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# Is tau approaching a tipping point in Alzheimer's drug development?

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Is tau the new amyloid? Leaders in the Alzheimer's field have high conviction in tau — both as a target and surrogate endpoint — and they aren't letting a string of clinical misses deter them. Sound familiar?

Yet tau stands apart from amyloid in key ways, including its closer relationship to symptoms and promise to avoid the worst side effects of anti-amyloid therapy. And this time, companies are armed with lessons learned from decades of designing clinical trials for the indication.

In some ways, tau is a trickier target than amyloid. It exists in multiple forms, and its pathogenic effects appear both intracellular and extracellular — a harder biology to pin down than amyloid's extracellular pathology.

However, tau has a strong rationale behind it that's more tightly aligned to symptoms than amyloid. The timing and location of tau aggregation in the brain closely track with the onset, pattern and progression of symptoms. These features not only strengthen tau's case as a target, but also bolster its credibility as a surrogate endpoint — though questions remain.

"Not only does tau correlate with cognitive decline, it predicts cognitive decline. That is what is so compelling about the human biology of tau aggregates," Fiona Elwood, VP, disease area stronghold lead for neurodegeneration at Johnson & Johnson (NYSE:JNJ), told BioCentury.

J&J sponsored a session at this month's AD/PD Conference in Vienna devoted to highlighting the evidence supporting tau PET as a surrogate endpoint. The session brought together six speakers, including moderator Reisa Sperling, a PI at Massachusetts General Hospital and neurology professor at Harvard Medical School. Real-time polling during the session suggested much of the audience — largely composed of academics — viewed tau PET as a viable surrogate.

The alignment of the speakers on tau's potential as a surrogate endpoint, and positive response from the audience, reflects the proactive consensus-building already underway, before any anti-tau therapy reaches FDA's doorstep. The Critical Path Institute is contributing to the effort through the development of cenTauR, a standardized scale akin to the centiloid system for harmonizing amyloid PET data.

Together, evidence building, standardization and early stakeholder engagement could preempt the kind of controversy that surrounded Aduhelm aducanumab, the first anti-amyloid

mAb granted accelerated approval via amyloid PET as the surrogate endpoint.

However, a critical piece of the puzzle is still missing — a convincing demonstration of clinical benefit with a tau-targeted therapy.

"It's clear that we need further evidence from treatment effects on tau PET from ongoing trials," with the biomarker findings "correlating hopefully with clinical outcomes to build the evidence base that's needed," Sperling concluded at the conference.

Given the field's high confidence in the target, more data are on the way, despite a string of early failures. The next Phase II proof-of-concept readouts are due next year, from J&J's anti-tau mAb posdinemab and antisense therapy BIIB080 from Biogen Inc. (NASDAQ:BIIB).

Those candidates represent two of the three major approaches companies are deploying against tau: using antibodies to block extracellular spread of misfolded tau seeds, and knocking down tau mRNA to prevent intracellular production of the protein. The third approach involves immunizing patients against pathologic tau via a vaccine. Here, too, J&J has the most advanced candidate; its JNJ-2056, developed by AC Immune S.A. (NASDAQ:ACIU), is in Phase II testing.

FDA has granted fast track designation to all three therapies.

### Evolving picture of tau's role

Not long ago, the dominant hypothesis was that tau might be a useful target once patients had progressed to moderate dementia, untreatable with anti-amyloid mAbs. The large volume of biomarker work done in recent years has disabused the field of that notion.

Although tau deposition in the brain is downstream of amyloid accumulation, it's become clear that both are early disease processes. The appearance of tau aggregation in the medial temporal lobe correlates with early memory deficits that often precede progression to dementia.

"When you have tau escaping from the medial-temporal lobe that is the best predictor we have of symptom progression," said J&J's Elwood.

According to an AD/PD presentation by Christopher Rowe, director of the Australian Dementia Network, tau accumulation in a region referred to as "meta-temporal" precedes cognitive decline by about four years. But when tau spreads to temporal-parietal cortical regions, patients generally have just one year before cognitive deficits can be measured on the Clinical Dementia Rating – Sum of Boxes (CDR-SB) scale, a standard endpoint used in clinical trials for Alzheimer's.

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And while there is fairly stereotyped pattern of tau spread through the brain, inter-patient variability indicates that those with less medial temporal tau have fewer memory deficits; whereas parietal and occipital tau load correlates with visiospatial deficits, and parietal and frontal tau with deficits in language and executive function.

These relationships are in stark contrast to the timing and pattern of amyloid deposition, which is much earlier than tau and does not track with symptom domains.

"Unlike amyloid PET, the anatomy of tau seems to matter, and we can see that particularly well with tau PET" versus fluid markers, said Sperling.

