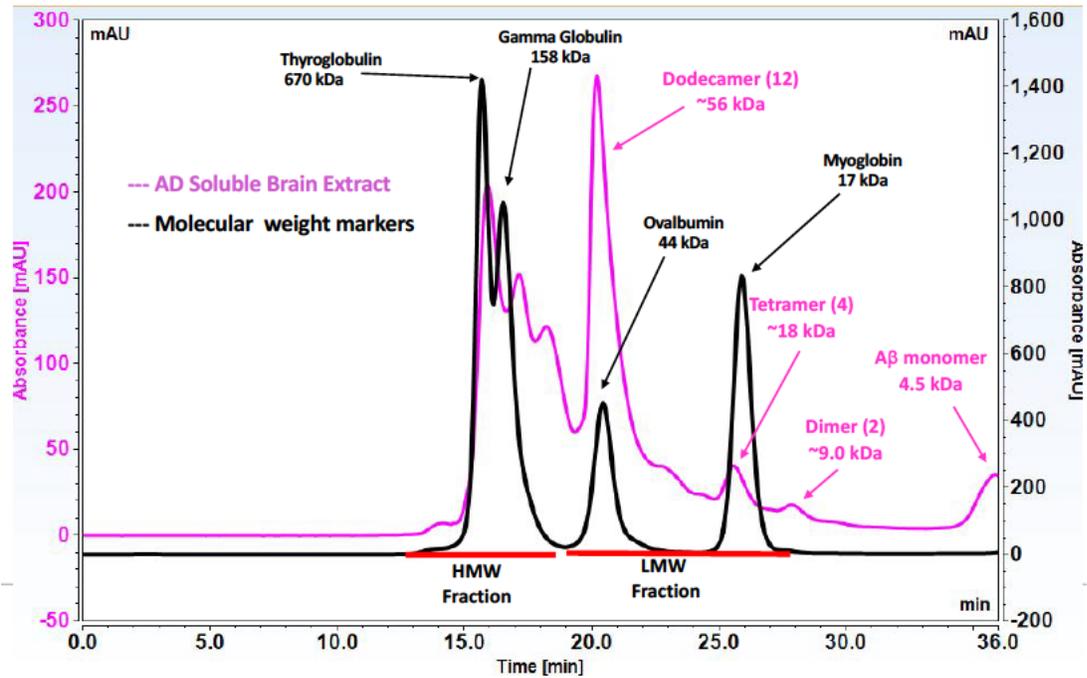
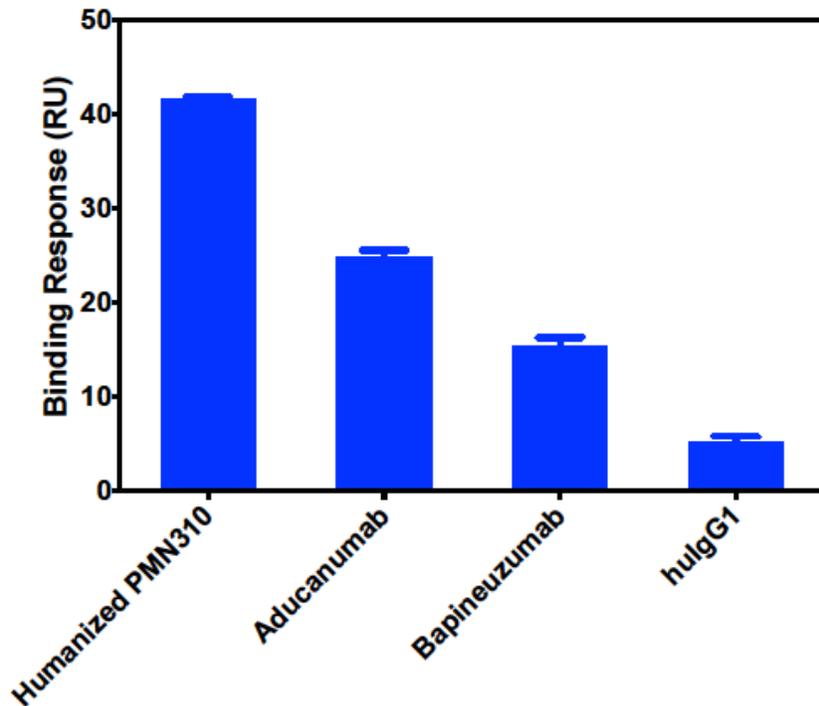


Figure 2 – Humanized PMN310 shows significantly better binding to the toxic oligomer-enriched LMW fraction of AD brain extract



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