SPECIAL FOCUS

NEUROSCIENCE/NEUROLOGY

The 'Tao' of tau?

In the recurring debate of tau vs. amyloid, we take a look at how anti-tau research is progressing

BY JEFFREY BOULEY

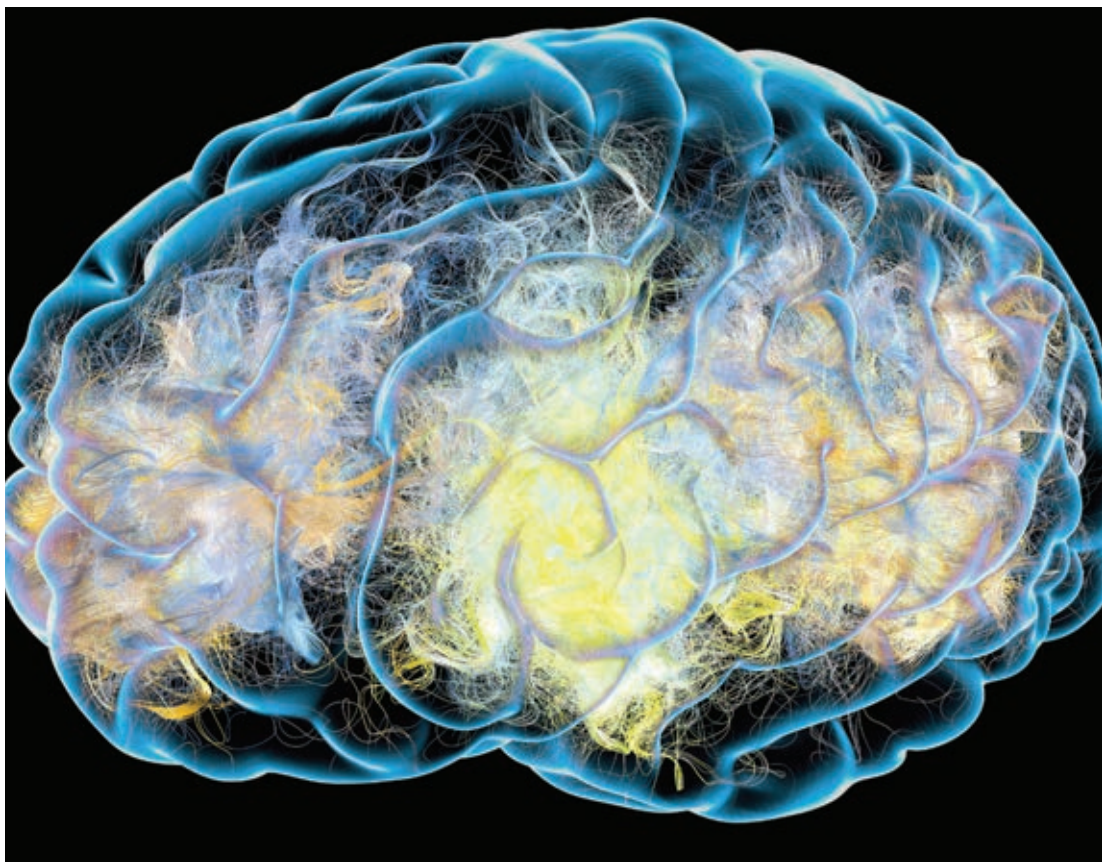
IN LOOKING AT NEURODEGENERATIVE DISEASES for this special focus section on neuroscience, it seemed fitting to check in not just on the consistently hot topic of Alzheimer's disease, but more specifically the issue of the tau protein and some of the recent insights and progress on the anti-tau front.

Alzheimer's has already proven to be a particularly complex and challenging disease for life-sciences researchers and pharma/biotech companies. And in a disease where sticky tangles of proteins seems to atrophy the brain and choke off cognition, one of the stickiest areas has been the issue of the amyloid protein vs. the tau protein. The aggregation of the tau protein is a hallmark of Alzheimer's disease, but traditionally much of the energy and effort has gone toward focusing on ways to reduce the number of amyloid plaques.

As Emily Underwood wrote in a 2016 article in *Science*, "One of the telltale signs of Alzheimer's disease (AD) is sticky plaques of ß-amyloid protein, which form around neurons and are thought by a large number of scientists to bog down information processing and kill cells. For more than a decade, however, other researchers have fingered a second protein called tau, found inside brain cells, as a possible culprit."

The topic Underwood was addressing was an imaging study of 10 people with mild AD that indicated tau deposits, rather than amyloid, are closely linked to memory loss, dementia and other AD symptoms. It wasn't evidence that actually resolved the amyloid-tau debate—almost certainly both proteins play major roles, and perhaps other factors as well—but the findings did serve as a potential jumping-off point for additional effort on tau-targeting treatments and better diagnostic tools.

