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Editorial Open Access

The Success of Solanezumab Should Drive Renewed Efforts to Develop Small Molecule Anti-Amyloid Agents for Alzheimer's disease Therapy

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It was announced at the recent Alzheimer's Association International Conference (AAIC), Washington, that solanezumab, an anti-amyloid beta peptide Monoclonal Antibody (mAb) developed by Eli Lily, revealed limited efficacy in phase III clinical trials of Alzheimer's disease (AD) patients [1]. Initial analysis of the trial outcome with this mAb had revealed that the treatment was ineffective at preventing cognitive decline in AD patients. However, further examination of the data revealed that there was a modest decline in loss of cognitive performance in patients with mild AD when treated with solanezumab. This effectively meant that the anti-amyloid mAb was able to slow the loss of memory that is characteristic of AD, but only in patients with mild disease symptoms. The original trial was extended and patients with mild AD that had not previously received the mAb (placebo patients) were subsequently treated with solanezumab. It was revealed at AAIC that patients who began treatment with solanezumab in the extension trial showed improvement at the same rate as those originally on solanezumab but did not reach the same level of protection (due to the shorter treatment time). This has been interpreted as evidence of a disease-modifying effect of solanezumab rather than a symptomatic treatment, in which case patients treated later should have 'caught up' to those started earlier. Whether this turns out to be the case will be dependent on further trials.

In support of the result are outcomes of another anti-amyloid mAb clinical trial involving aducanumab, developed by Biogen, which has similarly shown inhibition of cognitive decline in mild AD patients [1]. While a great deal of analysis and testing is still required, especially after the early failures of immunotherapy for AD, the results provide a glimmer of hope that anti-amyloid strategies may be effective, at least partially, and especially if started early (something that is likely to improve as the sensitivity and precision of cognition and amyloid measurements continues to evolve).

This outcome really should provide a great impetus to pursue small molecule anti-amyloid drug therapies. Even if mAb approaches are successful, there are still many drawbacks to these therapeutics including high cost of antibody production, method of delivery (regular intravenous injection), and immune-associated adverse outcomes including meningo-encephalitis and vasogenic edema. Small molecule drugs targeting amyloid can help to overcome many of these issues and the research in this field should now be able to accelerate in the knowledge that there is at least one therapeutic in the pipeline that has provided clinical evidence that this is a practical approach for AD treatment.

Anti-amyloid approaches may include small molecules that inhibit amyloid formation, enhance amyloid disaggregation, chelate or bind to metals that drive amyloid aggregation, or up-regulate amyloid clearance and/or degeneration e.g. by removal across the blood brain barrier, increased production of anti-amyloid enzymes such as matrix metalloproteases, or removal by brain macrophages [2]. Some of these approaches may even enhance the removal of amyloid by mAbs through stimulation of the neuro-immune system to remove antibody tagged amyloid.

In driving these efforts forward, researchers should be encouraged to bring together teams of scientists with knowledge of medicinal chemistry, cell biology, neuro-immune function, AD animal biology and behavior, and clinical/translational science. We should be aiming to move beyond simply designing compounds that modify synthetic amyloid aggregation *in vivo*, with the view that we now know that this is a valid approach. We need to focus on testing compounds in more relevant systems such as the 3D neural stem cell model reported by Choi et al. in Nature last year [3]. This model uses neural stem cells transfected to over-express human amyloid into a 3D Matrigel environment. The authors reported appearance of 'amyloid-like' structures surrounding the cells, providing an exciting new system to test anti-amyloid compounds in a cell model that more accurately reflects in vivo amyloid accumulation. Success in such an environment is likely to provide greater translational impact in AD animal studies and subsequently clinical trials.

It seems that the tools and innovative ideas are perhaps falling into place to accelerate development of small molecule anti-amyloid compounds. With renewed excitement and possibilities in this field it is hoped that we can bring a small molecule anti-amyloid to the clinic for AD in the near future. Such an achievement would be a revolutionary step forward for AD therapy.

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