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GUEST EDITORIAL

Alzheimer's disease: where next for anti-amyloid therapies?

The recent failures of the solanezumab Expedition 3 and the verubecestat phase II/III trials to significantly slow disease progression in mild or mild-to-moderate Alzheimer's disease are considerable disappointments. They are causing soul searching in the field: are we on the right track and what do we need to do to get effective mechanistic therapies? While there have been previous trial failures of anti-amyloid therapies, most of these had clear problems during their preclinical development, which perhaps should have allowed their failure to be foreseen (Karran and Hardy, 2014). The solanezumab trial, in contrast, had been approached with cautious optimism in the light of the marginally positive data on clinical slowing in mild disease in secondary analyses of the earlier Expedition and Expedition 2 trials (Doody *et al.*, 2014). Verubecestat appeared to be a safe and effective BACE-1 inhibitor (Kennedy *et al.*, 2016) allowing effective amyloid-β lowering in the CNS. Thus both approaches appeared to have overcome most of the shortcomings encountered in previous trials although the fact that biomarker confirmation of Alzheimer pathology was not required in the verubecestat trial was a clear shortcoming. In addition, the two approaches are complementary as they hit the amyloid-β peptide from either the clearance side (solanezumab) or from the production side (verubecestat). Thus, these were two serious tests of the amyloid hypothesis, and, in practical clinical terms, both turned out negative.

With the repetitive failing of trials, it is time to reconsider the 25-year-old amyloid cascade hypothesis (Selkoe and Hardy, 2016) and the clinical equivalent data summarized in the 'Jack curves' (Jack and Holtzman, 2013). Both imply a linear relationship between the amyloid-β pathology and neuronal cell death and dementia. Dementia is, however, the clinical manifestation of a much more complex process not only involving neurons, but also strong other cellular reactions from microglia, astroglia, oligodendrocytes and vasculature. Dementia may not be a direct consequence of amyloid-β toxicity but instead as the result of a decade long disease process called the 'cellular phase' of Alzheimer's disease (De Strooper and Karran, 2016). Genetic evidence for this complexity comes from the identification of microglial response genes as risk loci for Alzheimer's disease (Matarin *et al.*, 2015).

At a theoretical level, the negative outcome of anti-amyloid therapy was not excluded, even without putting the causal contribution of amyloid-β to Alzheimer's disease into question (Karran *et al.*, 2011). In one disease scenario, amyloid-β was proposed as a driver of the disease process. If this would be the case, any lowering of amyloid-β would slow disease progression. This possibility is ruled out by the failed clinical trials. In another scenario (Karran *et al.*, 2011), amyloid-β has to reach a certain threshold to cause harm. If amyloid-β therapy is not able to lower the amyloid-β level in the brain below that threshold, then no beneficial effects of anti-amyloid drugs would be expected. In the third scenario, amyloid-β is proposed to be only a trigger of the disease process (Karran *et al.*, 2011). If this is the case, then amyloid-β directed drugs would have no effect at all after the disease process has been initiated. It looks like the failed trials are consistent with both the threshold and the trigger scenarios. The alternative possibility that amyloid-β is an entirely innocent bystander of the disease process is unlikely as it is not reconcilable with genetic evidence that mutations in APP are sufficient to cause Alzheimer's disease.

More detailed analysis of the solenezumab trial data is possible because they were made entirely available by Eli-Lilly. ADAS-Cog scores showed tiny improvements, in the same direction as the trends in the earlier solanezumab trials (Siemers *et al.*, 2016). For example, in mild Alzheimer's disease, the improvement in ADAS-Cog over 80 weeks on drug was 44% in Expedition, 20% in Expedition 2 but only 11% in Expedition 3 ($P = 0.095$). These data overall may suggest some small influence of amyloid-β lowering on disease progression. We have to wait until all data from the verubecestat trail are made

available to see whether a similar weak positive signal was captured there.

What do the results mean for other amyloid-β antibody approaches? The next up is aducanumab. This targets plaque rather than soluble amyloid-β and has been shown to remove plaques in imaging studies (Sevigny *et al.*, 2016). This is indeed an interesting approach. However, although there is a sense of optimism about this, a potential concern is that bapineuzumab also partially cleared plaques, albeit in the context of amyloid-related imaging abnormalities, without evidence for clinical utility (Holmes *et al.*, 2008). This imperfect precedent argues that simple clearance is not the answer. Also, much has been made of the correlation between plaque reduction and improved cognitive function in this trial, but this is a little puzzling because it is well established that plaque load does not correlate with cognitive performance during disease development so it is surprising that it should correlate with plaque removal. We should be cautious about repeating our excitement over Phase 1 trial data.

What does this mean for therapeutic approaches targeting earlier stages of the amyloid-β cascade, particularly BACE inhibition? BACE inhibitors have the considerable advantage over antibodies in being relatively inexpensive and in having clear and simple endpoints. Human genetic data suggest that life-long BACE inhibition should protect against the disease (Jonsson *et al.*, 2012), although this hypothesis needs further confirmation both at the functional and the genetic level (De Strooper and Voet, 2012). The crucial question, then, is at what stage would BACE inhibition have clinical efficacy? Even at the stage of early clinical disease, the disease process is fairly advanced and plaque load is near saturation. The verubescestat data, optimistically interpreted, suggest that at this stage reduction of amyloid-β production comes too late, but that, taking the trigger hypothesis into account, an earlier intervention could still be effective. While the ethical and practical difficulties of preclinical treatment are clear, they are not insuperable, even in 'sporadic' disease (Escott-Price *et al.*, 2015).

What about other therapeutic approaches? The amyloid hypothesis has ruled supreme for 25 years, but the Jack curves make clear the long period from amyloid deposition to clinical symptoms. The clinical data suggest that the linear relationship between amyloid-β and dementia is not tenable. Instead, during this long prodromal period (the cellular phase) (De Strooper and Karran, 2016), many other processes are underway, these include the microglial response to amyloid deposition and, at least partly independently of amyloid deposition, tau pathology spread (Walker *et al.*, 2013). These processes are now in the spotlight and it will become hard to obtain further investments in anti-amyloid therapies unless the ongoing trials in preclinical Alzheimer's disease show a positive signal.

Four final points are worth making. First, while it has been fashionable to argue that transgenic mouse work has misled the field, a close analysis in fact reveals that the animal data have been accurate in predicting the outcome of treatment strategies: solanuzumab did not clear established plaques in the clinical trial and it did not do so in transgenic mice either (De Mattos *et al.*, 2001). BACE inhibitors had been shown to slow plaque development but had not been shown to clear existing plaques (Hyde *et al.*, 2012). Second, the simple idea expressed as 'amyloid loads the gun and tau pulls the trigger' is unsustainable (Karran *et al.*, 2011). It is difficult to imagine how, in the initial phases of the disease, amyloid-β and tau would interact biochemically, and subsequently become independent from each other (Small and Duff, 2008). Rather, one should think of amyloid-β pathology, once established, as pushing tau pathology indirectly, for instance by altering synaptic activity. Third, it might be interesting, considering the threshold hypothesis, to think about combination therapies, with BACE inhibitors blocking the generation of amyloid-β and antibodies like aducanuzumab to clear existing amyloid-β plaques. Fourth, with the solanezumab trial and the release of the data, Eli Lilly have done the field an enormous service and this has to be the model for future trials. Merck will hopefully do the same in the near future for the verubecestat data.

Systematic and open data analysis at all stages of disease investigation will be key if we want to make progress. Failed trials have value as long as they are taken as lessons to learn from and to improve our concepts and theories.

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