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TOOLS & TECHNIQUES

Synuclein PET project

BY ALLISON JOHNSON, STAFF WRITER

As the Parkinson's field starts to solve the problem of how to detect toxic α-synuclein in the brain, it's closing in on imaging agents that could de-risk clinical trials. Phase I data expected this year could give a glimpse of whether new PET agents are up to the job, avoiding the poor selectivity that has thwarted the tools' success so far.

The hope is that an α-synuclein PET agent could provide drug developers with a molecular diagnostic and a biomarker of therapeutic response for the disease.

Because α-synuclein aggregates are the key pathological feature of Parkinson's disease (PD), the hypothesis is that depleting existing aggregates, or preventing their formation, will treat the disease. At least 15 anti-α-synuclein therapies are in development, including seven in the clinic, according to BioCentury's BCIQ database.

However, there is no good way to visualize whether a therapy intended to reduce α-synuclein aggregates in the brain has actually done so.

Blood- and CSF-based assays can give approximations, but there is debate as to how accurately they measure toxic α-synuclein in the brain.

Ideally, PET agents would quantify and track the spread of α-synuclein aggregates, enabling researchers to directly test the hypothesis that α-synuclein drives PD, identify the right patients for trial enrollment and make go/no-go decisions on clinical development programs with more certainty.

Despite a decade's worth of searching, it's difficult to find compounds that differentiate between α-synuclein, β-amyloid and tau, which are often co-expressed in PD patients.

Two α-synuclein PET agent programs have been disclosed and should provide clinical readouts starting this year.

AC Immune S.A. and Biogen Inc. will begin a Phase I trial this half of their PET agent ACI-3710. Data are expected in the second half.

Aprinoia Therapeutics Inc. has a PET ligand and plans to take it into the clinic in early 2020. The company did not respond to an inquiry about when it expects data.

AC Immune and Biogen are also each developing therapeutics against α-synuclein. AC Immune has a small molecule morphomer α-synuclein and an anti-α-synuclein mAb in discovery. Biogen's anti-α-synuclein mAb BIIB054 is in Phase II.

"We don't know yet whether or not it's feasible to image α-synuclein in the brain," said Jamie Eberling, who headed the Alpha-Synuclein Imaging consortium run by the Michael J. Fox Foundation for Parkinson's Research (MJFF) from 2011-17. But she thinks even a hint of α-synuclein selectivity in AC Immune's data this year will be an important step forward for the field.

Vision for PET

Standard approaches to measuring α-synuclein levels apply antibody-based assays to CSF or blood samples. Biogen is using both assays to measure therapeutic response in its Phase II trial of BIIB054.

Because α-synuclein is expressed by tissues other than the brain, it's not clear how much changes detected in blood-based tests reflect changes in the brain.

CSF assays detect only brain-derived α-synuclein, but recognize the soluble version and not the toxic, insoluble species that developers are aiming to deplete. And it's unclear how soluble α-synuclein in the CSF relates to the toxic α-synuclein in the brain.

An anti-α-synuclein PET agent could help PD companies avoid some of the early mis-steps of the Alzheimer's disease (AD) field, where an initial lack of β-amyloid and tau imaging tools left drug developers unable to definitively determine whether failed trials were due to the drug, the target or the patient populations.

"We have a lot of negative trials in neurology and often at the end of it, we don't even if know if we can reject the original therapeutic hypothesis that stimulated the trial," Biogen EVP and CMO Alfred Sandrock told BioCentury. "A well-done negative study can be very useful if we learn from it and move on. But without these kinds of reagents, we don't learn as much as we could."

A key use of an α-synuclein PET agent would be to help patient selection for trials.

"We learned this the hard way in Alzheimer's," Biogen VP of Biomarkers John Beaver said.

For example, in two failed registrational trials testing Eli Lilly and Co.'s anti-β-amyloid mAb solanezumab in mild to moderate AD, 22.5% of the 390 patients that received β-amyloid PET imaging had no evidence of β-amyloid plaques at baseline. The retrospective analysis was published in 2016 in *Psychosomatics*.

Eberling and Beaver added said that unlike existing antibody-based assays, a PET agent could track the spread of α-synuclein plaques from the brainstem to the cortex, a phenomenon that coincides with disease progression.

AC Immune CEO Andrea Pfeifer thinks a successful anti-α-synuclein PET agent could advance precision medicine for neurodegenerative diseases.