Taking lessons from these findings, as well as recent learnings from the amyloid field, J&J has enrolled patients in its Phase II study of posdinemab who do not yet have high levels of tau accumulation in the brain. Elwood said the company is aiming for a "Goldilocks" tau phenotype where patients have some tau accumulation, suggesting the control group will progress during the study period, but not so much tau accumulation that an anti-tau mAb is no longer effective.

Because anti-tau antibodies work extracellularly, they intercept the spread of tau between neurons, rather than block its intracellular toxicities. This suggests the mAbs may be useful in slowing the escape of tau from the medial temporal lobe.

"We've got new methods of analysis where we're measuring what brain regions tau moves into, not just the amount of tau but the regional distribution," said Elwood.

### New antibodies, new epitopes

In addition to treating patients at the right disease stage, companies advancing the current crop of anti-tau antibodies aim to target the right epitope.

The first generation of anti-tau mAbs targeted the N-terminus and failed in the clinic. More recently, a mAb targeting a mid-domain epitope, bepranemab from UCB S.A. (Euronext:UCB), successfully slowed tau accumulation in PET scans and showed hints of efficacy, suggesting the protein's mid-region may be

a better target. The findings raised hopes that intercepting extracellular tau, without targeting its intracellular pathology, could yet be a viable strategy. The mAb did not, however, meet its primary Phase II endpoint.

"You can view that dataset as glass half full or glass half empty," Toby Ferguson, CMO of neurogenetic medicines company Voyager Therapeutics Inc. (NASDAQ:VYGR), told BioCentury. "I'm very much in the camp where, for the first time, we have seen evidence in a human being that an antibody administered IV can impact how accumulation and tau spread is measured by tau PET — you can actually impact that human biologic process."

Tau can be processed into a variety of fragments and phosphorylated at many sites, making it challenging to pin down the problematic species, of which there could be several.

Ferguson emphasized the importance of targeting "pathologic" tau, which he said can be operationalized by showing that an antibody produces no signal when staining human brain samples from people without Alzheimer's disease, but has a "clear signal characteristic of pathologic inclusions" in tissue samples from patient brains.

Voyager's Phase I candidate, VY7523, passes this test, he said, whereas bepranemab targets both non-pathologic and pathologic tau, which could dilute its activity.

VY7523 targets a C-terminal epitope on tau, as does Phase I candidate MK-2214 from Merck & Co. Inc. (NYSE:MRK). Ferguson said the two epitopes are similar but not identical. Merck's trial has a primary completion date in July, according to ClinicalTrials.gov, suggesting the field could get an early indication this year of the effect of targeting the C-terminus.

Bristol Myers Squibb Co. (NYSE:BMY) expects Phase II data in 2027 from BMS-986446, a mAb developed by Prothena Corp. plc (NASDAQ:PRTA). Prothena CEO Gene Kinney previously told BioCentury that the biotech took "a systematic approach" that involved making antibodies against many epitopes and choosing the top performer in its assays. BMS-986446 targets a microtubule binding domain region that likely partially overlaps with the tau243 — a fragment used as plasma biomarker that was recently shown to correlate closely with tau PET signal.

J&J's Elwood said posdinemab binds adjacent to microtubule binding domain. "I want to emphasize that this is a precision approach. We're targeting a disease-specific, mid-region, phospho-epitope and applying the Goldilocks tau approach to identify the right patients." The trial is fully enrolled, she said.

J&J is only the second company to stratify trial participants by baseline tau PET, following Eli Lilly and Co. (NYSE:LLY), which showed responses to anti-amyloid mAb Kisunla donanemab were much clearer in patients with intermediate than high levels of tau.

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### FIONA ELWOOD, JOHNSON & JOHNSON

### RNA knockdown surprises field

So far, two tau-targeting therapies that have successfully reduced tau PET signal in patients: UCB's bepranemab and Biogen's BIIB080. The Biogen result surprised the field.

None of the sources BioCentury spoke to expected the RNA knockdown approach to reduce the preexisting tau aggregates visible by PET. Those deposits, known as neurofibrillary tangles, were thought to represent the end stage of aggregation and likely the death or near death of neurons containing them.

But Biogen reported a reduction from baseline in tau PET in its Phase Ib study, not just a slowing of additional accumulation.

"The data was much better than expected," noted Ferguson. "Before that Biogen data the field had felt tau represented largely dead or dysfunctional neurons; they didn't think it could be removed. What that says to me is that there's a population of neurons that if you remove that inflow of pathologic tau, the existing cellular machinery can remove the preformed tau [aggregates]. I think that opens up a lot of different potential treatment possibilities."

The Phase Ib trial was small, and its exploratory clinical endpoints were compared with historical controls. But the findings are intriguing because the 2-point difference between treatment and the historical controls on the CDR-SB scale was larger than the 0.5-point change seen in Phase III trials of anti-amyloid mAbs.

Phase II data from BIIB080 are expected next year.

