Evaluate Vantage

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Anti-amyloid approaches come back from the dead

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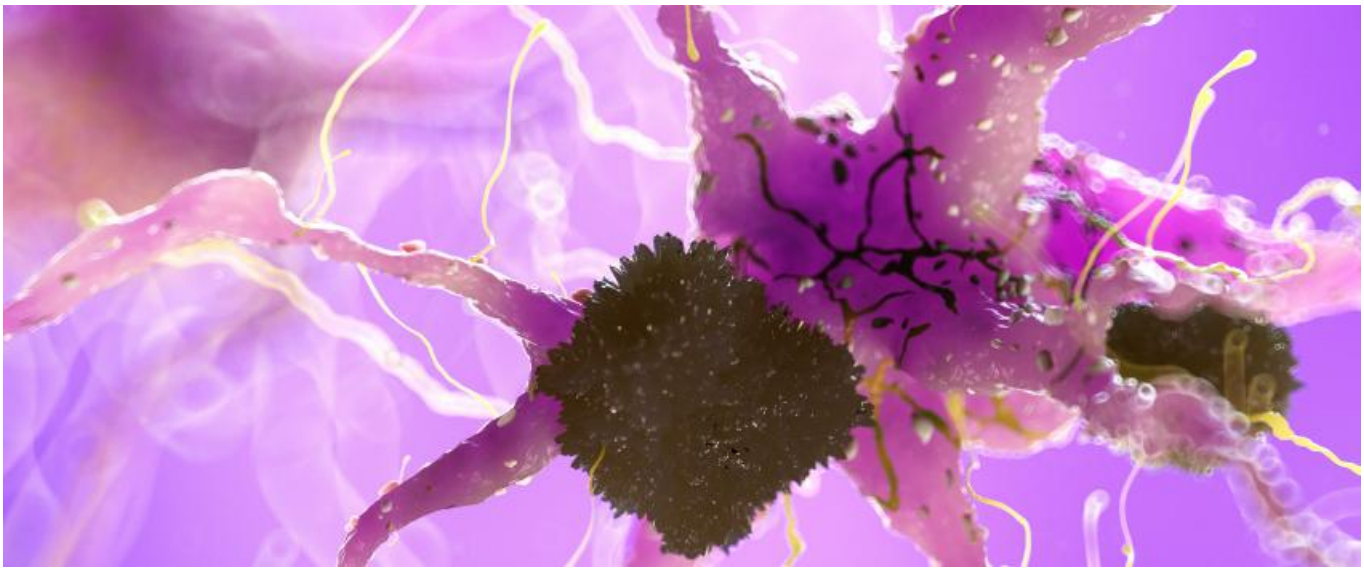

Lilly and Roche bask in the reflected glow of aducanumab's benign briefing documents.

With Halloween only a few days past, one drug class has just crawled out of the grave. Targeting beta-amyloid might be a legitimate approach in Alzheimer's again, following yesterday's favourable documents for Biogen's aducanumab.

At least this is what the markets seem to believe: Lilly, the company with the most beta-amyloid assets in development, climbed 13% yesterday, presumably on hopes that it could resurrect its lead Alzheimer's project, solanezumab. A look at the industry pipeline shows that it is not quite alone in keeping faith with this mechanism.

After the repeated failures of beta-amyloid antibodies, one hypothesis was that therapy had not been given early enough to prevent damage to the brain by toxic beta-amyloid. So many companies began testing their projects in ever earlier stages of disease.

Lilly has gone further than most – its current study of sola, called A4, is in older people with evidence of amyloid plaque build-up in their brains, but who do not yet have Alzheimer's.

Selected beta-amyloid MAbs in clinical development			
Prjectct	**Company**	**Disease setting**	**Note**
Filed			
Aducanumab	Biogen/Eisai	Early/mild	Pdufa Mar 7, 2021
Phase III			
BAN2401 (lecanemab)	Biogen/Eisai	Early	Clarity AD (NCT03887455) primary completion 2022
Gantenerumab	Roche	Early	Graduate 1 (NCT03443973) and 2 (NCT03444870), primary completion 2022
Solanezumab	Lilly	At-risk asymptomatic	A4 (NCT02008357), primary completion 2023
Phase II			
Donanemab (LY3002813)	Lilly	Early	Trailblazer-Alz (NCT03367403), primary completion Dec 2020
Crenezumab	Roche/AC Immune	Preclinical PSEN1 E280A mutation carriers	NCT01998841, primary completion 2022
Phase I			
RG6102 ("brain shuttle" gantenerumab)	Roche	Healthy volunteers	NCT04023994, completed Jul 2020
MEDI1814	Astrazeneca/Lilly	Mild-to-moderate	Ph1 completed in 2016 but still listed on Astra's pipeline
N3pG-Aβ mAb	Lilly	N/A	N/A
Source: EvaluatePharma.			

Still, focusing on an at-risk population did not help the Dian-Tu trial, which tested both sola and Roche's gantenerumab: the study was reported to have failed in February (*Another Alzheimer's failure for Biogen bulls to shrug off, February 10, 2020*).

Gantenerumab also has another shot in the Graduate 1 and 2 trials, which are enrolling 1,000 early Alzheimer's patients apiece and are set to complete in 2022.

But another test is coming sooner for Roche's antibody, with data due this year from the open-label part of the Scarlet Road trial in prodromal Alzheimer's. The trial was halted early in 2014 after failing to show a benefit at an interim look, but after a post-hoc analysis suggested a benefit at higher doses the study was converted to an open-label extension, with patients titrated up to 1,200mg.

Any signs of efficacy would be jumped on by markets now apparently convinced that amyloid is back. Roche also climbed yesterday, with its stock ending the day up 5%.

Similar but different

Still, the FDA briefing documents released yesterday, ahead of the aducanumab's advisory committee meeting on Friday, stress that the anti-beta-amyloid therapies "do not represent a single class of drugs", and that aducanumab has molecular properties that distinguish it from other candidates that have previously been tested.

Indeed, Biogen bulls have long pointed out the differences between aducanumab and the likes of sola and gantenerumab.

There are some slightly different amyloid-targeting approaches in earlier development. Roche, for example, has a "brain shuttle" formulation of gantenerumab, called RG6102, which is said to increase antibody concentrations in the brain.

Meanwhile, Lilly's N3pG antibody donanemab binds to pGlu-Abeta, which is involved in the formation of toxic oligomers. Lilly expects to report data from the phase II Trailblazer-Alz trial of this project early next year.

Lilly also has a next-generation N3pG antibody in phase I. During the group's recent third-quarter earnings call its chief scientific officer, Dan Skovronsky, said this had been designed not to trigger anti-drug antibodies, which are seen with donanemab.

Biogen, Lilly and Roche have kept plugging away with beta-amyloid, and Biogen could soon get its reward with a now widely expected approval for aducanumab. An FDA nod would give the amyloid hypothesis a shot in the arm.

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