

J&J's billion dollar punt on anti-amyloid antibody

Johnson & Johnson's \$1.5 billion deal with Elan provides the latest validation of bapineuzumab's commercial potential in Alzheimer's disease. The partnership not only highlights the flagship program targeting beta amyloid, but also neatly pulls Dublin-based Elan out of a financial tailspin (Box 1). But for the Alzheimer's field as a whole, the success or failure of bapineuzumab will likely have broader implications for the future direction of drug development.

The bapineuzumab development program will be run out of a newly formed company, which will acquire Elan's assets and rights related to Alzheimer's program with Wyeth (now Pfizer). The program aims to recruit about 3,600 patients and represents the single most exacting test of the so-called amyloid hypothesis, which defines the accumulation of beta amyloid and its deposition in plaques in the brain as the key pathological process driving Alzheimer's disease.

Clearing existing beta amyloid deposits from the brain, or hindering their formation, is the paradigm driving the vast majority of the Alzheimer's development programs currently underway (Table 1). The dominant view is that other processes, including the formation of neurofibrillary tangles of hyperphosphorylated tau—another pathological hallmark of

Alzheimer's—occur downstream from beta amyloid plaque formation.

Even if bapineuzumab fails, however, that basic thesis will not disappear, for other factors could be invoked to explain its downfall. "You're never quite sure whether you're testing the hypothesis or testing the molecule, because you have to do both at once," says Eric Siemers, medical director of Alzheimer's research at Eli Lilly, of Indianapolis.

But a negative result would be a significant setback for the field, after the recent failures of two other anti-amyloid drugs, the gamma secretase inhibitor Flurizan (R-flurbiprofen) and Alzhemed (tramiprosate), which were being developed by Myriad Genetics, of Salt Lake City, Utah, and Laval, Canada-based Neurochem (now Bellus Health), respectively. Neither failure implicated the basic goal of inhibiting beta amyloid formation or deposition. Flurizan, which prevents beta amyloid formation by inhibiting the cleavage of amyloid precursor protein into beta amyloid peptide, failed to achieve a sufficiently efficacious concentration in the brain. Alzhemed, a glycosaminoglycan mimetic, was designed to prevent beta amyloid aggregation. Here, though, "the preclinical evidence was not very strong," says Dennis Selkoe, professor of neurologic diseases at Brigham and Women's Hospital in Boston, who recently stepped down



Elan's recently revamped manufacturing and research facilities in Athlone, Ireland.

Table 1 Selected Alzheimer's therapeutics in development

Compound	Description	Developer (Location)	Clinical status
Bapineuzumab	Anti-beta amyloid humanized monoclonal antibody	Elan/J&J (New Brunswick, New Jersey)/Wyeth (now Pfizer, New York)	Phase 3
Dimebon (latrepirdine)	Small-molecule neuroprotective anti-histamine	Pfizer/Medivation (San Francisco)	Phase 3
Docosahexaenoic acid	Omega-3 fatty acid	Martek Biosciences (Columbia, Maryland)	Phase 3
Immune globulin	Intravenous polyclonal human IgG purified from human plasma	Baxter (Deerfield, Illinois)	Phase 3
Rosiglitazone	Small-molecule peroxisome proliferator activated receptor (PPAR) gamma agonist	GlaxoSmithKline (London)	Phase 3
Semagacestat (LY450139)	Small-molecule gamma secretase inhibitor	Eli Lilly (Indianapolis)	Phase 3
Solanezumab (LY2062430)	Anti-beta amyloid mid-domain humanized monoclonal antibody	Eli Lilly	Phase 3
ACC-001	Therapeutic vaccine consisting of a 7 amino acid fragment of beta amyloid from the N-terminal conjugated to a mutated diphtheria toxin protein CRM 197	Elan/J&J/Wyeth	Phase 2
BMS-708163	Small-molecule gamma secretase inhibitor	Bristol-Myers Squibb (Princeton, New Jersey)	Phase 2
CAD106	Therapeutic vaccine consisting of beta amyloid 1-6 peptide coupled to the Qbeta virus-like particle	Novartis (Basel)/Cytos (Zurich)	Phase 2
CERE-110	Adeno-associated virus delivery of nerve growth factor gene	Ceregene (San Diego)	Phase 2
ELND005	Scyllo-inositol inhibitor of amyloid plaque formation	Elan/Transition Therapeutics (Toronto)	Phase 2
PF-4360365	Anti-beta amyloid humanized monoclonal antibody	Pfizer	Phase 2
PF-0449700	Small-molecule RAGE (receptor for advanced glycation end products) antagonist	Pfizer/Transtech (High Point, North Carolina)	Phase 2
PBT2	Small-molecule tau hyperphosphorylation inhibitor, synthetic amyloid beta-formed toxic oligomer inhibitor and zinc ionophore metal-protein attenuating compound	Prana Biotechnology (Parkville, Australia)	Phase 2
R3487	Small-molecule nicotinic alpha-7 receptor agonist	Roche (Basel)	Phase 2
TRx0014 (methylene blue)	Small-molecule Tau inhibitor	TauRx (Singapore)	Phase 2