"In cancer, it was only when we had molecular diagnostics that we became successful. After you could determine the mutation, you could really do precise treatment," Pfeifer said.

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>
> ALFRED SANDROCK, BIOGEN

Getting specific

One of the biggest hurdles has been that screening assays yield non-selective compounds or compounds that translate poorly to humans. Another challenge is the limited availability of structural information about α-synuclein.

Beaver said that a poorly selective α-synuclein PET agent is likely to be soaked up by β-amyloid or tau before it finds its target, because β-amyloid and tau are more abundant and accessible than α-synuclein.

PET agents will also compete for binding with white matter, said Beaver, and as α-synuclein aggregates appear in a small area of the brain surrounded by white matter, it is difficult to differentiate in PET scans between white matter background noise and true positive signals.

Pfeifer said background from white matter prevented AC Immune from advancing its first-generation α-synuclein PET agent, which it tested in a first-in-human trial last year. The company has not reported data. Pfeifer said AC Immune's second-generation compound has undisclosed modifications designed to improve the signal-to-noise ratio.

AC Immune and Aprinoia use different starting points for their respective screening assays, but both methods are designed to identify compounds that bind α-synuclein aggregates and then optimize them for α-synuclein selectivity.

AC Immune's tissue-based screen uses patient samples containing α-synuclein aggregates, while Aprinoia's *in vitro* assay uses recombinant α-synuclein fibrils expressed by bacteria and aggregated with heparin.

Patient samples could increase the odds that hits from the screen will bind the forms of α-synuclein found in patients. However, the assay is more expensive than the *in vitro* one and the number of compounds it can screen depends on tissue availability.

Aprinoia SVP of Drug Discovery Paul Tempest said the company validates hits in human tissue using tritiated probes developed by an undisclosed pharma partner.

Both companies use structure-guided drug design to optimize the selectivity of PET candidates, but available structures for α-synuclein are either partial or derived from recombinant fibrils rather than patients.

Instead of increasing selectivity for α-synuclein, Aprinoia is decreasing selectivity for tau.

After identifying α-synuclein binders in its initial screens, it uses structure-guided drug design to remove moieties that could bind tau.

"Since we know more about the tau structure, it's easier to dial out tau affinity than to dial in α-synuclein affinity," Tempest said.

AC Immune dials in affinity for toxic forms of α-synuclein by using fibril structures of the target to guide drug design. The company did not respond to an inquiry regarding whether it uses recombinant- or patient-derived structures in its models.

Piecing together PET

Open questions include the precise structures of α-synuclein aggregates in patients, whether these structures evolve within the same patient as disease progresses or are different across patient populations, and whether it's possible to design a pan-α-synuclein PET agent.

"We don't typically know what forms the molecules are binding. Instead what we know is that the molecules bind in α-synuclein-rich brain tissues," Beaver said.

Robert Mach, a professor of radiology at the University of Pennsylvania and a member of MJFF's Alpha-Synuclein Imaging consortium, thinks obtaining the cryo-electron microscopy (cryoEM) structure of α-synuclein could accelerate PET agent development.

Mach said the key will be getting cryoEM structures from fibrils isolated from human tissue, rather than structures of recombinant fibrils commonly used in research that often don't have the same post-translational modifications or mutations found in patients.

Eberling said another key to solving the selectivity problem in PET agent development is publishing the structures of successful and failed PET candidates, which she said most groups don't do.

Some teams have found agents that recognize α-synuclein and β-amyloid, while others have discovered compounds that recognize α-synuclein and tau, and Eberling said comparing each set of structures could help researchers understand what shared components among them drive selectivity for each aggregate.

"Synuclein is going to be every bit as complicated as tau and you're probably going to need different PET probes to image the different forms of aggregated α-synuclein," Mach said.

Pfeifer said AC Immune's agent binds selectively to α-synuclein in patient samples with PD, or with the synucleinopathies multiple system atrophy (MSA) and dementia with Lewy bodies (DLB). It will enroll patients from all three indications in its trial this year.

COMPANIES AND INSTITUTIONS MENTIONED

AC Immune S.A. (NASDAQ:ACIU), Lausanne, Switzerland
Aprinoia Therapeutics Inc., Taipei, Taiwan
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
The Michael J. Fox Foundation for Parkinson's Research (MJFF), New York, N.Y.
University of Pennsylvania, Philadelphia, Penn.

TARGETS

α-synuclein (SNCA)
tau (MAPT; FTDP-17) - Microtubule-associated protein τ

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