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Attacking the Right Therapeutic Target in Alzheimer's Disease

Zeroing in on amyloid-beta oligomers

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Alzheimer's disease (AD) stakeholders have become increasingly frustrated by the successive failures of developmental drugs in late-stage clinical trials and the failure of any disease-modifying drug based on the amyloid-beta (Aß) hypothesis to attain FDA approval. Despite doubts about its validity, however, the Aß hypothesis is alive and well. Clinical trial failures of Aß pathway-based drugs are understood in the context of right pathway, wrong therapeutic target. Soluble Aß oligomers (AßOs) have emerged as the right target—the causative agent and most validated and compelling therapeutic target for AD. Two drugs with promising results in Phase II and III clinical trials, BAN2401 and aducanumab, respectively, target AßOs, among other Aß conformers.

Many drugs that fail in clinical trials because of low or no efficacy are directed against targets in the Aß pathway that do not cause neuronal toxicity and AD, such as Aß plaque, fibrillar Aß, and monomeric Aß. In some cases, drugs demonstrate a low level of activity against AßOs but no efficacy in clinical trials because of off-target distraction. That is, they also attack other, nontoxic targets, leading to ineffective AßO targeting and efficacy failure. The wrong target can also cause safety failures. Drugs that target Aß plaque may cause serious adverse effects (AEs), notably amyloid-related imaging abnormalities-edema (ARIA-E), and fail because of unacceptable AE profiles.

New drug candidates selectively targeting soluble AßOs are now in development and expected to demonstrate greater efficacy and improved AE profiles compared to first-generation Aß-based drugs. To date, small companies and research institutions are leading the way. Challenges range from the technical (e.g., AßOs are found in small quantities and are difficult to isolate) to business (e.g., high-cost failures have had a discouraging effect on R&D funding of new, novel drugs for AD).

Biopharma industry must pursue soluble AβO-based drug R&D

It has long been clear that very strong scientific evidence supports a causal role for the Aß pathway in AD. There are no plausible alternative hypotheses to the genetic evidence showing that APP, PSEN1, and PSEN2 mutations cause production of Aß plaques and familial

Alzheimer's disease and early-onset Alzheimer's disease in virtually all carriers. A large body of additional scientific and clinical data supports the role of Aß in sporadic AD.

Discoveries of other factors associated with AD, including viruses, bacteria, metals, medical conditions, and others, are sometimes presented as alternative explanations for the disease. But, rather than contradict the Aß hypothesis, they fit into it as risk factors that may regulate expression of AD risk genes and Aß processing genes. Any alternative hypothesis of AD pathogenesis would need to account for Aß pathway activation and the cytotoxicity, pathology, and disease progression findings consistent with the natural history of AD.

"Which specific Aß pathway product/species is the neurotoxic, causative agent in AD?" was the burning issue in the 1990s after Aß plaque was found to be not toxic (or minimally neurotoxic) and incapable of causing the massive neuronal cell death found in AD. Soluble AßOs were identified as the neurotoxic Aß species and causative agent; and the Aß hypothesis was revised by 2002. The revision had two critically important implications for AD drug developers: targeting Aß plaque would not be effective; and drug R&D must shift to targeting AßOs. It is striking to observe that, more than 15 years after the Aß hypothesis was revised, none of the anti-Aß monoclonal antibody (mAb) drugs tested in Phase II or III clinical trials was designed or optimized to selectively target soluble AßOs. And funding of internal or external R&D programs based on AßO targeting have not been announced by mid-sized or large biopharma companies. Figure 1 shows that Aß target specificities can predict efficacy and adverse effects.

The absence in late-stage clinical trials of any drug candidate selectively targeting AßOs is explained, in part, by delays caused by initial R&D efforts in pursuit of the wrong target (Aß plaque) and the years required to pursue new R&D targets from discovery through regulatory approval. The failure to invest in AßO-targeted R&D, however, is the most important factor. As a result, drugs that have reached Phase II or III clinical trials were discovered in the 1990s or early 2000s. None selectively targets AßOs, but aducanumab and BAN2410 demonstrate significant binding to AßO, among other Aß conformers.

