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Eli Lilly backs away from Bace but not from novel Alzheimer's targets



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The amyloid beta hypothesis persists in spite of repeated failure as biopharma refines targets and mechanisms of action.

Eli Lilly's ousting of two more early-stage Alzheimer's projects is at least a sign that the group has taken to heart the "fail faster" philosophy that could keep it from repeating the mistakes of the unsuccessful solanezumab programme.

However, termination of the Bace inhibition projects will not give comfort to those working under the belief that amyloid beta is the culprit in cognitive degeneration. Along with other big pharma and small biotechs, Lilly is forging ahead mostly following the amyloid-beta hypothesis, spiced with some new mechanisms and refined targets.

Let the Bace drop

Lilly dropped two projects, a selective Bace 1 inhibitor, thought to be LY3202626, and an N3PG/Bace combo, likely LY3202626 plus LY3002813. The company noted that its N3PG antibody LY3002813 will continue to be developed as a monotherapy. Lilly's decision to abandon its Bace could be seen as ominous for Eisai's elenbecestat and Novartis/Amgen's CNP520, which are also Bace inhibitors.

"The decision to drop Bace was based on a couple of factors," Lilly's chief scientific officer, Daniel Skovronsky, said during the company's third quarter earnings call. "One was what we've seen across the field with various Bace inhibitors, where these drugs don't have a benefit. And they actually cause some increased rate of cognitive worsening. With our particular Bace inhibitor, we did see some increases in psychiatric adverse events that gave us some pause, as well as changes on imaging, [such as] increased rate of brain shrinkage."

Death or glory: the Alzheimer's pipeline and graveyard

Mechanism of action	Still alive	Dead and buried
Anti-amyloid beta antibodies	Aducanumab, gantenerumab, crenezumab, MEDI1814 (anti-AB42 Mab)	Bapinezumab, solanezumab*, ponezumab
Bace inhibitors	Elenbecestat, CNP520	Lanabacestat, verubecestat, JNJ-54861911, Lilly Selective BACE 1 Inhibitor Research Project, LY3202626
Tau protein modulators	LY3303560, ABBV-8E12, BIIB092, LMTX	RG7345
N3pG amyloid beta inhibitor	LY3002813, PQ912	-
Amyloid beta vaccine	ACI-24, CAD106	-
*Still in investigator-led preventive trials.		

In the world of Bace, Lilly's projects were preceded by Johnson & Johnson's atabecestat (JNJ-54861911), Merck & Co's verubecestat, and lanabecestat, which Lilly was co-developing with Astrazeneca.

Of the Bace projects that are still in play, elenbecestat is currently in two phase III trials in early Alzheimer's patients due to read out in 2021. Novartis and Amgen have taken a more ambitious approach with their candidate, CNP520, testing it in those at risk for developing Alzheimer's disease, including people with Apo E4 mutations, as part of the Generation and Generation S2 trials ([Preventive Alzheimer's trials keep amyloid hope alive, April 26, 2018](#)).

The disappointing results with Bace inhibitors so far tend to cast as much doubt on the amyloid hypothesis as the failures of amyloid-blocking antibodies like Lilly's solanezumab, since the Bace inhibitors target a biological pathway involved in the production of amyloid beta.

Another try

Nonetheless, failures with both anti-amyloid antibodies and Bace inhibitors has not stopped work on amyloid-targeting compounds in Alzheimer's, with projects like Biogen's aducanumab designed to directly bind to the peptide in the brain plaques thought to impair cognition. It is therefore hoped to have a better therapeutic benefit than solanezumab, which targeted free-floating monomers of amyloid.

Lilly has bounced back in amyloid beta inhibition with the Astrazeneca-partnered MEDI1814, which targets amyloid beta 42, thought to be the most toxic form of the peptide. And, of course, solanezumab is not fully dead as long as the preventive trials Dian-Tu and A4 continue.

Another target within the amyloid beta space is pGlu-Abeta, which is involved in formation of toxic oligomers. Lilly's LY3002813 binds directly to pGlu-Abeta, and Probiobrug's PQ912 blocks an enzyme that converts amyloid beta into pGlu-Abeta.

Executives at the German company must have breathed a sigh of relief when they heard that LY3002813 was continuing as a monotherapy, since they have been watching Lilly's work with interest ([Interview - Probiobrug hopes to avoid Alzheimer's amyloid abyss, April 16, 2018](#)). Indeed, Probiobrug might have taken comfort in comments from Lilly executives: Mr Skovronsky said the antibody "shows, I think, deep and rapid clearance of amyloid plaque from the brain".

Outside of amyloid-beta targeting, Lilly has a card to play in tau targeting, with the antibody LY3303560 joining assets from Abbvie and Biogen. This space is looking just as risky as amyloid beta, however, as the role of tau tangles in Alzheimer's is not entirely clear. Nonetheless, should amyloid beta be jettisoned, tau will become biopharma's best hope for a drug to modify disease progression until basic research can further explain what causes cognitive decline.

