Curing What Ails Alzheimer's Drug Development

BY RACHEL LAING, ALESSIA DEGLINCERTI, ALAIN J. GILBERT, FRANK BOROWSKY AND MARK RATNER

Developing an Alzheimer's disease drug is notoriously expensive and high risk. A single success could open research and investment as immunotherapy did in oncology over the past decade. But the mechanisms at work in progression to AD are not nearly as well characterized as those in oncology.

Combining digital measurements, genetic risk factors and biomarker measurements for amyloid, tau or neuroinflammation could provide a way to funnel patients likely to progress to AD into the system, preventing costly treatment of individuals with dementia not related to Alzheimer's.

So what? The best chance for success for biopharma companies entering the space is to work with diagnostics and high tech companies to develop a screening paradigm for patients that will increase the odds of clinical success and pave the way for commercialization.

Curing What Ails Alzheimer's Drug Development

Biomarkers will be key to winning the race to a successful AD drug. Even then, drugmakers must build the infrastructure for getting therapies to the right patients at the right time.

BY RACHEL LAING, ALESSIA DEGLINCERTI, ALAIN J. GILBERT, FRANK BOROWSKY AND MARK RATNER

As the drug industry has seen over the past decade with immunotherapy in cancer, success breeds success and opens the door to investment in new targets and rationales. That's long been the hope in Alzheimer's disease (AD) drug development, where a hard-to-segment patient population and large, lengthy, expensive trials have continued to frustrate companies. The pharma industry claims to be learning from the past, but the pattern of high-profile, late-stage failures, most recently by **Axovant Sciences Ltd.** and **Merck & Co. Inc.**, is unbroken. Success remains elusive. *(Also see "Disappointed, Yes, But Roivant's Not Roiled By Axovant's Alzheimer's Failure" - Scrip, September 26, 2017 and "Another Nail In Amyloid Hypothesis Coffin? Merck Ends Pivotal BACE Inhibitor Study" - Scrip, February 14, 2017.)*

On the bright side, it is conceivable that in the next two to four years, one of the AD drug candidates now in late-stage trials may well become the first true disease-modifying agent approved. But when trials of those drugs began, the first exploratory measures of biomarkers – specifically, amyloid burden and APOE gene status – were just being introduced. Similarly, the notion of enrolling early-stage patients – to be able to better demonstrate a treatment effect – was relatively new.

An understanding of how to use more refined tools for gauging which individuals, among those showing the early signs of mild cognitive impairment, will progress to AD and how quickly that progression could occur, is only now emerging. This understanding will be key to future efforts. Companies contemplating entering the space should learn about these tools and plan accordingly.

A Changed Development Landscape

The amyloid-targeting antibodies, including the failed bapineuzumab, from a collaboration between **Pfizer Inc.** and **Johnson & Johnson**'s **Janssen Pharmaceuticals Inc.**, **Eli Lilly & Co. Inc.**'s solanezumab, and the current late-stage hopefuls aducanumab, from **Biogen Inc.**, and crenezumab, from **Roche**, are all somewhat different in how they target amyloid deposition. "They are asking different questions," says Steven Paul, MD, president and CEO of **Voyager Therapeutics Inc.** and former VP, discovery research and neuroscience research at Lilly.

Through the development of these compounds and others over the last decade, the field has learned that the pathogenesis of AD has a certain sequence of events, Paul explains. Amyloid accumulation is an early pathogenic lesion that is necessary but not sufficient to cause neurodegeneration. It even starts 10, 20

years before the prodrome of mild cognitive impairment. Following an initial insult by amyloid deposition comes tau deposition, microglial activation, inflammatory reactions, then neuronal loss.

It is therefore not surprising that treating patients who already have moderate disease and have lost neurons, to try to reduce amyloid deposition, hasn't worked. "It doesn't make any sense, yet it took a number of failed trials to realize that," Paul points out. It also took a number of failed trials to realize that many people enrolled in those clinical studies didn't have any amyloid in their brain. In the community, the numbers thought to have AD but later shown to not have amyloid are close to 50%.

Dosing was also an iffy proposition in the early days, owing to the lack of an accessible pharmacodynamic marker, and was most likely too low to identify a therapeutic effect in a subpopulation of trial enrollees. That's changed. Aducanumab, for example, appears to reduce amyloid burden in the brain in a dose-dependent manner. Better information has similarly allowed crenezumab to be given at much higher doses than the earlier antibodies.