And on the subject that tau and amyloid likely represent more of a "pair of culprits" rather than an "either-or" situation, we can go back a couple years to a *JAMA Neurology* paper by G.S. Bloom that cast ß-amyloid protein and tau in a "trigger and bullet" metaphor. As the author noted in the abstract, "During the past dozen years, a steadily accumulating body of evidence has indicated that soluble forms of Aβ and tau work together, independently of their accumulation into plaques and tangles, to drive healthy neurons into the diseased state and that hallmark toxic properties of Aβ require tau. For instance, acute neuron death, delayed neuron death following ectopic cell cycle reentry, and synaptic dysfunction are triggered by soluble, extracellular Aβ species and depend on soluble, cytoplasmic tau. Therefore, Aβ is upstream of tau in AD pathogenesis and triggers the conversion of tau from a normal to a toxic state, but there is also evidence that toxic tau enhances Aβ toxicity via a feedback loop."



There is no resolution as to whether amyloid plaques or tau tangles are more important in the etiology of Alzheimer's disease—or if either is more important than the other—but tau continues to gain interest as a target even as the shadow of amyloid research continues to loom over it.

Druggability of tau

So, fast forwarding back to the present day—or June 28, 2018, at least—we see one company continuing the trend toward more focus on tau as news came out of Cantabio Pharmaceuticals Inc. that the company, which is working on therapeutics for AD, Parkinson's disease and related neurological disorders, had seen publication of a peer-reviewed article. Lead authored by Cantabio's CEO Dr. Gergely Toth, along with collaborators at the Hungarian Academy of Sciences and German Center for Neurodegenerative Diseases (DZNE), the work appeared in the journal *ACS Chemical Neuroscience*.

The paper was titled "The structural basis of small molecule targetability of monomeric Tau protein" and reported structure-based evidence that native monomeric tau can be a viable target for drug-like small molecules despite its heterogeneous structure.

As the company noted of the news, the aggregation of monomeric tau protein is linked to the onset and progression of Alzheimer's disease and other tauopathies, and this study and the scientific team's previous findings provide theoretical and experimental evidence for the ability of monomeric tau to be a receptor of small molecules designed to prevent the aggregation, which leads to toxicity and cell death.

As per Prof. Eckhard Mandelkow, a co-author of the publication and group leader at DZNE in Bonn, this is further evidence that inhibition of tau aggregation by small molecules may be a viable therapeutic approach for tauopathies such as Alzheimer's disease. He noted that "These molecules are currently being evaluated in animal models of tau-induced pathology."

"We are excited to publish further scientific evidence that establishes a structural biology basis for Cantabio's tau small-molecule pharmacological chaperone program, which aims to prevent and reduce aggregation of tau protein as a therapeutic strategy for Alzheimer's disease and other tauopathies such as concussion-related chronic traumatic encephalopathy," said Cantabio's CEO, Dr. Gergely Toth. "The tau protein has long been a major target for Alzheimer's drug development, but due to the nature of its structure, it has historically proven to be a difficult target for small-molecule drug candidates. Our work at Cantabio represents a significant step forward in developing a therapy that is able to prevent the formation of the toxic protein aggregates that are associated with neurodegeneration in these diseases."

Tau as a therapeutic and diagnostic target

And, perhaps in a sign of how much tau research remains in the shadow of amyloid research, our next piece of fairly recent news comes from

the end of last year, when AC Immune SA, a clinical-stage biopharmaceutical company with a broad pipeline focused on neurodegenerative diseases, shared the top-level insights from a key opinion leader (KOL) luncheon meeting on the importance of tau as a target in Alzheimer's disease and other neurodegenerative diseases. The meeting featured presentations by KOLs Dr. Khalid Iqbal of the New York State Institute for Basic Research in Developmental Disabilities and Dr. Michael Rafii of the University of California, San Diego, and the University of Southern California.

Iqbal highlighted the critical importance of tau as a therapeutic target in Alzheimer's disease and other neurodegenerative diseases and how inhibition and prevention of the Tau pathology can potentially rescue the pathology of Alzheimer's disease and cognitive impairment, commenting: "Neurodegeneration leads to tau pathology, and tau pathology leads to neurodegeneration. Where there is no tau pathology, there is no Alzheimer's disease. Tau-based therapeutic approaches have significant potential to treat a range of neurodegenerative diseases."

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Dr. Gergely Toth, CEO of Cantabio Pharmaceuticals

Rafii discussed tau-mediated pathology and the importance of tau diagnostics in people with Down syndrome, a population with a genetic predisposition to develop Alzheimer's-related neuropathological changes, including ß-amyloid plaques and tau tangles.

