Cognition Therapeutics, Inc.
www.cogrx.com

Focusing on synaptic protection in Alzheimer's

Cognition Therapeutics, Inc. has a first-in-class, clinical-stage, highly brain-penetrant and orally bioavailable small molecule designed to halt the initiation and progression of Alzheimer's disease. The company is looking to partner on this and other small molecules targeting neurodegenerative diseases.

Cognition Therapeutics, Inc. (CogRx) specializes in clinical-stage small-molecule therapeutics with a focus on the discovery and development of novel drugs for neurodegenerative diseases.

Using a phenotypic screening approach—testing the activity of compounds with a bioassay that re-creates Alzheimer's disease (AD) in a dish—the company has pinpointed a receptor complex on brain cells that binds β-amyloid (Aβ) oligomers and sets off the neurotoxic effects that lead to AD. CogRx's lead compound, CT1812, is a first-in-class small molecule that displaces bound Aβ oligomers and inhibits binding of Aβ oligomers to the receptor complex, restoring synapse function and thereby stopping and even reversing memory loss in models of AD. CT1812 was well tolerated in phase 1a clinical trials in healthy young and elderly volunteers[1]. The compound is in first-in-patient clinical trials as of Q3 2016 and will be entering phase 2a trials in 2017.

CogRx is looking to advance CT1812 through late-stage clinical trials in collaboration with external partners.

Stopping AD in its tracks

AD is characterized by a loss of memory that most scientists agree is caused by a build-up of the protein Aβ in the brain[2]. Over time, and owing to an imbalance between production and clearance, Aβ monomers start self-associating to form toxic Aβ oligomers. These oligomers bind to receptor proteins on synapses, interfering with synaptic function and leading to memory failure.

Most strategies to combat AD aim to reduce the number of Aβ oligomers by targeting Aβ peptides with antibodies or by targeting secretases, the enzymes involved in Aβ formation, with small-molecule inhibitors. These efforts have yet to yield definitive solutions, and their clinical development has been complex and expensive because of the need for earlier intervention and length of time before a response to these therapies can be observed (months to years).

CogRx has taken a different approach. Instead of targeting the upstream players in AD—Aβ and secretases—its drug candidates tackle the initial steps of the physiological cascade involved in causing synaptic malfunction: the binding of Aβ oligomers to synaptic receptor complexes. CogRx was one of the first companies to focus on this target for AD, and its efforts led to the identification of several drug candidates capable of displacing Aβ oligomers bound to the receptor complexes and of preventing oligomer binding in the first place[3]. This approach is highly differentiated from monoclonal-antibody-based approaches, which do not specifically target the neurotoxic oligomers that exist in low concentrations in the brain[4] (**Fig. 1**).

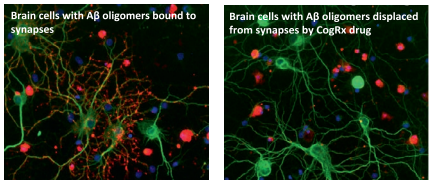

Figure 1: Cognition Therapeutics combines proprietary biological assays and medicinal chemistry platforms to discover new protein drug targets for neurodegenerative diseases and to develop small molecules to tackle them. In AD, the company has pinpointed the sigma-2/PGRMC1 receptor as a mediator of Aβ synaptotoxicity and developed drug-like small molecules that competitively block Aβ binding to the receptor, stopping memory loss in disease models.

There are currently no other therapeutics that demonstrate direct displacement of the toxic protein that causes synapse loss, memory failure and AD. This novel strategy to attack this disease at its root protects synapses from Aβ, and should enable other therapeutic strategies to work more effectively.

Assay advantage

Central to CogRx's competitive advantage has been its unique ability to combine proprietary biological assays with its proprietary medicinal chemistry platform NICE (Novel Improved Chemical Extracts) to identify novel targets and develop low-molecular-weight, stable small-molecule drug candidates directed at these targets, respectively.

CogRx's bioassay platform uses mature primary hippocampal neuronal cell cultures to recreate AD in a dish by exposing the brain cells to Aβ oligomers. Molecules capable of stopping the protein's toxic effects can be rapidly identified and optimized, and novel molecular targets can be pinpointed that could translate into alternative intervention points in neuro- and synaptotoxicity.

The NICE platform enables CogRx to generate sets of small molecules derived from natural chemical scaffolds. These initial compounds are of high quality and purity, allowing for their rapid optimization into drug candidates, accelerating development and reducing the risk of candidate failure.

Together, these platforms provide an important and novel way to accelerate the discovery of therapeutic drugs, and they also represent an entirely new approach to small-molecule drug discovery that distinguishes CogRx's approach from those of its competitors. "By strategically combining both biological and chemistry discovery platforms, our technologies have given us a significant advantage. We have been able to discover therapeutics in half the time and for a quarter of the cost of our competitors," said Susan Catalano, founder and CSO of CogRx. "We have begun to apply these technologies to other neurodegenerative diseases such as Parkinson's disease, and are quite excited about what we've found."

Therapeutic targets and drug candidates discovered with these platforms have already demonstrated potential for improving memory performance in two different mouse models of AD in both acute and chronic settings, and the lead molecule, CT1812, is currently being tested for safety and tolerability in patients diagnosed with mild to moderate AD.

Focus on partnerships

CogRx is in an ideal position to partner on innovative therapies for the prevention and treatment of AD and related neurodegenerative diseases.

The company's main focus is to advance its pipeline of first-in-class small-molecule AD therapeutics through late-stage clinical trials and into market in collaboration with external partners. CogRx is open to considering all relevant opportunities, including regional deals.

In addition, the company is interested in partnerships that can further leverage its discovery platforms and address other neurodegenerative diseases characterized by abnormal protein aggregation, such as Parkinson's disease.

CogRx CEO Hank Safferstein summed it up this way: "Our novel approach to AD, first-in-class drug candidate and its stellar clinical track record make an excellent partnering opportunity. We are quite excited about the collaborative opportunities ahead of us."

1. Catalano, S.M. *et al. Alzheimers Dement.* (in the press).
2. Selkoe, D.J. & Hardy, J. *EMBO Mol. Med.* **8**, 595–608 (2016).
3. Izzo, N.J. *et al. PLoS One* **9**, e111899 (2014).
4. Izzo, N.J. *et al. PLoS One* **9**, e111898 (2014).

contact
Hank Safferstein, CEO
Cognition Therapeutics, Inc.
Pittsburgh, Pennsylvania, USA
Tel: +1-412-481-2210
Email: hsafferstein@cogrx.com