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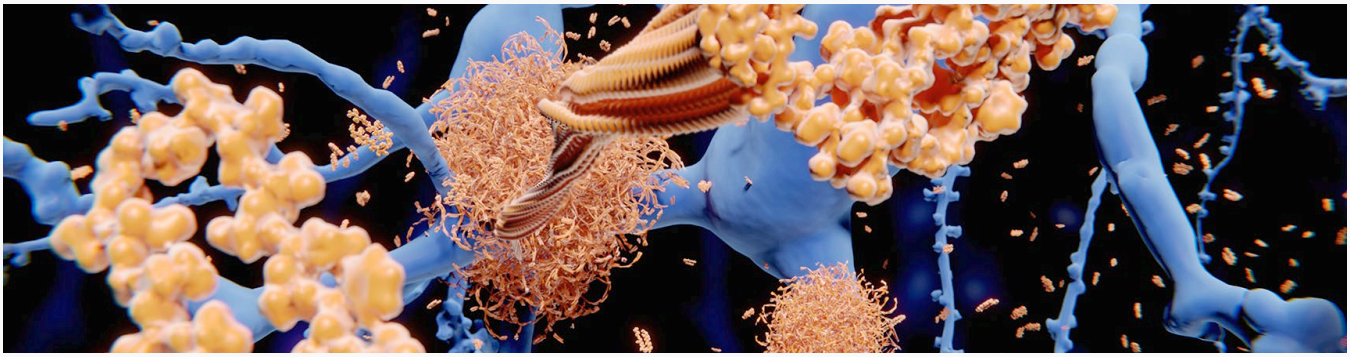

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PRODUCT DEVELOPMENT

How the amyloid hypothesis holds its grip

BY SELINA KOCH, SENIOR EDITOR

By now, two things are clear about the amyloid hypothesis of Alzheimer's disease: one is that the amyloid peptide is somehow involved; the other is that it's a terrible target.

β amyloid has had an irresistible pull on drug developers because human genetic data strongly argue the peptide causes the disease. But at least 20 failed Phase III trials, and zero successful ones, argue equally strongly that it's not the path to success.

Yet the hypothesis appears here to stay for the foreseeable future. Even Biogen Inc.'s April 24 announcement that it would call off all Phase III studies of aducanumab, widely considered the most promising anti-amyloid candidate to date, does not represent an abandoning of the hypothesis. The biotech and its partner Eisai Co. Ltd. have two other amyloid-lowering therapies in late-stage trials.

For the believers, what's left is to define whether there is a "kill experiment" whose results would persuade them to walk away from β amyloid as a focus for therapeutic intervention. So far, with each failed trial of a β amyloid-lowering therapy, these companies and their academic collaborators have concluded that either the compound or the trial design was at fault (see "Amyloid: How Did We Get Here And What We Can Learn?").

At least nine pharmas or biotechs remain committed to development of agents that aim to block β amyloid or prevent its production, and over a dozen compounds are in clinical development, according to BioCentury's BCIQ database.

"Billions of dollars are being spent on a target that really in any other indication would have died," Howard Fillit, founding executive director and CSO of the Alzheimer's Drug Discovery Foundation, told BioCentury. "I applaud the industry for keeping at it, but on the other hand, in doing so they are taking resources that could be used for novel targets."

Even the staunchest advocates of the amyloid hypothesis are starting to hedge their bets, and smaller biotechs are exploring a wide range of new approaches. About two thirds of the 78 AD candidates in the clinic are targeted outside the amyloid pathway (see "Baby Steps Beyond Amyloid").

Nevertheless, all 10 academic and industry KOLs who spoke to BioCentury remain convinced that amyloid causes or at least plays a major role in the disease. Most likely, it is the trigger, they say. The problem is that the peptide builds up for decades before symptoms start, and by the time a patient seeks help, other mechanisms are in the driver's seat. The prime suspects are tau aggregation, the second major hallmark of the disease, and neuroinflammation, which has been implicated by genome-wide association studies (GWAS).

Still, there's little agreement among the KOLs on what — if anything — would convince them to jettison β amyloid. Two

argued the field should have already moved on, and another three were not ready to describe an exit strategy. The rest are reserving judgment until even more data are available.

The greatest agreement was that the best play left for the amyloid hypothesis is in disease prevention. At least five Phase II or III trials in presymptomatic patients are slated to read out between 2020 and 2024 (see Table: "Still Plugging Away at Amyloid").

Even if all these fail, it may not mark the end of the hypothesis. One pharma suggested the results, positive or negative, could spur additional studies, and several KOLs think combinations of amyloid inhibitors with other mechanisms could be in the offing.