"Biomarkers of Alzheimer's, including Tau-PET, can be readily studied in adults with Down syndrome as in other preclinical AD populations," Rafii noted. "By understanding the link between Alzheimer's and Down syndrome, we may not only be able to help the Down syndrome community, but the broader population as well. People with Down syndrome are an important population to study as we enhance our understanding of early intervention and prevention of Alzheimer's disease in general."

Also at the KOL meeting, Dr. Andreas Muhs, chief scientific officer of AC Immune, highlighted the company's relevant Tau programs:

- ACI-35, an anti-tau vaccine in Phase 1b and developed in collaboration with Janssen Pharmaceuticals under a 2014 licensing agreement
- RO7105705, an anti-tau antibody in Phase 2 and developed in collaboration with Genentech under a 2012 licensing agreement
- Morphomer Tau, a small molecule in preclinical development and developed in-house
- PI-2620, a Tau-PET imaging agent developed in collaboration with Piramal Imaging under a 2014 licensing agreement.

"We are delighted to share the valuable insights of these world-leading experts with our investors and stakeholders. These types of exchanges are vital so we can all work more

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CREDIT: AC IMMUNE SA

AC Immune is heavily invested in neurodegenerative research and conducted a key opinion leader luncheon last year at which experts weighed in on the importance of the tau protein both as a therapeutic and diagnostic target.

CREDIT: CANTABIO PHARMACEUTICALS INC.

Cantabio researchers recently published evidence that native monomeric tau can be a viable target for drug-like small molecules despite its heterogeneous structure.

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effectively together to achieve the common goal of an approved disease-modifying therapeutic and earlier diagnosis of Alzheimer's disease—one of society's biggest challenges of the century," said Prof. Andrea Pfeifer, CEO of AC Immune.

Potential monotherapy?

Also late in 2017, TauRx Therapeutics Ltd. reported the full results from its second Phase 3 clinical study of LMTX, a tau aggregation inhibitor for Alzheimer's disease, which were published online in the *Journal of Alzheimer's Disease*. The company noted that results from this study (TRx-237-005) are consistent with those from the first Phase 3 study, recently published in *The Lancet* in mild to moderate Alzheimer's disease, in supporting the hypothesis that LMTX might be effective as monotherapy at a dose as low as 4 mg twice daily.

The results of the earlier study showed significant differences in favor of two higher doses of LMTX (75 mg and 125 mg twice daily) when taken as monotherapy compared with the intended 4 mg control dose taken as monotherapy or as add-on therapy to currently approved treatments for AD in prespecified *post-hoc* analyses. In a further analysis, the same difference in favor of monotherapy compared with add-on treatment was found in patients taking the 4 mg twice-daily dose.

According to TauRx, in both the LMTX monotherapy and add-on therapy groups, whole brain atrophy (measured via MRI scans) initially progressed as expected for patients with mild Alzheimer's disease. However, after nine months of treatment, the annualized rate of whole brain atrophy in monotherapy patients reduced significantly and became typical of that reported in normal elderly controls without Alzheimer's disease. The comparable rate seen in the add-on therapy group progressed as reported for patients with mild Alzheimer's disease.

And early this year, the company reported preclinical study results, published online in *Frontiers in Molecular Neuroscience*, showing that LMTM, the active pharmaceutical ingredient in the LMTX product developed for the treatment of Alzheimer's disease, may also be useful for the treatment of Parkinson's disease.

It is worth noting that in 2016, there was some significant disagreement regarding LMTM when Phase 3 results were presented showing that the drug missed its co-primary endpoints of slowing cognitive and functional decline in mild to moderate AD. Some had argued that the placebo and drug results were nearly identical and, as a commentator on the Alzforum website argued, a scientist involved in the trial presented "a subgroup analysis that held no statistical credence yet purported to show a strong benefit on cognition and brain atrophy."

Some other takes around the same time contended that LMTM might not benefit AD patients who are receiving standard of care but, as a monotherapy, the drug might stabilize cognition and reduce brain atrophy. ■

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Dr. Michael Rafii of UC San Diego and USC

Picking apart PD

A roundup of recent news on R&D related to Parkinson's disease

BY JEFFREY BOULEY

NEW YORK—A recent study from researchers at the Icahn School of Medicine at Mount Sinai provides new insights into a link between inflammatory bowel disease (IBD) and Parkinson's disease (PD), and may have significant implications for the treatment and prevention of PD.