It is the continued failure of biopharma industry to embrace and invest in AßO-based drug R&D programs that is more surprising. Reasons include companies are awaiting completion of Phase III trials, the recent trend to treat very early AD has caused uncertainty in the clinical development paradigm, AßOs have been a technically challenging target, and lack of understanding of mechanisms underlying AßO toxicity. AßOs, formed by Aß protein misfolding, act as Aß seeds for propagation of toxic structures via a corruptive protein templating mechanism. This prion-like propagation and spread of toxic AßO is consistent with patterns of insoluble Aß deposition and the role of soluble AßO as the causative agent in AD. Recent research has proved the transfer of amyloid pathology between humans through proteopathic Aß seeds present in surgically transferred material. These findings demonstrate how soluble AßOs, which are present in the brain in small quantities, cause Aß amyloidosis and AD.

Exhibit: specific Aβ targets of monoclonal antibodies explain failure and success in AD

mAb therapeutic		Aβ Conformations Recognized				Status
	Isotype	Monomer	Oligomer	Fibril	ARIA-E	
Bapineuzumab	IgG1	Yes	Yes	Yes	High	Discontinued; severe AEs
Solanezumab	IgG1	High	Weak	No	Low	Ph3; possible weak cognitive benefit in retrospective subset; monomer distraction
Gantenerumab	IgG1	Weak	Yes	Yes	High	Ph3 (very early AD); possible cognitive benefit; AEs may limit
Crenezumab	IgG4	Yes	Yes	Yes	Low	Ph3 halted after no benefit in interim analysis
Ponezumab	IgG2	Yes	No	No	None	Discontinued; no cognitive benefit
BAN2401	IgG1	Weak	Yes	Yes	Low	Ph2; cognitive benefit and dose response
Aducanumab	IgG1	No	Yes	Yes	High	Ph3; cognitive benefit and dose response; AEs may limit
PMN310	IgG4	No	Yes	No	?	Preclinical; see text

Source: adapted from van Dyck 2018 and modified.

Notes:
- Aβ monomers are non-toxic. High levels of monomer binding may occur at the expense of AβO binding and reduce efficacy (off-target distraction).
- Fibrillar Aβ/ plaque is non-toxic (off-target distraction) and also can contribute to severe amyloid-related imaging abnormalities-edema (ARIA-E) and ARIA-hemorrhage (ARIA-H) adverse effects.
- Oligomers, specifically LMW AβOs, are the causative agent in AD and desired target.
- IgG isotype of mAb therapeutics: IgG4 antibodies appear to be safer than IgG1 antibodies with regard to potential to cause vasogenic edema/ ARIA adverse effects.

PMN310: A highly selective anti-AβO mAb

ProMIS Neurosciences has developed a platform for discovery of highly selective mAbs that target misfolded toxic oligomers. The platform is based on visualization technology for prediction of epitopes (both target sequence and

conformation) that are inaccessible by other techniques, followed by generation and characterization of antibodies. Drug candidates are selected based on selectivity of binding profiles and in vitro and in vivo tests of functionality. In AD, the ProMIS platform targeted epitopes displayed on toxic AßOs but not on other forms of Aß (monomer, plaque, and protofibrils). The company's lead drug, PMN310, is a mAb with greater selectivity for AßOs than aducanumab (Phase III) and BAN2401 (Phase II), which are the most developmentally advanced mAbs that significantly target AßOs. Neither aducanumab nor BAN2401 was designed or optimized to selectively target AßOs, and both bind to other Aß species.

In preclinical efficacy studies, PMN310 demonstrated greater therapeutic potency than aducanumab and BAN2401, CNS penetrance equal to that reported for aducanumab and no off-target monomer binding (i.e., no potential for off-target distraction). Findings from preclinical safety were positive. PMN310 did not bind to Aß plaque in AD brain tissues, unlike aducanumab and BAN2401, which demonstrated binding to Aß plaque (fibrils) in the brain and blood vessels. These findings suggest the potential for a restricted maximum dose and ARIA-E adverse effects with these two drugs. [In fact, the maximum dose of aducanumab has already been restricted because of the potential for ARIA-E adverse effects.] In addition, PMN310 is based on an IgG4 antibody isotype, which carries no known ARIA-E risk factor. BAN2401 and aducanumab are based on IgG1 antibody isotype, which increases the risk of causing ARIA-E AEs. Based on all comparative studies, to date, PMN310 demonstrates the potential to become the best-in-class, selective AßO-targeted therapeutic for safe and effective treatment of AD.

IND enabling development work is underway to prepare PMN310 for an initial Phase I, ascending dose clinical trial, with initial clinical results reporting by the end of 2020. GEN

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