Between the UCB and Biogen datasets, and the additional data on the way, "I think tau is at a bit of a tipping point, or soon to be at a tipping point, where we're gonna really know the importance of this molecule for treatment of Alzheimer's," said Ferguson.

Other companies aiming to knock down tau RNA include Eli Lilly, with LY3954068, and Novartis AG (SIX:NOVN; NYSE:NVS), with NIO752; both siRNA therapies are in Phase I.

Voyager presented non-human primate data at AD/PD from a gene therapy encoding an anti-tau siRNA in its CNS-penetrating, liver de-targeted viral vector. The vector's use of a blood-brain barrier receptor to facilitate transcytosis enables broad distribution within the brain. "What you're doing is taking advantage of the vast network of blood vessels that feed the brain to get better biodistribution than you would with an injection into the lower spine," as is the typical route of administration for CNS-targeting RNA knockdown therapies, said Ferguson.

Also aiming for CNS-specific activity is San Francisco Bay Area biotech Switch Therapeutics Inc., which is developing an siRNA that conditionally activates in the presence of a cell-specific biomarker.

The fact that these therapies do not eliminate all tau production may be important for safety, given the physiological role of normal, non-misfolded tau in supporting axonal transport in neurons.

### Vaccine program aims to prevent Alzheimer's

While the mAbs and RNAi therapies in the clinic are being developed to treat early symptomatic patients, such as those with mild cognitive impairment or mild dementia, J&J and its partner AC Immune are taking their vaccine candidate upstream — into the presymptomatic setting.

The approach is bold, considering how few trials have been run in otherwise healthy people at high risk of progressing to symptomatic disease.

"A vaccine is a very patient-friendly approach," Elwood said. Rather than frequent IV infusions, patients get three intramuscular injections in six months, then maintenance doses.

Like posdinemab, "our tau active immunotherapy also targets a phospho-epitope adjacent to microtubule-binding domain, so we're focusing on disease-specific epitopes in that business part of tau," said Elwood.

Vaccines against self-antigens have had safety issues in the past. To head this off, JNJ-64042056 was developed against an aggregated rather than linear epitope.

It's taken J&J and AC Immune 10 years to get to this point. The pair partnered in 2015 to develop an active immunotherapy and had to go back to the drawing board after an initial Phase I study of an earlier version of the candidate did not elicit "the antibody repertoire we were looking for."

In the meantime, the learnings in the field, "because of all of the natural history data that's become available," have helped inform J&J's clinical development strategy, said Elwood.

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**TOBY FERGUSON, VOYAGER**

"It's the predictive endpoints, such as tau PET, that are making this doable," she said.

In the Phase II ReTain trial of new and improved candidate JNJ-64042056, J&J is employing tau PET to identify symptom-free patients with a level of baseline tau accumulation in the brain that suggests they are likely to progress within the study's four-year window.

The company is measuring a variety of biomarkers in addition to tau PET and using the Preclinical Alzheimer's disease Cognitive Composite 5 (PACC-5) as the primary endpoint. The trial began in the second half of last year.

AC Immune also has a vaccine against β-amyloid, partnered with Takeda Pharmaceutical Co. Ltd. (Tokyo:4502; NYSE:TAK), and a wholly owned vaccine against α-synuclein.

### Toward a surrogate endpoint

The presymptomatic setting may be where a surrogate endpoint is most useful, given the difficulty of measuring cognitive and functional changes during the period. Plus, the more successful a drug is at delaying the conversion to dementia, the longer patients would need to be tracked, a phenomenon oncology drug developers have increasingly had to contend with as overall survival timelines have lengthened.

That's not to say a surrogate endpoint wouldn't be useful in the symptomatic setting. The devastating nature of Alzheimer's disease, the lack of highly effective therapies, and the long duration of trials all point to value in a surrogate.

An issue that needs to be worked out is how to collect the data needed to confirm a drug's benefit after an accelerated approval, when it may become unethical to keep patients on placebo.

According to C-Path VP of Neurology Diane Stephenson, other discussions the field needs to have now are around standardization and sharing of data.

At the AD/PD Conference, she implored companies to standardize their PET protocols, from the tracer and camera used to the brain regions analyzed to the choice of analysis software.

"The more we can advocate and recommend specific standards for acquisition of data, the collection of the data and the analysis of data," the better the outcome for the whole community, she said. "Otherwise, when we get this data through the meta-analytic framework, it's not all going to line up. The standards are key."

A surrogate endpoint won't be possible without some data-sharing between companies, she added, urging companies to "look at a list of all the trials that have read out and ask yourself 'could you do it on your own?'" She pointed to the work FDA did to deem amyloid PET a reasonable surrogate endpoint, which involved aggregating data across many programs and showing a correlation between amyloid reduction and cognition across them.

"It's going to be almost impossible for anyone to do it on their own," said Stephenson. "My call to action is for people not to be so nervous about this. The risk of not sharing is higher than sharing."


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