The study, published in *JAMA Neurology*, shows that individuals with IBD are at a 28-percent higher risk of developing PD than those without IBD. However, if they are treated with anti-tumor necrosis factor alpha (anti-TNFα) therapy, a monoclonal antibody that is commonly used to control inflammation in IBD patients, then their risk of developing Parkinson's goes down significantly, and becomes even lower than that in the general population.

These new insights may allow for better screening of IBD patients for Parkinson's disease, given that IBD onset usually precedes that of PD by decades, and they also offer evidence to support exploring anti-TNFα therapy to prevent PD in at-risk individuals.

While previous research had shown genetic and functional connections between IBD and Parkinson's disease, clinical evidence linking the two has been scarce. The authors of the study previously identified a number of genetic variants that contributed to either an increased risk of both PD and of Crohn's disease, a type of IBD, or a decreased risk of both diseases, which prompted them to further study the co-occurrence of the two diseases.

"Systemic inflammation is a major component of IBD, and it's also thought to contribute to the neuronal inflammation found in Parkinson's disease," explained Inga Peter, a professor in the Department of Genetics and Genomic Sciences at Mount Sinai and lead investigator in the study. "We wanted to determine if anti-TNFα therapy, could mitigate a patient's risk in developing Parkinson's disease."

The Mount Sinai team found a 78-percent reduction in the incidence of Parkinson's disease among IBD patients who were treated with anti-TNFα therapy when compared to those who were not.

It was previously thought that anti-TNFα therapies had limited effects on the central nervous system, the site where molecular mechanisms of PD are found, because the large molecules in the anti-TNFα compounds cannot independently pass through the blood-brain barrier. The outcomes of this study suggest that it may not be necessary for the drug to pass through the blood-brain barrier to treat or prevent inflammation within the central nervous system, or that the blood-brain barrier in patients with IBD may be compromised, allowing the large molecules of the compound to pass through.

Preclinical evidence for DJ-1 protein targeting

SAN FRANCISCO—Cantabio Pharmaceuticals Inc. recently presented results of the company's DJ-1 protein-targeting small-molecule pharmacological chaperone therapeutic program at the Neuro4D Conference (Advances in Drug Discovery for Proteopathic Neurodegenerative Diseases) in Mainz, Germany.

Loss of DJ-1 protein function has been linked to the onset of a variety of diseases, such as Parkinson's disease, Alzheimer's disease, stroke, amyotrophic lateral sclerosis, chronic obstructive pulmonary disease and type 2 diabetes. The DJ-1 protein is considered to be one of the primary therapeutic targets for Parkinson's disease, as it is genetically linked to the onset of familial PD.

The presentations described the positive therapeutic activity in cellular models and in an MPTP mouse model of PD of Cantabio's novel DJ-1 candidates.

"We are excited to present positive *in-vivo* efficacy results of one of our orally bioavailable DJ-1 protein targeting small-molecule pharmacological chaperones. This drug candidate has shown excellent drug-like characteristics and its significant protective function in a recognized mammalian disease model for Parkinson's disease is a major step forward for Cantabio's drug development programs," said Cantabio's CEO, Dr. Gergely Toth. "We are looking forward to testing this molecule in further disease models of Parkinson's and Alzheimer's disease and to the further development of multiple candidates from our other programs. These results also provide excellent validation of our in-house DJ-1 drug discovery platform's ability to generate prospective drug candidates and for our DJ-1 targeting therapeutic program's potential for becoming a disease-modifying therapeutic for Parkinson's and Alzheimer's disease."

Axovant licenses investigational gene therapy

BASEL, Switzerland—Axovant Sciences in early June announced that it had licensed the exclusive worldwide rights to develop and commercialize OXB-102, now AXO-Lenti-PD, from Oxford BioMedica. AXO-Lenti-PD is an investigational gene therapy for Parkinson's disease that delivers three genes encoding a critical set of enzymes required for dopamine synthesis in the brain. Oxford BioMedica is a world leader in lentiviral vector product development and manufacturing, and will be the clinical and commercial supplier of AXO-Lenti-PD. Axovant expects to initiate a Phase 1/2 dose escalation study of AXO-Lenti-PD in patients with advanced PD by the end of 2018.

Under the terms of the license agreement with Oxford BioMedica, Axovant obtained rights to AXO-Lenti-PD, as well as its predecessor product ProSavin, for an initial payment of $30 million in cash, $5 million of which will be applied as a credit against the process development work and clinical supply that Oxford BioMedica will provide to Axovant. Oxford BioMedica is also eligible to receive additional development, regulatory and commercial milestone payments potentially in excess of $812 million, and tiered royalties on net sales of AXO-Lenti-PD, if approved. Roivant has agreed to purchase $25 million of Axovant common shares, which will support the clinical development of AXO-Lenti-PD and additional business development activities. ■