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>
> HOWARD FILLIT, ADDF

Solid foundations, shaky ground

By conventional wisdom, the foundations of the amyloid hypothesis are solid, rooted in converging lines of genetic data that point to β amyloid as the primary disease driver. The persistence of the hypothesis also results from the unique combination of a disease with a very slow time course, no therapeutic alternatives, a huge and growing number of patients, and enough missteps early on to explain failures as tactical errors in trial strategy.

Then came the blow on March 21, when Biogen and Eisai announced they were stopping two Phase III trials of aducanumab for futility. Based on the results, Biogen subsequently said it would also cancel a planned Phase III trial of the compound in the disease prevention setting.

"The aducanumab study was the first Phase III trial where the antibody was used at doses that should be removing plaque," said David Holtzman, professor and chair of neurology at Washington University School of Medicine in St. Louis and scientific director of the Hope Center for Neurological Disorders.

Before aducanumab, supporters of the hypothesis pointed to design flaws in trials of other amyloid-lowering agents. For example, some trials enrolled patients whose disease was too advanced, or failed to confirm patients had amyloid build up in the brain at baseline.

Above all, amyloid advocates argued that other agents simply did not remove enough of the protein from the brain (see "Not Dead Yet").

Biogen has not yet released the data. But that rationale appears to have collapsed, given that aducanumab's substantial amyloid-reducing activity in Phase Ib did not yield a cognitive benefit in Phase III.

Notwithstanding that conclusion, Eisai announced on March 22 it would start a Phase III trial of BAN2401, another anti-amyloid mAb in a deal with Biogen.

The partners also have a pair of ongoing Phase III trials testing elenbecestat, an inhibitor of BACE, one of the enzymes responsible for generating β amyloid from its precursor APP. Novartis AG also has a BACE inhibitor in Phase III. However, at least three BACE inhibitors have already failed to show a cognitive benefit in Phase III.

Eisai declined to be interviewed for this story, and Biogen did not respond to requests for an interview.

When to walk away?

Given the failures and the widely held belief that amyloid kicks off the disease process decades before symptoms appear, opinions differ most on whether amyloid inhibition is a viable approach after symptoms have started.

Fillit and industry commentator Derek Lowe think it's time to move on.

"It wasn't any one single result that made me lose my belief in it. It was more the steady number of clinical failures," said Lowe. "Watching the behavior of the people who still held on to it didn't increase my confidence, either. There was always some reason why this trial was going to be a big one, and then always some reason why, actually, it wasn't run the right way," he added.

Others are waiting to see the Phase III aducanumab data before dismissing the target in symptomatic patients.

Holtzman thinks trial design might again be at fault.

"I don't want to jump to a conclusion about what the result means," he said. "They had to titrate the dose up. So I don't know until they release all the information how long it took to get to that dose," meaning patients might not have had long enough time at the right dose.

Matthew Kennedy, a principal scientist in neuroscience at Merck, agreed. The pharma's BACE inhibitor verubecestat was among the three that failed in Phase III.

He suggested combinations may give the amyloid camp an extended lease on life.

"I think we still need to see the aducanumab data," Kennedy said. "If they still achieved the same level of biomarker change that they described in their Phase Ib studies, where many people became plaque negative, then with the BACE data, that would be very convincing to not continue exploring amyloid therapies alone in mild to moderate and prodromal patients."

Several other KOLs told BioCentury the complexity of AD may call for combination therapies targeting multiple disease mechanisms. While some envision an amyloid therapy in the mix, they are hesitant to jump into such combinations until a tau inhibitor or another new MOA has a clinical win.

But expecting an amyloid therapy to work in combination when it hasn't shown efficacy alone is a risky proposition. A recent example was

Still plugging away at amyloid

Despite dozens of failed Phase III trials of amyloid-lowering compounds in Alzheimer's patients whose symptoms have begun, at least five more Phase III trials are currently recruiting patients. One of these compounds, gantenerumab, failed two prior Phase III trials when delivered at a lower dose. Earlier stage trials of amyloid-targeting therapies are not shown.

Based on the widely held belief that amyloid aggregation is the first step toward Alzheimer's disease, clinical trials of at least five amyloid inhibitors now aim to stop the dementia before it starts. All of these are considered secondary prevention studies because they enroll patients with mutations or risk factors for AD. Three of the five compounds — solanezumab, gantenerumab and crenezumab — previously failed Phase III trials in symptomatic patients. The DIAN-TU study is being sponsored by Washington University School of Medicine, and the other four prevention trials have non-profit or academic collaborators. Readout times are "primary completion" dates from ClinicalTrials.gov. *Source: BCIQ: BioCentury Online Intelligence, ClinicalTrials.gov*

