

Therapy focus - Early beginnings for Alzheimer's vaccines



[Joanne Fagg](#)

The unrelenting series of failures of numerous antibodies against Alzheimer's disease has not deterred biopharma, as shown most recently by Roche starting new phase III trials of crenezumab and gantenerumab in prodromal or mild disease.

But it is a separate approach - Alzheimer's vaccines - that represents the next frontier of research, and one in which crenezumab's originator, AC Immune, is particularly active. As with MABs the premise is to start treatment very early, and while the most advanced asset will not yield data until after 2020 several earlier trials could report in the next two years (see table below).

Of course, risk of failure is still high; most Alzheimer's vaccines target beta-amyloid, though two in the clinic attempt to hit tau, a downstream product of beta-amyloid toxicity. The MAB approach has consistently failed to support the utility of targeting beta-amyloid as an Alzheimer's treatment.

Dismal past

Most recently Lilly saw yet another failure for solanezumab in November, this time in mild patients, while a trial of Merck & Co's Bace inhibitor verubecestat, which also aimed to reduce amyloid levels in the brain, was stopped for futility ([Verubecestat halt fails to stop the Bace chase, February 15, 2017](#)).

Vaccine developers will hope that the problem lies not in the underlying beta-amyloid hypothesis, but in the way that deposits of these peptides have been targeted. The vaccine approach aims to raise an immune system response against beta-amyloid or tau.

The most advanced vaccine, Novartis's CAD106, is recruiting into Generation, a phase II/III trial in 1,340 healthy individuals at risk of the onset of clinical symptoms of Alzheimer's. Participants have to carry two ApoE4 genes, a genetic risk factor for Alzheimer's - this homozygous genotype occurs in nearly [19%](#) of familial late-onset Alzheimer's patients.

Generation is part of the [Alzheimer's Prevention Initiative](#) led by the Banner Alzheimer's institute. The primary measures are time until diagnosis of mild cognitive impairment or dementia due to Alzheimer's, and change in cognitive score through study completion, which is unlikely before 2023.

In [phase IIb](#) CAD106 induced strong serological responses in 55.1% of patients on a 150µg dose, and 81.1% with 450µg, though 24.5% of patients on active drug had serious adverse events versus 6.7% in the placebo group. Three of the 26 serious adverse events in the CAD106 total group were classified as possibly drug-related.

Beta-amyloid-specific

CAD106 targets a small fragment of beta-amyloid and is conjugated to a carrier, aiming to stimulate a beta-amyloid-specific antibody response while [avoiding T-cell autoimmune responses](#).

This inflammatory response was the downfall for the first Alzheimer's vaccine - Elan's AN-1792, whose development was suspended when 6% of patients developed signs of aseptic meningoencephalitis. It was suspected that the choice of adjuvant, QS-21, alongside the use of a full-length beta-amyloid peptide that activates B and T-cell responses, was to blame.

Grifols and Araclon Biotech's ABvac40 also targets beta-amyloid, comprising multiple repeats of a short C-terminal fragment of the 40-peptide form Aβ40. Different forms of amyloid beta exist owing to [enzyme cleavage of its precursor protein](#), and those ending at position 40 are the most abundant, but the slightly longer 42 peptide version is the main type deposited in the brain.

In a [phase I](#) trial that read out last August, 11 of 12 mild to moderate Alzheimer's patients who received three ABvac40 injections generated antibody titres. The vaccine was associated with injection site swelling, headache and erythema, but there was no vasogenic oedema or microhemorrhage; the phase II study has

been under way since 2015, with phase III planned for this year.

The companies' second offering, ABvac42, targets the beta-amyloid 42 protein, but is at an earlier stage of development, with phase II expected to start this year.

