Sola setback spawns new Alzheimer’s work for Lilly

Despite widespread failures biopharma presses on in Alzheimer’s, with approaches including BACE and Tau inhibition.

Taking a $9bn valuation penalty for the failure of solanezumab was not enough to dissuade Lilly from investing more in Alzheimer’s disease research. Now a new clutch of candidates are working their way into the clinic, some reflecting lessons learned from numerous setbacks.

The Indiana-based group can claim five active phase I Alzheimer’s disease or dementia projects, one of the richer pipelines in big pharma – moreover, it is exploring at least one combination as a potentially more potent therapy for arresting the development of toxic amyloid plaques in the brain. Competitors might want to consider scouring early-stage drug developers for similar candidates, as Lilly appears to be first in at least two classes (see table below).

**First BACE**

After solanezumab’s final farewell it is easy to forget that Lilly has another late-stage Alzheimer’s catalyst approaching in the form of phase II/III data for the BACE inhibitor lanabecestat, on which it is collaborating with Astrazeneca.

The 2,200-patient Amaranth trial is due to read out next year. However, with Merck & Co having terminated phase III work for verubecestat because of futility, hopes are probably not high for the Astra-Lilly venture (Verubecestat halt fails to stop the Bace chase, February 15, 2017). A second Lilly BACE inhibitor, LY3202626, is in phase II, with data also due next year.

BACE inhibitors and beta amyloid antibodies alike work under the hypothesis that, by blocking the development of amyloid plaques, Alzheimer’s degeneration can be slowed. So far, this approach has not borne fruit – however, the laboratory work in amyloid beta has provided clues about promising new targets, with the more toxic forms of amyloid beta being identified.

To that end, Lilly has advanced new projects LY3002813 and MEDI1814 into phase I. These are antibodies blocking N3pG and amyloid beta 42 respectively.

**Toxic**

LY3002813 binds to a beta amyloid peptide known as pGlu-Abeta that is prominent in the plaques of Alzheimer’s disease patients. Likewise, the 42 amino acid amyloid beta peptide (Abeta 42) has been identified as a major component of plaques and is seen as a more toxic form than the more soluble Abeta 40, and thus provides a more promising target, which MEDI1814 – licensed from Astra for $30m up front – aims at.
Lilly's phase I Alzheimer's disease and dementia projects – and their rivals

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<th>Project</th>
<th>Pharmacology class</th>
<th>Competitors</th>
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<td>LY3002813</td>
<td>N3pG-A MAb</td>
<td>PQ912, PBD-C06 (Probiodrug)</td>
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<td>MEDI1814</td>
<td>Anti-beta-amyloid 42 MAb</td>
<td>DNA A 42 Vaccine (Vitruvian Biomedical)</td>
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<td>Tau MAb Research Program (LY3303560?)</td>
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<td>Selective BACE 1 Inhibitor Research Project</td>
<td>BACE 1 inhibitor</td>
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<td>D1 Potentiator Research Project</td>
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Source: EvaluatePharma, company presentation.

Lilly is fortunate that neither of these appears to have much competition for now. Probiodrug's PQ912 is a small-molecule inhibitor of the pGlu-Abeta pathway that has got as far as phase II, and the group also has a selective antibody against pGlu-Abeta called PBD-C06 that has yet to enter the clinic.

Meanwhile, projects targeting Abeta 42 are scarce; Texas-based Vitruvian Biomedical has conducted preclinical testing of a vaccine, although the latest news from that company has been the licensing in of an amyloid beta and tau vaccine.

One of the selling points of LY3002813 is its potential synergistic effect in combination with a BACE inhibitor, which Lilly claims has resulted in “near complete removal of pre-existing beta-amyloid” in preclinical models. To that end, a selective BACE 1 inhibitor is in phase I, according to Lilly’s third-quarter presentation, although the research code for the asset is not immediately clear.

**Tau are you doing?**

Following another hypothesis, that blocking tau tangles inside brain cells can slow disease progression, Lilly also claims to have a tau deposit antibody, although it did not identify a code for investors – presumably, this is LY3303560, as the group featured preclinical data on that project at the Alzheimer's Association International Meeting this year.

How this will differentiate itself from such projects as, for example, Bayer and Taurx Pharmaceuticals’s LMTX is not immediately clear (Time for tau – for now, May 26, 2017). However, after an amyloid-only chase Lilly has shown itself to be pursuing tau as a second option.

Finally, in the broader field of non-Alzheimer’s dementia, Lilly has a D1 potentiator, which also does not appear to have been identified with a research code. The field of D1 modulation is largely focused on Parkinson’s disease and other CNS disorders, and Lilly thinks that it might provide symptomatic relief by improving memory and other cognitive functions.

Of course, much of this discussion is academic if it turns out that impeding amyloid beta and tau accumulation in the brain is not the chief driver of the disease. If cleverer ways of addressing how these two molecules impair brain function emerge an answer could yet be found.

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