Timmerman Report

Where Does Alzheimer's R&D Go Now? Plenty of Directions

By Luke Timmerman / October 9, 2017

Axovant Sciences had quite a yarn.

Boy wonder at hedge fund with exquisite timing sees potential Alzheimer's blockbuster where pharma graybeards didn't. The 29-year-old raises a $315 million truckload of IPO cash to revive drug candidate from the GSK scrap heap. The establishment scoffed that another old 5HT6 receptor antagonist would never be relevant. Who was right? The old guard or the brilliant newcomer?

This play crackled with tension for two years. But the protagonist of this story didn't find his pot of gold at the end of the rainbow. Axovant dug itself another ditch in the Alzheimer's drug development graveyard.

The expensive flameout of Axovant's 1,315-patient study of intepirdine, a 5HT6 receptor antagonist, in tandem with the acetylcholinesterase inhibitor donepezil (Aricept) begs a few questions:

What else does the industry have in the hopper? What other mechanisms are thought to have promise? How far away are we from a true disease-modifying therapy? Should we be optimistic?

Biogen's beta-amyloid clearing antibody, aducanumab, gets a lot of attention as a Phase III asset scheduled to provide data from the EMERGE study and ENGAGE study in 2019. We expect to wait on a similar timeline for Phase III results from the APECS trial of Merck's beta-secretase inhibitor (BACE) verubecestat for Prodromal (early-stage) forms of Alzheimer's. This drug has failed once in a Phase II/III study called EPOCH.

Plenty of rational outsider observers look at essentially a 100 percent failure rate and get discouraged. Not Steve Paul. He says there's a lot to like in the early-stage industry pipeline. He's the CEO of Voyager Therapeutics in Cambridge, Mass., a gene therapy company with a discovery-stage program for Alzheimer's. He's also the former head of R&D at Eli Lilly when it spent a lot of time and money advancing solanezumab as a beta-amyloid clearing antibody for Alzheimer's. It didn't work, but Paul the field is learning.


Steven Paul, CEO, Voyager Therapeutics

“I’m more optimistic than ever,” Paul said. “5HT6 was just not a compelling target. It’s marginal at best. It was wishful thinking. I learned a long time ago that wishful thinking in drug development isn’t a good thing.”

Paul is still bullish on the amyloid hypothesis, the idea that accumulation of misfolded amyloid proteins is a major driver of disease, and that a clever pharmacologic approach will stop the devastating chain of accumulation, tangles, and memory loss. The APOE4 genetics are “indisputable,” he says, noting that those with a single copy of mutated APOE4 have three-times greater than average risk of getting Alzheimer’s and those with two mutated copies (from Mom and Dad) are 15-20 times more likely than average to get the disease by age 80.

Will an antibody like Biogen-NeurImmune's aducanumab, intervening early, be able to stop neurodegeneration, or prevent the onset of disease? Selecting patients carefully with advanced imaging, and intervening early, are a couple of the big learnings from beta-amyloid failures of the past.

Optimistic as Paul may be for the amyloid hypothesis and aducanumab in particular, Voyager is taking a different tack. It’s using gene therapy to deliver heavy and light-chain genes for making anti-tau antibodies.

The beta-amyloid adherents (Baptists) may disagree with the tau evangelists (Tauists), but tau over the last five years, Paul said, is rising to the fore. It has increasingly become implicated via mouse genetics studies in various forms of neurodegeneration and dementia. Mice with antibodies against tau appear to do better on memory-based tasks. While there’s no such thing as a great animal model for a disease that typically strikes humans in old age, this has strengthened the rationale for getting rid of the tau, and preventing the neurofibrillary tangles.

Voyager’s idea is that by using an adeno-associated viral (AAV) vector, it can create a therapy that can cross the blood-brain barrier, where it can begin expressing anti-tau antibodies. Gene therapy could be useful here, because the typical recombinant antibody is too large to cross the blood-brain barrier. There’s also an issue with repeat administration of a full-length antibody. A gene therapy should deliver long-lasting antibody expression in the brain with a single shot, Paul said.