Even Lilly's third Phase III failure with solanezumab, announced in November 2016, while disappointing but not overly surprising, was also greeted with some optimism. *(Also see "Lilly's Solanezumab*

Fails, But The Surprise Would Have Been Success" - Scrip, November 23, 2016.) Although the magnitude of the effect size was not what people were hoping, "the fact that you were able to intervene with amyloid and actually have an impact, even though it may have not been the right drug or at least not the right dose," sustained people's faith in the amyloid hypothesis, says Jamie Mullen, MD, global clinical leader, neuroscience, **AstraZeneca PLC**. Mullen's firm is partnered with Lilly on lanabecestat, a Phase III inhibitor of beta secretase (BACE), an amyloid precursor protein cleaving enzyme.

The biggest opportunities around biomarkers are to use them as enrichment strategies to identify the most likely responders to a drug candidate, especially because the goal in AD trials today is to slow the course of the illness rather than reverse it. "We need to identify individuals who have a great enough rate of decline so we can measure the impact of our drugs within a reasonable time frame," Mullen notes. It's also critical to pick individuals at the right stage of the disease. Trials of lanabecestat are targeting those with mild cognitive impairment due to AD as well as early AD. "We think that is the sweet spot in disease progression," Mullen says. That is, people who haven't progressed so far that you won't be able to have an impact on the course of the disease, but who still have a rate of decline that will allow you to differentiate from placebo effects.

With biomarker-driven patient selection now focused on earlier stages of disease or prodromal individuals, doses are three to four times those used in the early studies of mild to moderate disease patients. But that said, the question remains whether that will have any impact on the progression of the disease – will it slow down the cognitive impairment that occurs over time?

The trend is toward identifying presymptomatic patients. Several current trials are aimed even earlier, at prevention. These include the A4 (Anti-Amyloid treatment in Asymptomatic Alzheimer's) study funded by the **National Institute of Health**'s **National Institute on Aging**, Lilly and several philanthropic organizations; the DIAN (Dominantly Inherited Alzheimer Network) trial sponsored by

> ❝
> *Lessons learned about tau biology – the spread of tau protein in the brain and the tauopathy seen in AD, aided by the availability of amyloid and tau PET imaging tools – are also shining brighter light on how and when AD starts and how to intervene to halt or reverse it.*
> ❞

Washington University School of Medicine; and the Colombian study, a prevention trial in cognitively healthy individuals with a genetic predisposition, run by the NIH, the Banner Alzheimer's Institute, the University of Antioquia in Colombia and Roche's **Genentech Inc.** unit. *(Also see "Alzheimer's Prevention: The Next Big Idea For Fixing Drug Trial Failures" - Scrip, September 27, 2017.)*

Lessons learned about tau biology – the spread of tau protein in the brain and the tauopathy seen in AD, aided by the availability of amyloid and tau PET imaging tools – are also shining brighter light on how and when AD starts and how to intervene to halt or reverse it. Tau may correlate much better with disease progression than does amyloid imaging or pathology.

The genetics underlying some of AD is on more solid ground as well: dominant mutations are known to cause early onset disease and 20 or more risk factor genes have been identified in multiple genome-wide association studies. These include the validated risk allele APOE4 and genes that play a role in regulating brain immunity and microglia activity. These genetic factors could represent new biomarkers or new targets for drug development. Some of these gene-driven pathways are shared across diseases: people with Parkinson's disease, for example, exhibit inflammatory reactions. Misfolded proteins are also a common feature of many of these diseases: similarities exist, for example, between α-synuclein in Parkinson's Disease, the huntingtin protein that causes Huntington's disease, amyloid and tau. "The more we learn about misfolded proteins the more we will know about when and with what patients to intervene," Mullen says.