Selected clinical-stage Alzheimer's disease vaccines

Project	Company	Construct*	Disease stage	Trial ID	Primary completion
<i>Phase II/III</i>					
CAD106	Novartis	Multiple copies of A β 1-6 peptide derived from N-terminal B-cell epitope of A β , coupled to a Q β virus-like particle	Healthy adults aged 60 to 75, with two copies of APOE4 allele	2015-002715-15 NCT02565511	2023
<i>Phase II</i>					
ABvac40	Grifols/Araclon Biotech	Multiple repeats of a short C-terminal fragment of A β 40, conjugated to keyhole limpet cyanine carrier protein and formulated with alum hydroxide adjuvant	Mild to moderate	?	?
ACI-24	AC Immune	Array of A β 1-15 sequences, sandwiched between palmitoylated lysines at either end; uses lipid adjuvant MPLA	Mild to moderate	2008-006257-40 (PhI/II) NCT02738450 (PhI)	2019 (PhI)
UB-311	United Neuroscience/United Biomedical	Couples helper T-cell epitope designed with United Biomedical's UBITH platform to the A β 1-14 sequence, packaged in proprietary delivery system.	Mild	NCT02551809	2017
AADvac1**	Axon Neuroscience	Synthetic peptide derived from amino acids 294 to 305 of tau sequence, coupled to keyhole limpet hemocyanin; uses aluminum hydroxide adjuvant	Mild	NCT02579252	2019
<i>Phase I</i>					
ACI-35**	Johnson & Johnson/AC Immune	Contains 16 copies of synthetic tau fragment phosphorylated at pathological phosphorylation residues and anchored into a lipid bilayer; uses MPLA adjuvant	Mild to moderate	2013-000803-18	2017
Lu AF20513	Lundbeck/Otsuka Holdings	Intersperses three repeats of the first 12 amino acids of the A β peptide with sequences of tetanus toxin.	Mild	NCT02388152	2017
ABvac42	Grifols/Araclon Biotech	Multiple repeats of a short C-terminal fragment of A β 42	?	?	?

*Note: *sourced from www.alzforum.org; **anti-tau vaccine; all others are beta-amyloid vaccines.*

Lundbeck/Otsuka's Lu AF20513 is further behind, being due to complete its phase I trial in May, according to clinicaltrials.gov. Three different doses are being tested, with safety, tolerability and antibody titre measured over two years.

This vaccine consists of repeats of the first 12 amino acids of beta-amyloid with sequences of tetanus toxin. The aim is to stimulate an elderly population of non-self memory T cells originally generated by childhood tetanus vaccinations to stimulate T helper cells, which in turn activate a B-cell response to produce antibodies against beta-amyloid.

Tau to tangle

Meanwhile, as the amyloid hypothesis continues to come under scrutiny work on tau could become more prominent. Excessive or abnormal phosphorylation of tau, which is said to be a [downstream product of amyloid-beta toxicity](#), leads to neurofibrillary tangles.

There are two tau vaccines in clinical development: Axon Neuroscience's AADvac1 and Johnson & Johnson/AC Immune's ACI-35. At the end of last year [phase I results](#) showed 29 of 30 patients given AADvac1 developing an immune response, with no brain inflammation or vasogenic oedema, though two patients withdrew owing to undisclosed serious adverse events.

The vaccine is a peptide derived from certain amino acids of the tau sequence, and the aim is to trigger antibodies to prevent the tau protein from aggregating, and to facilitate the removal of aggregates. Its phase II Adamant study has recruited 44 out of 185 patients with mild disease, and is expected to read out in 2019.

AC Immune's ACI-35 aims to elicit an immune response specifically to phosphorylated tau without also causing an autoimmune B or T-cell response, but the company's other Alzheimer's vaccine, ACI-24, which targets beta-amyloid, is more advanced.

ACI-24 is in a phase Ib study in mild to moderate disease comparing three doses over six months in 24 patients, versus placebo. Participants are also given a booster injection, and primary measures include safety and immunogenicity with MRI and cerebrospinal measurements. The primary completion date is June.

The years ahead

In addition to this and the Lundbeck/Otsuka asset, 2017 could also see initial safety data from UB-311, a project in development by United Biomedical and its spin-out company United Neuroscience. All will be hoping to avoid the adverse events seen with Elan's AN1792.

Developers will also be keen to overcome the dismal reputation that has followed cancer vaccines. That said, there are key differences in the immune responses triggered against pathogens or tumour cells, and those against self-antigens such as amyloid-beta.

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