It's an idea.


John Alam, founder and CEO, EIP Pharma

John Alam, founder and CEO of EIP Pharma, has placed his own rather large personal bet on a different mechanism – inflammation that contributes to synaptic dysfunction (See my column from December on EIP and its “unfashionable science.”) Alam licensed a compound from his former employer, Vertex Pharmaceuticals, which came from structure-based drug design in the 1990s and went all the way through Phase 2a clinical trials as a treatment for rheumatoid arthritis, before being shelved.

At a BioCentury conference last month, Alam took square aim at the Alzheimer's establishment, which essentially put all its eggs in one basket for 25 years. The amyloid hypothesis was

essentially born out of a trio of academic papers published in 1991 – which Alam points out was the same year the Soviet Union fell, the top movie was Terminator 2, and Michael Jordan and the Chicago Bulls won their first NBA title.

His main point: It's time to consider other approaches.

“Twenty-six years is a long time to go without a drug,” from the original beta-amyloid insights, Alam said.

EIP’s drug, neflamapimod, is designed to inhibit p38 mitogen activated protein kinase alpha (p38 MAPKα). Researchers know that p38 MAPKα regulates inflammation through effects on immune cells. More recently, scientists have observed that the target is expressed in neurons in times of stress and disease. In those situations, p38MAPKα appears to play a major role in synaptic dysfunction, making it harder to achieve synaptic plasticity.

The drug failed for other clinical indications in Vertex's hands partly because it concentrated twice as much in the brain as it did in peripheral blood, Alam said. That might be too toxic for a systemically circulating rheumatoid arthritis drug, but it's a feature, not a bug, for an Alzheimer's drug.

Interestingly, EIP Pharma reported a year ago at the CTAD Alzheimer’s conference on some intriguing human data. A total of 25 patients with mild cognitive impairment due to Alzheimer’s, and mild Alzheimer’s, were enrolled in studies that ran 12 weeks, and 6 weeks. Patients on a 40 milligram dose saw their immediate memory improve from baseline, and their long-term memory improve after 12 weeks, on the Wechsler Memory Scale. Three of eight patients on the 40 milligram dose also showed lower brain amyloid plaque loads, as measured by PET scans.

Alam says neflamapimod is being prepped for a 150-patient, randomized, placebo-controlled trial that will look at whether it can improve memory. That would be a real proof-of-concept study. If successful, it would force a lot of R&D teams to think harder about synaptic dysfunction.

Ken Rhodes, chief scientific officer at Yumanity Therapeutics in Cambridge, Mass., agrees with the notion of an inflammatory component to Alzheimer’s, but he's not completely sold on p38 targeting. “There’s a strong inflammatory component of Alzheimer’s and other neurodegenerative diseases. That’s been appreciated a while. What’s not appreciated is what’s driving that response,” Rhodes said.

Yumanity is currently focused on APOE4 as a drug target, partly because of the compelling genetic case for its role in raising the risk of Alzheimer’s. The company is using a yeast cell-based phenotypic screening platform for ways to protect cells from toxic consequences of having too much APOE4, Rhodes said. As a secreted protein, it's found primarily on astrocytes, but also gets expressed on neurons, “I feel strongly that [APOE4] is druggable,” Rhodes said.

Once the underlying biology gets a bit more clear, it becomes easier to imagine clinical development plans sharpening up around the appropriate moment to intervene, better imaging to stratify patients, biomarkers to measure interim progress, and behavioral/environmental combination treatments. Crossword puzzles, or apps maybe? Akili Interactive Labs is one interesting company in that category, which has reportedly worked with Pfizer to see if it can using a gaming app to tell if a person has amyloidosis or not.

