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Science-Business eXchange

Gladstone's AD venture

By Lev Osherovich, Senior Writer

The **Gladstone Institute of Neurological Disease** is launching a philanthropically funded translational research center to aid the preclinical development of Alzheimer's disease candidates emerging from the institute's research. The center hopes to pursue AD targets and mechanisms that go beyond the usual suspects like β-amyloid and TAU protein aggregation.

Gladstone's internal pipeline includes at least two new AD compounds—one handed back by **Merck & Co. Inc.** after a recently terminated co-development deal and the other a novel neuroprotective agent.

This week, the institute received a $6 million seed donation from the **S.D. Bechtel, Jr. Foundation** to set up the Center for Comprehensive Alzheimer's Disease Research. Gladstone hopes to raise an additional $34 million in gifts from philanthropic organizations or individuals over the next 9 years to fund the center's work.

The center aims to shepherd discovery-stage compounds through the lead optimization and preclinical testing that neither academics nor investors in early stage biotechs are keen to take on alone.

Gladstone ultimately expects to commercialize the work through startups or licensing deals with pharma. Instead of building in-house facilities, the new center will do its work through a consortium of other academic institutions and CROs.

"The idea is to provide assistance all the way from discovery to Phase I, using consultants to connect our investigators to the right outside facilities," said Lennart Mucke, director of the institute.

Mucke, who will head the new AD center, also is a professor of neurology and neuroscience at the **University of California, San Francisco**.

He said the AD center's core staff of about a dozen people will coordinate access for Gladstone researchers to compound libraries and pharmaceutical chemistry facilities at other California institutions, including the **California Institute for Quantitative Biosciences** (QB3) and the **Sanford-Burnham Medical Research Institute**. Sanford-Burnham has used its drug discovery capabilities to cultivate extensive ties with pharma,[1] which could open doors for Gladstone's discoveries.

Preclinical development will mostly take place at CROs.

New targets needed

The center initially will focus on targets beyond β-amyloid (Aβ) and microtubule-associated protein-τ (MAPT; TAU; FTDP-17), which are neuronal proteins that misfold and aggregate to drive AD.

Mucke said recent clinical setbacks in efforts to prevent the production or accumulation of Aβ have called into question whether the protein can be effectively targeted.

Aβ can form large aggregates as well as smaller oligomers, and Mucke added that there is no consensus about which variants of Aβ are truly critical to disease and can be affected by therapeutics in the clinic.

"What concerns me about many of the Aβ approaches is that we don't have clear data about whether these treatments affect oligomers, which we think are important for disease," he said.

Likewise, intracellular TAU aggregates are hard to hit directly, he noted.

Thus, "there is a diversification going on in drug development away from strategies focused on Aβ and TAU and toward mechanisms that make the brain more resistant to these players," said Mucke. Gladstone researchers already have several targets and compounds directed against such mechanisms.

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> ***—Lennart Mucke, Gladstone Institute of Neurological Disease***

A case in point is apolipoprotein E4 (APOE4). Robert Mahley, president emeritus and investigator at **The J. David Gladstone Institutes**, and fellow Gladstone investigators Karl Weisgraber and Yadong Huang have championed the idea that APOE4 adopts an abnormal intracellular form that promotes neurodegeneration independently of Aβ.

The Gladstone Institute of Neurological Disease collaborated with Merck to identify small molecules that correct the structure of APOE4 and decrease its toxicity in cell culture.[2] The pharma discontinued the collaboration last year for budgetary reasons.

Mucke said Gladstone is negotiating with Merck to obtain full rights to the compounds and hopes to use the AD center to advance their development and then spin them out into a new company.

Another candidate for development by the new AD center is JM6, a small molecule inhibitor of kynurenine 3-monoxygenase (KMO). Last month, a Gladstone Institutes team led by Paul Muchowski reported that the compound decreased the severity of AD symptoms in mice.[3] Muchowski also is an associate professor of biochemistry and biophysics at UCSF.

Muchowski said that JM6 is derived from compounds previously in preclinical development for stroke by **Roche** that were not advanced into the clinic for undisclosed reasons. He added that JM6 has a distinct structure and is covered by a new composition-of-matter patent.

The precise mechanism of how JM6 acts is unknown. It does not appear to affect Aβ or TAU but rather makes neurons resistant to the proinflammatory and metabolic effects of these toxic proteins.

Muchowski hopes to use the AD center to complete toxicology

studies that would be part of a data package for potential investors in an as yet unnamed neurodegenerative disease startup that he is founding.

"Although this is one of the furthest-along projects at Gladstone, there are still some gaps" in the preclinical data package needed to win VC seed funding, said Muchowski. "At this point [potential investors] are mostly convinced about the efficacy and just want to see toxicity data for chronic dosing."

"The AD center's money and infrastructure will help fill those gaps. We have to do a bunch of *in vitro* and animal safety studies with this compound, including more studies in animals about how late we can dose," he said.

Although generating IND-ready AD compounds is the AD center's mission, Muchowski noted that JM6 would not necessarily first go into humans for that indication. Instead, he thinks JM6 could first be tested in Huntington's disease (HD).

Encouraging effects on cognition in an HD trial, together with preclinical data in AD models, would help build a case for testing the compound in AD, for which trials are typically larger and more complex than those in a genetically defined orphan indication like HD.

Mucke also noted that the AD center would support other, earlier stage projects that require large-scale screening but have not yet produced development-ready compounds.

He cited work by Gladstone investigator Li Gan that suggests TAU is differentially acetylated in AD patients compared with healthy patients.[4] The AD center will help Gan screen RNAi libraries to identify targets involved in TAU acetylation.

Osherovich, L. *SciBX* 4(27); doi:10.1038/scibx.2011.754
Published online July 14, 2011

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COMPANIES AND INSTITUTIONS MENTIONED

California Institute for Quantitative Biosciences, San Francisco, Calif.
Gladstone Institute of Neurological Disease, San Francisco, Calif.
The J. David Gladstone Institutes, San Francisco, Calif.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Sanford-Burnham Medical Research Institute, La Jolla, Calif.
S.D. Bechtel, Jr. Foundation, San Francisco, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of California, San Francisco, Calif.