from Elan's board but remains a scientific consultant to the company.

Expectations surrounding the bapineuzumab trial have been tempered by its performance to date. It failed to demonstrate statistically significant efficacy in a phase 2 trial, although it did work in a subgroup of patients: noncarriers of the Apolipoprotein E4 (ApoE4) allele, a known genetic risk factor for Alzheimer's. "It will not be a home run. It may be a double. I hope it's not only a single, but if a single is evidence of disease modification that might be good news," says Selkoe, who was a founder of Athena Neurosciences, the San Francisco-based firm acquired by Elan in 1996 and was a director of the latter company until mid-July.

Ian Sanderson, analyst at Cowen in New York, gives bapineuzumab a 50% likelihood of reaching the market, based on clinician surveys conducted by the investment bank. "The phase 3 trial, while very robust in terms of patient numbers, arguably has the doses wrong," he says. None of the studies is testing a dose below 0.5 mg/kg, which was the most effective dose in the phase 2 study. "The optimal dose may be somewhere between 0.15 mg/kg and 0.5 mg/kg, but it's difficult to tell," he says. On bapineuzumab's chances, J&J spokesperson Srikant Ramaswami says: "I'm not going to speculate about what analysts or anybody else are saying about this - we believe this represents a significant opportunity for us."

It could be late 2011 before the data become available. "They're frankly having trouble enrolling the largest component [of patients], which is the ApoE4 noncarriers," Sanderson says. Clinical investigators generally find noncarriers harder to access, he says, as carriers of the ApoE4 allele—a known genetic risk factor for Alzheimer's—are more usually treated at academic medical centers. The incidence of vasogenic edema (fluid build-up in the brain) that was observed in the phase 2 program, although low, particularly in noncarriers, may be at issue. "The risk-reward [benefit] is a little bit skewed in patients' minds," Sanderson says.

A key issue for all Alzheimer's drugs is the status of patients who are recruited into trials of new therapies. Most have mild-to-moderate disease, and it may be too late to undo the damage at that stage. Starting patients earlier, particularly those with a known genetic risk, is becoming a more realistic prospect, however. "That's going to start soon. There have been many discussions," Selkoe says. The Dominantly Inherited Alzheimer's Network, led by John Morris at Washington University in St. Louis, is coordinating one such initiative. "Within families [genetically predisposed to Alzheimer's], the age at onset is fairly tight, and presymptomatic genetic prediction is reliable. That might be the setting in which efficacy of anti-amyloid therapy is most likely to be demonstrable," says Sam Gandy, pro-

fessor of neurology and psychiatry at Mount Sinai School of Medicine in New York.