Alzheimer’s still strikes me as a field in some kind of dark age, at least compared to the almost-daily blast of insights we see emerging in cancer and with rare diseases. The mere fact that a company can raise $300 million in an IPO to recycle an old, discarded idea tells you something about the slim pickings in the late-stage Alzheimer's pipeline, and the urgent need. Lest anyone forget, the disease, which affects 5.5 million Americans, already costs us an estimated $259 billion a year. As the population ages, the bills are expected to quadruple by 2050, according to the Alzheimer’s Association.

I like to imagine what the biotech industry could do with $300 million spread among 100-200 interesting early-stage discovery approaches at hungry startups.

Like a lot of VCs, Bob Nelsen, the managing director at Arch Venture Partners, shook his head after the Axovant blowup:

> I don't find it surprising the old approach where you have no understanding of target-engagement in a relevant disease mechanism in a human at all should have any different outcome than past failures. Kind of like pounding your hand with a hammer over and over and wondering why your hand hurts.
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> The way to do this right is to understand that you have a relevant disease mechanism, and how to measure it in humans, and to do real drug development. That is happening, using new genetic tools and novel delivery systems. It may still fail, but the odds are much better.

Here are a few of the companies working on different approaches against Alzheimer's. I'm sure there are many more out there. If you know of others you'd like to tell me about, don't hesitate: luke@timmermanreport.com.

Company	Approach	Stage	Backers
Yumanity	Yeast-cell based screening. APOE4 targeting.	Discovery	Fidelity, Redmile Group, Alexandria, Biogen, Sanofi-Genzyme BioVentures,
Voyager Therapeutics	Tau-directed antibodies, delivered via gene therapy	Discovery	Third Rock Ventures, Fidelity, Bain Capital, Adage Capital
EIP Pharma	p38alpha-directed small molecule for synaptic dysfunction	Phase 2b ready, repurposed from Vertex	John Alam, Sylvie Gregoire, angel investors
Annexon Biosciences	Antibodies vs. C1Q, early components of classic complement cascade to prevent synaptic dysfunction	Stated goal of clinical trial in Q12017. Unclear if met	NEA, Correlation Venture Fund, Novartis Venture Fund, Clarus
vTv	Azeliragon, small molecule to inhibit the receptor for advanced glycation endproducts (RAGE). Found on endothelial cells and microglia	Completed Phase 2b	Franklin Advisers, Massachusetts Financial Services, Sphera Funds
Alzheon	Anti-amyloid drug candidate, optimized prodrug of tramiprosate	Completed Phase 2	Ally Bridge Group
Cognition Therapeutics	Drug candidates that compete with amyloid-beta oligomers for receptor targets preventing synapse loss and improving memory.	Phase I	Golden Seeds, Bios Memory SPV1, Cowtown Angels, Scale Investors, Dolby Family Ventures et al
Denali	Small-molecule RIP1 inhibitor, intended to regulate inflammatory signaling that contributes to glial dysfunction. Anti-APOE4 antibodies to cross blood-brain barrier	N/A	ARCH Venture Partners, F-Prime Biosciences, Flagship Ventures and the Alaska Permanent Fund

Alector	Antibodies. Undisclosed targets, but currently seeking to hire a neuroscientist to "analyze current scientific literature to help identify new targets or new strategies for existing targets."	N/A	OrbiMed, Polaris, GV, Merck, Amgen, AbbVie
NeurImmune	Developer of aducanumab anti-beta-amyloid antibody in Phase III. Developer of anti-tau antibody, BIIB076, now in Phase I	Phase III (amyloid) and Phase I (tau).	
Rodin Therapeutics	Synaptic resilience with brain penetrant small molecules	Preclinical	Atlas Venture, GV, Hatteras Venture Partners, Remeditex Ventures, and Third Point Ventures.
Tetra Discovery Partners	PDE4D inhibitor	Phase II	NIH’s BluePrint Therapeutics program.
Cognito	Gamma oscillation	Preclinical	MIT spinout