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Developing a new generation of Alzheimer's disease treatments

Probiodrug is using a multi-pronged approach to reduce brain levels of pyroglutamate–amyloid-β peptides; results from the SAPHIR IIa trial for the company's lead candidate PQ912 reveal positive early efficacy data that are highly attractive for further development.

Alzheimer's disease is the most common cause of dementia in older adults; it affects millions of people worldwide, and this number is expected to rise dramatically owing to increases in life expectancy. Despite the prevalence of this disease, currently available drugs treat only the symptoms and do not halt the progression of the disease or provide sustainable improvement. These treatments produce only modest and transient positive effects on cognitive functions and activities of daily living, and they may have side effects.

The prevailing scientific view today is that it is not the plaques but soluble Aβ aggregates, known as Aβ oligomers, that cause the early pathological changes in Alzheimer's disease. Recent research has shown that the formation of highly synapto-/neurotoxic soluble Aβ oligomers is triggered by a specific form of Aβ called pyroglutamate-Aβ (pGlu-Aβ)[1].

Probiodrug's focus is on blocking pGlu-Aβ via two complementary modes of action (**Fig. 1**): the use of PQ912 to reduce the production of pGlu-Aβ through inhibition of the pGlu-Aβ-forming enzyme glutaminylcyclase (QC), and clearance of existing pGlu-Aβ from the brain by means of a highly specific pGlu-Aβ-binding monoclonal antibody (PBD-C06).

"We have identified a new therapeutic concept linked to disease initiation and progression," said Konrad Glund, CEO of Probiodrug. "We look forward to working with partners to further develop our product candidates as a new class of therapeutic solutions for Alzheimer's disease and other neurodegenerative disorders. Clinical setbacks with anti-Aβ solanezumab and the BACE inhibitor verubecestat highlight the importance of tackling the more toxic forms of Aβ, such as pGlu-Aβ."

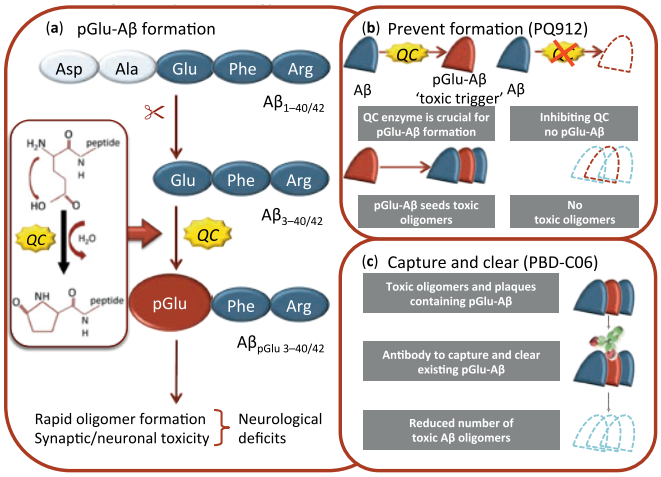

Figure 1: Strategies to treat Alzheimer's disease. (**a**) Full-length Aβ (Aβ 1–40/42) is truncated by the two amino acids. Glutamate (Glu) is then accessible to glutaminyl cyclase (QC) and, the enzyme forms pyroglutamate (pGlu), thereby changing the physicochemical properties of the Aβ molecule and triggering the pathophysiological changes described. (**b**) QC modifies Aβ to pGlu-Aβ; an enzyme inhibitor (PQ912) blocks this reaction and thereby prevents the cascade of formation of synaptotoxic oligomers. (**c**) A pGlu-Aβ-specific monoclonal antibody (PBD-C06) binds with high specificity to existing pGlu-Aβ and promotes its clearance, thereby reducing or eliminating neurotoxicity.

PQ912: a QC inhibitor in phase 2

PQ912 is a first-in-class, highly specific and potent QC inhibitor that has shown therapeutic effects in animal models of Alzheimer's disease[2]. In a phase 1 study with healthy volunteers, both young and elderly, PQ912 was shown to be safe and well tolerated; the results revealed dose-dependent brain exposure reaching high QC inhibition as measured in the spinal fluid[3].

PQ912 was evaluated in a phase 2a randomized, double-blind, multi-center trial (the SAPHIR study) that included 120 patients with early Alzheimer's disease treated for three months with a dose of 800 mg BID. The results showed that PQ912 was safe; adverse events affecting the skin and gastrointestinal organ system were observed at a higher frequency in the PQ912 arm than in the placebo group and occurred in the majority of patients in the first half of the treatment period.

With respect to the secondary exploratory endpoints, PQ912 showed a very strong target engagement of 92% QC inhibition, significant cognitive improvements in working memory in the 'one card back' test, and a clear trend on psychomotor speed in the detection test. At the functional level, a very significant positive effect was found on the EEG theta power. Regarding exploratory biomarkers in the spinal fluid, encouraging positive results were obtained on synaptic and inflammatory cerebrospinal markers.

"In summary, the positive effects on secondary exploratory efficacy markers strongly support the hypothesis of pGlu-Aβ being a synaptotoxic Aβ variant, and with this, the therapeutic concept pursued by Probiodrug," said Inge Lues, Probiodrug's CDO. "Future studies will evaluate different doses and longer treatment durations. The study revealed a positive benefit–risk ratio of PQ912 and provides important guidance on how to move forward in the development of PQ912 as a disease-modifying drug for Alzheimer's disease. Altogether, the results make the program highly attractive for further development."

Complementary approach

As a complementary mode of action, the company is also developing PBD-C06, which targets pGlu-Aβ and selectively enhances its clearance while leaving nontoxic forms of Aβ untouched[4]. A comprehensive preclinical target-validation package has been established. The antibody has entered upstream chemistry, manufacturing and control (CMC) development. In addition, animal studies have shown that the combination of PQ912 and PBD-C06 results in additive effects that reduce levels of pGlu-Aβ and total Aβ in the brain.

1. Nussbaum, J.M. *et al. Nature* **485**, 651–655 (2012).
2. Hoffmann, T. *et al. J. Pharmacol. Exp. Ther.* **362**, 119–130 (2017).
3. Lues, I. *et al. Alzheimers Dement. (NY)* **1**, 182–195 (2015).
4. Piechotta, A. *et al. J. Biol. Chem.* **292**, 12713–12724 (2017).

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