For now, however, the mechanisms at work in progression to AD – whether those responsible for the build-up of amyloid or tau or neuroinflammation – are not nearly as well characterized as are those in other therapy areas, such as oncology. Indeed, knowing a target does not necessarily mean that modulating it will have a beneficial therapeutic effect. Amyloid beta (Aβ) and tau are known, but we do not yet know their importance. Unlike in oncology, translating knowledge about the biological changes observed in

Exhibit 1
A Pharma-Diagnostics Partnership Model In AD

ADVANTAGES FOR PHARMA COMPANIES	ADVANTAGES FOR DX COMPANIES
Facilitate recruitment of patients for trials	Gain access to patient data to validate test
Ensure right patients are selected for the right trial	Inclusion in a pharma company sponsored clinical trial
Potential to reduce trial costs	Potential for pharma funding
Differentiate use of a product in a crowded space	Link test's clinical utility with treatment outcomes
Generate key data and endpoint measurements	Generate clinical data to support test approval
Establish leadership in AD	Establish leadership in AD
Support payer negotiations upon approval and launch	Leverage pharma resources to secure test reimbursement
Mitigate risk	Raise awareness/adoption of the test

SOURCE: Bionest analysis

AD patients has not led to the emergence of targeted drug approaches and more efficient trials.

Drugmakers can help maximize the chances for success by ensuring the identification, development and ultimate commercial availability of biomarkers. Diagnostics companies, conversely, need access to hundreds or thousands of patient samples to validate their assays. The only place to go for that is to a pharma company's clinical trials. (*See Exhibit 1.*)

A variety of tools will be needed to make better determinations about patient status, both as screening tools and potentially as diagnostics. These include biochemical markers of $A\beta$, tau protein and neuroinflammation as well as digital devices that collect information on changes in gait, eye movement, speech and other measures linked to cognitive decline.

Combining digital measurements, genetic risk factors and other biomarker measurements for amyloid, tau and/or neuroinflammation could provide a way to funnel patients likely to progress in the disease, thus preventing costly treatment of individuals with impaired cognition not related to AD. But history tells us that the investment needed to facilitate the emergence of such a system may not happen until an effective treatment emerges. It's a catch-22 that must be over-come. Moreover, unlike other therapy areas, the infrastructure to diagnose and deliver an AD therapy barely exists. The lack of infrastructure limits awareness about possible advances in diagnosis and makes physician education challeng-ing. It's a looming problem: significant preparation will be needed to prime the market once a disease-modifying therapy for AD is in hand.

Calling All Biomarkers

The development and commercialization goals for AD diagnostics are less clear than in other therapy areas. As a result, pharma companies are more hesitant to fully commit to a collaborative partner-ship to develop the assays they will need.

To help drive innovation in the field, the **Roche Diagnostics** division of Roche convened a satellite symposium on bio-markers at the *World CNS Summit* last February to launch the development of a "NeuroToolKit." Working with indus-try and academic partners, it will take a group of 20 discrete biomarkers with potential application in AD and other neurodegenerative diseases and move them forward into a prototype assay stage to run on Roche's *Elecsys* electro-luminescence immunoassay platform. (*See Exhibit 2.*)

"The need for high-quality, standard-ized biomarkers is clear," says Jacob Hunter, director, companion diagnostics partnering for Roche Diagnostics. The goal is to use the NeuroToolkit to identify AD co-pathologies, identify and charac-terize disease progression, and identify and characterize treatment response.

Roche already has assays for measur-ing $A\beta42$, phosphor-tau and total tau that run on its platform, using a sample of ce-rebrospinal fluid (CSF). The markers have shown concordance with PET amyloid imaging – the primary tool established scientifically and in a regulatory setting for amyloid detection. But widespread use of PET demands a much greater in-frastructure – and reimbursement – to obtain the type of scale and support that will ultimately be required for treating AD patients. CSF assays come with a much lower price tag that makes large-scale implementation easier. However, given that CSF is collected via lumbar puncture, some prospective patients may find the procedure too invasive and not accept-able, especially as we move into earlier disease diagnosis.

