EMERGING COMPANY PROFILE

THE ROAD TO TAU

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Asceneuron S.A. is working to treat neurodegeneration by preventing formation of neurofibrillary tangles in the hopes this mechanism will fare better in treating Alzheimer's disease than amyloid-targeted products.

Neurofibrillary tangles arise when microtubule-associated protein tau (tau; MAPT; FTDP-17) aggregates into helical filaments and larger structures, a process associated with tau hyperphosphorylation. Glycosylation by enzymes such as O-linked N-acetylglucosamine (GlcNAc) transferase (OGT) protects against tau hyperphosphorylation; however, this glycosylation is reversed by the enzyme O-linked N-acetylglucosaminidase (O-GlcNAcase).

Asceneuron's ASN-561 is a small molecule O-GlcNAcase inhibitor. Inhibiting O-GlcNAcase may promote glycosylated tau, thereby preventing hyperphosphorylation and subsequent tangle formation.

CEO Dirk Beher said Asceneuron chose to focus on tau, the lesser explored of the two major AD pathologies, because of potential partners' interest in the space and the chance to establish proof of concept in progressive supranuclear palsy (PSP). PSP is an Orphan neurodegenerative disorder associated with tau accumulation that could be faster and more tractable than AD.

Beher said Asceneuron doesn't think targeting beta amyloid is wrong, but the company doubts it will be sufficient on its own.

"What we think is happening — since people are making slow progress with amyloid — is most likely we need therapies for both these pathologies to have success in humans," he said.

But Beher said tau-based approaches might do better as monotherapy than amyloid targeting agents have because increased tau deposits correlate better with late-stage AD.

"The progression of tau pathology matches the decline in Alzheimer's disease much better than beta amyloid," he said.

ASCENEURON S.A.
Lausanne, Switzerland

Technology: Small molecule O-GlcNAcase inhibitors preventing formation of tau tangles

Disease focus: Neurology

Clinical status: Preclinical

Founded: 2012 by Dirk Beher, Christoph Wiessner and Frank Armstrong

University collaborators: Undisclosed

Corporate partners: None

Number of employees: 8

Funds raised: €5 million ($6.4 million)

Investors: MS Ventures

CEO: Dirk Beher

Patents: None issued

At the 2014 Alzheimer's Association International Conference, Asceneuron reported that JNPL3 tau transgenic mice given single oral doses of ASN-561 daily for five days showed dose-dependent increases in O-GlcNAcylated tau in the forebrain, brain stem and spinal cord that reached levels up to 12 times higher than levels seen in vehicle-treated mice.

Beher said Asceneuron plans to begin Phase I by early 2016 and hopes to partner the program after conducting Phase Ib studies to show safety, tolerability and target engagement.

Asceneuron plans to raise $25 million in a series A round to support ASN-561 through a Phase II/III study in PSP.

At least one company has a more advanced PSP program. Cortice Biosciences Inc.'s TPI 287, a microtubule stabilization agent, is in Phase I as an intravenous infusion to treat tauopathies including PSP and AD. Cortice also is studying an oral formulation in preclinical testing.

At least three companies have clinical tau-targeted AD programs. The most advanced is TauRx Pharmaceuticals Ltd.'s LMTX, a second-generation tau aggregation inhibitor in Phase III to treat AD and frontotemporal dementia (FTD). Beher said unlike TauRx and most others in the space, Asceneuron is targeting tau indirectly, though he noted it's unclear what advantage this may confer.

Alectos Therapeutics Inc. is discovering and developing modulators of O-GlcNAcase to treat AD and other disorders under a deal with Merck & Co. Inc.

Beher thought the competitors were using carbohydrate-based inhibitors that mimic O-GlcNAcase's substrate, whereas Asceneuron's program uses a non-carbohydrate scaffold that could confer better brain penetration.

Alectos CSO David Vocadlo declined to give an update on the status of the collaboration or say what scaffolds the partners are using, but he acknowledged that a non-carbohydrate scaffold could help with efficient brain penetration.

Asceneuron also has an M1 positive allosteric modulator program slated to enter the clinic in 2016 as a cognitive enhancer for AD.

Asceneuron spun out of Merck KGaA's Merck Serono unit in 2012. The biotech has four patent applications covering small molecules targeting tau and muscarinic acetylcholine receptor M1 (CHRM1; HM1).

COMPANIES AND INSTITUTIONS MENTIONED

Alectos Therapeutics Inc., Burnaby, B.C.
Alzheimer's Association, Chicago, Ill.
Asceneuron S.A., Lausanne, Switzerland
Cortice Biosciences Inc., New York, N.Y.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
TauRx Pharmaceuticals Ltd., Singapore, Singapore

REFERENCES

Flanagan, M. "New tack on tau." *BioCentury* (2010)
Hansen, S. "Serono's starter kit." *BioCentury* (2013)