Looking outside amyloid in Alzheimer’s disease

Madeleine Armstrong

The amyloid hypothesis of Alzheimer's has taken another battering - and some companies are finally taking a new approach.

The amyloid hypothesis behind Alzheimer’s disease has been battered again this week with data on Biogen/Eisai’s BAN2401 turning out to be far from emphatic. New approaches are needed, but they have so far been hard to come by.

Things could be changing, with three novel candidates joining the fray in the past few days (see table below). The projects, from Biohaven and a little-known private player, Alector, still have a long way to go, but at least they could be a sign that companies are finally willing to try something different.

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Source: Company communications.

The most advanced of the trio is Biohaven’s glutamate modulator trigriluzole. This project is about to start a phase II/III trial that the company hopes could be used for a regulatory filing.

Trigriluzole aims to tackle elevated levels of glutamate in the synapses between neurons. This excitatory neurotransmitter is needed for normal nerve cell function, but too much can lead to overstimulation and neuronal death.

Targeting glutamate in Alzheimer’s is not new: the NMDA glutamate receptor antagonist memantine has been available as a symptomatic therapy since the early 2000s.

Glutamate vacuum
According to Biohaven’s chief medical officer, Robert Berman, memantine is like a hammer, whereas trigriluzole is more subtle approach that “vacuums” out some of the excess glutamate, restoring levels to normal.

No other glutamate modulators appear to be in active development for Alzheimer’s. Trigriluzole is a prodrug of riluzole, which is approved for amyotrophic lateral sclerosis; an investigator-sponsored study of the latter in Alzheimer’s is ongoing, but Mr Berman believes that trigriluzole could have improved pharmacologic properties over the older drug.

And unlike riluzole, which has been available generically since 2013, trigriluzole is still patent-protected. Biohaven hopes that trigriluzole could be a disease-modifying treatment, as well as addressing Alzheimer’s symptoms. Neuronal death occurs early in the development of Alzheimer’s, “probably soon after the amyloid starts getting put into plaques”, Mr Berman told EP Vantage.

As for the amyloid hypothesis, he believes that this is still valid, but only partly explains the development of Alzheimer’s. He added that, eventually, the disease might be best treated with a cocktail of drugs, of which trigriluzole could be one ingredient: “The mechanism of trigriluzole would be complementary to any agent that’s in development.”

First the project has to succeed in a phase II/III placebo-controlled trial, which will enrol around 290 patients with mild to moderate Alzheimer’s. Mr Berman hopes that enrolment will take around six months, and the dosing period will be a year, so it will be at least 18 months before we know whether this approach is valid.

**Immu-no-neurology**

Meanwhile, San Francisco-based Alector, which just raised a $133m series E round, hopes to harness the immune system for brain diseases in a similar way to how this has been used in cancer immunotherapies; predictably, the company calls this approach “immuno-neurology”.

It is further behind in development, with two Alzheimer’s candidates set to hit the clinic late this year or early in 2019, and both aim to reactivate the microglia, immune cells in the brain that Alector’s chief executive, Arnon Rosenthal, describes as the organ’s “control centre”.

“The microglia collect the garbage and they also secrete growth factors that promote the formation and function of synaptic connection,” he told EP Vantage. “If the microglia shut down, pathological proteins accumulate, synaptic connections are destroyed and nerve cells die.”

Alector’s first candidate, AL002, aims to activate microglial cells by stimulating the TREM2 system, which Mr Rosenthal likened to pressing the accelerator in a car.

The group’s second Alzheimer’s asset, AL003, has the opposite effect, releasing the brakes on the microglia by inhibiting SIGLEC-3. This makes the project analogous to PD-(L)1 inhibitors in cancer. “But we’re doing it in the brain and it’s a different cell type – it’s part of the myeloid innate immune system instead of T cells,” Mr Rosenthal said.

According to the chief exec, no one else is close to going into the clinic with a similar approach, although larger companies including Biogen, Amgen and Roche have begun talking about this strategy.

Alector has its own big pharma partner, Abbvie, which has rights to opt in to development at the end of phase II.

Again, Alector believes that its candidates could be used in combination – either with each other or other disease-modifying drugs like the anti-amyloids.

After this week’s confusing data with BAN2401, getting an amyloid drug approved does not seem any closer. But work on novel targets shows that previous failures have not diminished the appetite for new Alzheimer’s therapies.