The ultimate goal is to have easy-to-use fluid biomarkers from blood/plasma or even saliva, which can be measured in a simple immunoassay and used to screen the general population to help determine whether or not individuals should go for confirmatory CSF or PET. They could become a binary gate: Older individuals

Exhibit 2
Roche's Neurotoolkit: Potential Assays

ASSAYS AVAILABLE AS IVD OR PROTOTYPE	CORE ASSAYS FOR ALZHEIMER'S AND PARKINSON'S DEMENTIA	NEW DEVELOPMENTS
BDNF	Aβ40	Neurofilament
GDF-15	Aβ42	Neurogranin
IGFBP-7	α-synuclein	Soluble TREM2
IL-6	Total tau	SNAP-25
S100β	Phosphor-tau	TRAIL
YKL-40	—	VILIP-1
NSE	—	TDP-43
MMP3	—	—
Osteopontin	—	—
Ferritin	—	—

SOURCE: ACT Biomarkers meeting, Boston, 2017

or people with a known genetic predisposition might be screened as part of an annual physical with their primary care provider. But development of such biomarkers will require more time and investment for validation before they become acceptable tools in clinical practice.

Incorporating The Information

Lilly, which markets the amyloid PET imaging agent *Amyvid* through its 2010 acquisition of **Avid Radiopharmaceuticals Inc.,** is collaborating with Roche on the CSF programs. It is also active in assessing potential new biomarkers in AD – to a greater degree than other big pharmas with late-stage AD programs.

"We need better tools – or a comprehensive suite of tools – to better identify an appropriate population and lead us into a better capability to actually predict people who are likely to progress into disease," says Thomas Fagan, Jr., senior director of Lilly's Bio-Medicines Business Unit. "There is a lot of reinforcement for the fact that patient selection needs to be and can be improved, but we don't yet have a study to validate [how this effort] would contribute to clinical research," he says.

Many companies are piloting innovative ideas in their studies to try to identify who will respond to various drug candidates. Medical history, clinical evaluation of cognitive assessment scores, evidence of amyloid or tau either by PET imaging or by CSF lumbar puncture, volumetric MRI and plasma biomarkers are all in play. More experience with biomarkers could reduce the number of participants needed for trials by enriching the population with more likely responders.

"The trials themselves take a long time and are costly, but the enrollment period for them is just way too long," says Fagan. One example: a new Phase II/III trial of **Novartis AG**'s BACE inhibitor CNP520, which aims to prevent or slow disease progression in presymptomatic patients, may screen 30,000 individuals to find 2,000 with the APOE4 gene variant. *(Also see "Amgen, Novartis May Screen 30,000 Patients To Find 2,000 For Alzheimer's Trial" - Scrip, November 2, 2017.)* Lilly's EXPEDITION 3 trial for solanezumab took 20 months to enroll 2,000 patients total worldwide and a comparable time period in the US to find 1,000 patients. Plus, several studies have shown that approximately 30% of the people clinically evaluated as having Alzheimer's

disease ended up having negative PET scans at the end of the evaluative process for enrollment into the study. "We need to be able to tighten up the time it takes to identify patients for these studies," Fagan says.

Lilly also sees a need to support and train physicians on how and when to appropriately use these various tools – not just to familiarize them with novel biomarkers and possible future diagnostics, but even how to implement existing cognitive assessments and scales.

Drug developers must find ways to make clinical trials more user friendly: cognitive tests and imaging studies take a lot of time and effort not only on the part of the individual, but also on the part of their care provider. "Until we have more expeditious biomarkers and assessments, we will have to make really conscious efforts to engage and make these as user friendly as possible," says AstraZeneca's Mullen.

"We need to have measures of not only these biomarkers and of cognition," he says, "but also measures of functional and health outcomes that we can use to determine whether the things we measure in clinical trials are clinically meaningful." Indeed, PET imaging showing amyloid burden may not correlate with an ability to treat AD because by the time the deposition is evident, the time to arrest cognitive decline may have passed. In a similar fashion, it does not follow that producing improvements in psychological test measures will help with real-world functioning, activities of daily living or the ability to be independent, or will reduce health care expenses.

Multiple non- or less-invasive technologies for measuring cognition and cognitive decline are in the prototype phase. These include digital-based cognitive assessment tools (generally iPad), wearables to measure gait and digital tools to evaluate cognition by looking at speech.

Making these tools part of the primary care evaluation paradigm is critical, says Brian Smith, director, Alzheimer's diagnostics strategy at Lilly, to enable PCPs to readily identify who should continue on in the treatment cycle. Tablet (such as iPad)-based tests are probably the easiest and most readily adaptable. They offer a better opportunity for a truer evaluation

of a patient, versus a test where patients can practice beforehand, like having a loved one help them draw a clock. A digital clock-drawing test is being used in research, but could be limited in use because it calls for a unique tablet and an individual electronic pen – a problem in busy primary care offices where it would be difficult to keep track of a single pen used only on one test.