In the meantime, several other phase 3 programs are edging closer to conclusion. After bapineuzumab, Lilly's solanezumab is the next most advanced anti-beta amyloid antibody. It has a subtly different mechanism of action. "Our antibody only binds to soluble Abeta [beta amyloid] monomers. So it does not bind directly to the plaques," Lilly's Siemers says. Although beta amyloid monomers are themselves not considered to be toxic to neurons, depleting these monomers in solution may mobilize plaque-bound beta amyloid into solution, he says. Recent work, by Selkoe's lab and other groups, have demonstrated that various oligomers, including dimers, are synaptotoxic. Second- or third-generation therapies could conceivably be designed to target these species. But Selkoe is skeptical: "frankly speaking I do not think that's necessary," he says.

Lilly is also developing the industry's most advanced gamma-secretase inhibitor, semagacestat, which progressed to phase 3 trials on the basis of biomarker, rather than efficacy, data. Drugs in this class carry a danger of inhibiting Notch signaling, which is involved in multiple cellular control processes. "From a practical standpoint, we're not seeing this as a major problem in these studies," Siemers says.

"The word on that is it's probably not going to show efficacy because they're dosing it for

IN brief

Virus stalls Genzyme plant

Genzyme of Cambridge, Massachusetts, faces millions in lost revenue from its top-selling specialty drugs Cerezyme and Fabryzyme as result of a viral contamination at its Allston, Massachusetts plant. The company has announced that it will temporarily shut down the facility owing to a bioreactor contamination with Vesivirus 2117, which does not cause human infections, but impairs growth of the biologics-producing Chinese hamster ovary (CHO) cells. It reportedly originated from tainted nutrient medium and belongs to the same strain that caused delays at the Allston site and its European biologics plant in Belgium last year. Genzyme anticipates supply constraints of Cerezyme (imiglucerase), a treatment for Gaucher disease, and Fabryzyme (agalsidase beta), used to treat Fabry disease, while the facility shuts down for 6 to 8 weeks to allow decontamination. Although Genzyme also produces Myozyme (alglucosidase alpha) at the plant, no runs were scheduled during the presumed period of shutdown so supplies of that drug will not be affected. With sales of \$1.2 billion for Cerezyme and \$494 million for Fabryzyme in 2008, analysts estimate the manufacturing crisis will result in \$100–300 million in lost sales. The US Food and Drug Administration (FDA) has contacted rival manufacturers Shire of Basingstoke, UK, and Carmiel, Israel-based Protalix, who have enzyme replacement therapies for Gaucher disease in clinical trials, to file treatment protocols, which would allow physicians to use their drugs ahead of approval. The situation could also boost sales of Aillschwil-based Actelion's Zavesca (miglustat).

Victor Bethencourt

Stem cell funding widens

The National Institutes of Health (NIH) issued new guidelines for federal funding eligibility of human embryonic stem cell (hESC) research, loosening almost a decade of constrained financial support for academic researchers. Under the new rules, which took effect July 7, the NIH will establish a registry of fundable lines to which scientists can apply for inclusion. Stem cell lines derived before this date will be reviewed case by case for eligibility. In March, President Barack Obama lifted restrictions on hESC research established by the Bush administration (*Nat. Biotechnol.* **27**, 407, 2009), and requested the NIH draw up new rules. The draft guidelines released in April, established that fundable research must be limited to in vitro fertilization leftovers, and this requirement remains unchanged in the final guidelines. But outdated informed consent rules included in the draft, which would have forced laboratories to discard valuable lines, have been revised. Some restrictions remain, such as the exclusion of stem cells derived from embryos created for research, though overall, researchers are satisfied. "The new guidelines will hopefully open new opportunities for grants on the new lines, reduce some of the administrative burdens in the lab, and be better all around for our science," says George Daley, director of stem cell transplantation at Children's Hospital in Boston.

James Netterwald

safety," says Cowen analyst Sanderson. "I think there's a lot of excitement about the potential of the mechanism, but people are working with no clinical data at the moment."