Treat Symptomatic Patients							
Roche (SIX:ROG; OTCQX:RHHBY) / **Genentech Inc.** / **Morphosys AG** (Xetra:MOR; NASDAQ:MOR)	Gantenerumab	β amyloid	Ph III GRADUATE 1	Early AD	760	2 years	May 2022
			Ph III GRADUATE 2	Early AD	760	2 years	May 2022
Eisai Co. Ltd. (Tokyo:4523) / **Biogen Inc.** (NASDAQ:BIIB)	Elenbecestat	BACE	MissionAD1	Early AD	1,330	2 years	June 2021
			MissionAD2	Early AD	1,330	2 years	June 2021
BioArctic AB (SSE:BIOAB) **/ Eisai Co. Ltd.** (Tokyo:4523) / **Biogen Inc.** (NASDAQ:BIIB)	BAN-2401	β amyloid	Ph III Clarity AD	Early AD	1,566	1.5 years	March 2024
Prevent Symptom Onset							
Eli Lilly and Co. (NYSE:LLY)	Solanezumab	β amyloid	Ph III A4	Positive amyloid PET scan, age 65-85	1,150	6.5 years	July 2022
			Ph II/III DIAN-TU	Autosomal dominant mutation carriers	490	4 years	Dec. 2020
Roche (SIX:ROG; OTCQX:RHHBY) / **Genentech Inc.**	Gantenerumab	β amyloid	Ph II/III DIAN-TU	Autosomal dominant mutation carriers	490	4 years	Dec. 2020
Novartis AG (NYSE:NVS; SIX:NOVN) / **Amgen Inc** (NASDAQ:AMGN)	CNP520 + amilomotide	BACE/ β amyloid	Phase II/II GENERATION1	APOE4 homozygotes	1,340	5 years	Aug. 2024
Novartis AG (NYSE:NVS; SIX:NOVN) / **Amgen Inc** (NASDAQ:AMGN)	CNP520	BACE	Phase II/II GENERATION2	APOE4 heterozygotes with elevated amyloid	2,000	5 years	Jul 2024
AC Immune S.A. (NASDAQ:ACIU) / **Roche** (SIX:ROG; OTCQX:RHHBY) / **Genentech Inc.**	Crenezumab	β amyloid	Ph II Alzheimer's Prevention Initiative (API) ADAD	Autosomal dominant mutation carriers	252	5 years	Feb. 2022

last year's failed attempt to boost anti-PD-1 activity by adding an IDO inhibitor, which had no single agent activity (see "Lessons From the ECHO Chamber").

Dennis Selkoe, one of the original authors of the amyloid hypothesis, is holding out hope that amyloid therapies could still work as single agents in a subset of symptomatic patients. He thinks the target should be abandoned in the setting "only if" Eisai's BAN2401 Phase III trial in mild symptomatic patients "shows no cognitive benefit vs. placebo in any subset of those patients." Selkoe is a professor of neurologic diseases at Harvard Medical School and co-director of the Center for Neurologic Diseases at Brigham and Women's Hospital

BAN2401's efficacy signal in Phase II was largely driven by carriers of APOE4, a genetic risk factor for late-onset AD (see "Data Raise Possibility BAN2401 Primarily Benefits Alzheimer's Subgroup").

Other KOLs are not ready to outline the circumstances that would cause them to walk away.

"In our view, crenezumab and, more generally, the Aβ therapeutic strategy should continue to be investigated," said Andrea Pfeifer, CEO of AC Immune S.A. The biotech was the originator of Roche's amyloid oligomer-binding mAb crenezumab and has ACI-24, a cellular vaccine against β amyloid, in Phase I testing.

"All the data generated are essential for building up our understanding neurodegenerative diseases and ultimately, how to prevent or treat

them," said Pfeifer. "In short, we do not yet have the data to show the precise solution and as such, must continue to test all the possibilities."

John Sims, senior medical director and global brand development leader for neuroscience at Eli Lilly and Co., responded similarly. "I don't think we know yet" what would lead Lilly to abandon amyloid, he said. "Scientifically, the rationale is still there and it's still extremely strong."

Novartis is running two Phase II/III prevention trials in APOE4 carriers. GENERATION S1 is testing the BACE1 inhibitor CNP520, and GENERATION S2 is testing CNP520 in combination with the amyloid vaccine CAD106.

In an emailed statement to BioCentury, the pharma left open the door to additional studies, regardless of the outcome.

"THERE WAS ALWAYS SOME REASON WHY THIS TRIAL WAS GOING TO BE A BIG ONE, AND THEN ALWAYS SOME REASON WHY, ACTUALLY, IT WASN'T RUN THE RIGHT WAY."

DEREK LOWE, INDUSTRY COMMENTATOR

Lilly is aiming for a more homogeneous patient population through its "tau Goldilocks" trial design, which uses tau levels to indicate disease progression and optimize when targeting amyloid can be effective.