"The adoption in a primary care office is what will accelerate finding the right patients and what comes along with that, clearing the wrong patient and not advancing them into therapy," Smith says. "We have to show those health economic benefits to payers."

"I can see a time quite soon where someone develops the right app that goes on a smartphone," Smith predicts. A physician tells a patient to download the app and turn it on for some time, and the device will send the information to the cloud for a report, then turn off automatically. Payers might even pay for these data collection devices. "They would have an economic benefit to provide the access to obtain the input and output analysis of the data," Smith says. In neurodegeneration and dementia, changes take time to manifest, so the availability of that interface does not have to be continuous.

"Everyone has their individual trajectory," Smith points out: comparing an individual over time is better than using a test that generates a normalized score at one point in time – a blunt instrument by comparison. "If we can collect this passively, we could potentially have a truer sense [of an individual] and find the right patient," he says. Plus, the data could become digital endpoints in a clinical trial to measure response to therapy.

Prepare For A Market, Now

The heavy lifting of validating biomarker tools, building a clinical practice infrastructure and educating physicians has barely begun. Because no disease-modifying treatments have made it across the development finish line for AD, it has been difficult to get the universe of primary care physicians to pay attention to new developments underway in late-stage clinical development, much less early-stage science. Plus, the payers, who

> "
> *The trend is toward identifying presymptomatic patients. Several current trials are aimed even earlier, at prevention.*
> "

will likely set a high bar for the evidence required to show that a drug works in a well characterized population before reimbursing an expensive therapy, will not focus on AD until there is a drug for their consideration.

The best chance for success is for drugmakers, diagnostics companies and makers of digital health tools to work together to develop a screening paradigm for patients that will increase the odds of clinical success and pave the way for commercialization.

Traditionally in AD, the development risks were so high you only saw well-capitalized institutions that could spread the risk across multiple programs, like Roche or Pfizer/Janssen or Lilly, participate. That still holds: of the 240 clinical studies ongoing for AD in October 2017, 78% of which are actively recruiting, the late-stage trials remain top-heavy with big pharmas. *(Also see "A Status Check Of The Alzheimer's Trial Landscape" - Scrip, December 1, 2017.)*

Even with the incorporation of amyloid PET tracers and possibly CSF assays for amyloid or tau, biomarkers will not influence the course of existing late-stage programs to a greater extent than they have already. Those ships are too hard to steer. That's not the case for preclinical and early-stage clinical development efforts.

On the bright side, past failures may finally be paving the way for future success in the field, and investment in new targets is beginning to swell: witness the October 2017 collaboration between **Abbvie Inc.** and **Alector LLC**, in which Abbvie contributed $205 million up front to join in the development of antibody drugs targeting immune system deficiencies thought to contribute to progression of AD and other neurodegenerative diseases. *(Also see "AbbVie Goes Boldly Into Immuno-Neurology With Alector" - Scrip, October 24, 2017.)* Alector was also the first investment of the US-UK Dementia Discovery Fund, which received a $50 million boost from Bill Gates in November to develop new approaches to AD drug discovery and look beyond the traditional amyloid and tau drug targets. *(Also see "Gates Injects UK-US Dementia Discovery Fund With $50m And Fresh Purpose" - Scrip, November 14, 2017.)*

"Given the nature of the tools – both from the target perspective as well as from the advancements in diagnostics that hopefully are coming along, AD is a good place to make a bet," says Terry McGuire, general partner at Polaris Partners, an investor in Alector. As with the development of antibody drugs generally, the tools need to catch up with the opportunity, he says. "We know the problem and we have a couple of the pieces." ▶

IV005246

Rachel Laing (rlaing@bionest.com) is a principal with Bionest Partners based in Basel, Alessia Deglincerti (ADeglincerti@bionest.com) is a senior associate consultant and Frank Borowsky (fborowsky@bionest.com) is an associate consultant with Bionest, both based in New York, and Alain J. Gilbert (alain@bionest.com) is Bionest's co-chairman based in Paris. Mark Ratner (mlratner@verizon.net) is a contributing editor to In Vivo.