Though New York-based Pfizer will have a stronger hand in Alzheimer's once it completes its acquisition of Wyeth, it already has one of the most intriguing late-stage Alzheimer's drug candidates in the form of Dimebon (latrepirdine), a compound with a 25-year history as an anti-histamine in Russia, which has demonstrated cognitive benefit in a phase 2 study (*The Lancet* **372**, 207–215, 2008). Gandy and colleagues reported at last month's International Conference on Alzheimer's Disease in Vienna that Dimebon, surprisingly, increased the release of beta amyloid from cultured nerve cells and isolated nerve terminals, and it raised levels of beta amyloid in the brains of

transgenic mice expressing human amyloid precursor protein. The compound interacts with multiple receptors, including several serotonin (5-hydroxytryptamine) receptor subtypes. Gandy admits that the work raises more questions than it answers. "I think that if the cognitive benefit is confirmed [in the phase 3 trial], then dissecting the molecular basis for the mechanism of action will take on major importance," he says.

Although the amyloid hypothesis can claim quite an amount of scientific validation, it still harbors several mysteries. "My guess is that anti-amyloid therapies would be much more successful as prophylaxis, but getting from here to there is a challenge. I'm still a believer, but the absence of any signal from any of the trials to date is discouraging," Gandy says.

Cormac Sheridan Dublin

Box 1 Saving Elan

The Johnson & Johnson (J&J; New Brunswick, New Jersey, USA) deal is a life preserver for Elan, which has been in financial trouble since last summer, when it revealed that the phase 2 trial of bapineuzumab (AAB-001) had missed its primary endpoints, albeit with some efficacy in certain patient subgroups. Days later, Elan also announced that two more patients taking its multiple sclerosis drug Tysabri (natalizumab) had contracted the potentially fatal brain disease progressive multifocal leukoencephalopathy. These events combined to drive down Elan's stock from more than \$33 last summer to less than \$10, where it still languishes today.

Elan ended 2008 with about \$375 million in cash and equivalents. With the summer's bad news still hanging around its neck (and stock price) and expecting to spend around \$350 million in R&D this year, the company needed to hunker down. In January, it hired Citigroup to review "strategic alternatives," including a merger or an outright sale of the company. In the first quarter, it closed offices in New York and Tokyo. In February, it also cut 230 positions (~14% of the total workforce), including research and clinical development positions, and looked to further curtail spending by saying it would "reassess" investing in a biologics manufacturing facility and suspending fill-finish activities in preparation for launching bapineuzumab until after the phase 3 results are known.

Despite these savings, Elan has still been wrestling with how to pay for its promising—though expensive—lead product in Alzheimer's. Last year, Elan spent \$113 million on its Alzheimer's Immunotherapy Program (AIP), partnered with Wyeth (in the process of being purchased by Pfizer), and estimated it would spend as much as \$500 million on bapineuzumab and the rest of the portfolio over the next three or four years. This was looking more and more impossible for Elan, given its dwindling cash position and a troubling net debt of \$1.4 billion.

The J&J deal solves both problems. First, J&J takes over the AIP, which includes the intravenous formulation of bapineuzumab, as well as a subcutaneous version and an Alzheimer's vaccine (AAB-001), in phase 2 development. J&J will build a new joint venture around AIP and own 51.1% of it (with Elan holding the rest), and J&J will dump up to \$500 million into development, thus relieving Elan of about \$100 million in annual R&D expenditure. Second, J&J invested \$1 billion into Elan itself, receiving about 18.4% of Elan's outstanding shares in return—making it the largest shareholder. This influx of cash will allow Elan to reduce its net debt by 70%, to \$400 million. Elan believes that the reduction in R&D spending, coupled with an expected growth in Tysabri sales, will allow the firm to post a pre-tax profit and be cash-flow positive by the end of 2010.

Brady Huggett