The design is being tested in Lilly's Phase II TRAILBLAZER-ALZ trial of donanemab, which binds amyloid plaques. Patients must have a positive amyloid PET scan plus the right amount of tau pathology assessed via PET.

"Whether this strategy works, I can't tell you," said Sims. "I can tell you at least that population is going to be more homogeneous than other populations in the past," including aducanumab's trials, "because they only selected for amyloid."

Roche is also testing its plaque-binding gantenerumab in symptomatic patients. After the failed Phase III SCarletRoAD trial in 2014, the pharma started two additional Phase III studies. GRADUATE 1 & 2 are testing a 1,200 mg dose of the mAb, about fourfold higher than the dose used in SCarletRoAD. The trials are slated to readout in 2022.

Faith in prevention

The greatest consensus among KOLs is that disease prevention is the best chance left for amyloid therapies.

At least five Phase II or III trials of amyloid agents are being run in secondary prevention settings, meaning that patients carry mutations known to cause AD or have other risk factors, such as APOE4 expression or a positive amyloid PET scan. These trials can use epidemiology to help figure out when to treat patients.

Companies are just beginning to learn how to conduct these trials, and the first wave of results, if negative, may not dent enthusiasm of the amyloid proponents.

"We believe that at the end of the Generation Program we will be able to answer if intervening prior to symptom onset for a longer duration of time with amyloid-based approaches provides benefit," said Novartis. "This may give rise to further questions about the point of treatment intervention."

APOE4 carriers have an increased risk of developing AD. But not all will get the disease, and those who do will get it late in life, like the general population. This leaves a very large window to start treatment. It also suggests that seeing an effect could require a long treatment period. Both Novartis trials are tracking patients for about five years.

Some commentators have called the Phase II Alzheimer's Prevention Initiative API ADAD study and the Phase II/III DIAN-TU study the last, big tests of the amyloid hypothesis, because they are going after more highly refined patient populations.

Both trials are enrolling patients with autosomal dominant mutations, meaning their mutations will lead to disease rather than just increase risk. The API ADAD study is in a Colombian family with a mutation that typically triggers disease around age 45, and DIAN-TU is enrolling patients with a variety of mutations that lead to early onset disease.

However, both trials are testing compounds with a track record of failures. API ADAD tests crenezumab, which failed the Phase III CREAD1 & CREAD2 trials in January. DIAN-TU has treatment arms testing Roche's gantenerumab, which failed SCarletRoAD and Marguerite RoAD, and Lilly's solanezumab, which failed the three Phase III EXPEDITION trials.

"If we are lucky as a field to have both of the agents work, that would suggest there are multiple ways to target this and it's just more about treating early or having a homogeneous population," said Lilly's Sims.

Lowe agrees that running prevention trials in genetically defined populations is a reasonable strategy.

But those still leave out the bulk of patients, and doing trials in young healthy people is not a viable option.

"The problem with dosing truly presymptomatic patients is that you're giving drugs to people who aren't sick. You really need a lot of very solid reasons to do that, medically and ethically, and to be honest, I don't think that the amyloid hypothesis is solid enough to go with," said Lowe.

The Phase III A4 trial of Lilly's solanezumab is the closest to a prevention trial in the general population. According to Selkoe, it's the only study enrolling "everyday people" with no clinical signs of AD and no mutations that cause the disease.

The subjects need to have a positive amyloid PET scan and be between the ages of 65 and 85, making the trial setting secondary rather than primary prevention. And it is a massive effort. To power it, assuming about 3% of the patients will develop clinical disease annually, given their age, the researchers had to screen roughly 15,000 people to get the desired amount of over a thousand subjects, according to Selkoe.

Fillit is skeptical the economics of prophylactically treating a wide swath of people with an amyloid therapy will make sense. "Imagine an antibody that has to be infused or given subcutaneously, that is going to cost quite a bit of money and is going to be widely used, I don't see how that is going to work from a population perspective."

"I don't know of any drug that didn't work in symptomatic patients that was later brought to the market because it did work for primary prevention. That's not how it usually goes," he said. bc

COMPANIES AND INSTITUTIONS MENTIONED

AC Immune S/A (NASDAQ:ACIU), Lausanne, Switzerland
Alzheimer's Drug Discovery Foundation, (ADDF), New York, N.Y.
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Brigham and Women's Hospital, Boston, Mass.
Eisai Co. Ltd. (Tokyo:4523), Tokyo, Japan
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Harvard Medical School, Boston, Mass.
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Washington University School of Medicine, St. Louis, Mo.

TARGETS

APOE4 - Apolipoprotein E ε4
APP - Amyloid precursor protein
BACE1 - β-site APP-cleaving enzyme 1
PSEN1 (PS1) - Presenilin 1
Tau (MAPT; FTDP-17) - Microtubule-associated protein τ

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