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NeuroNascent Aims to Reverse Neurodegenerative Damage

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Staff Writer

A slew of recent failures in Alzheimer's disease (AD) could prove providential for NeuroNascent Inc., which has ambitious plans to halt and potentially reverse a range of neurodegenerative diseases.

The Clarksville, Md.-based firm was founded in 2004 by Judith Kelleher-Andersson, president and chief scientific officer, who had two decades of experience in drug development and research in neurological disease – particularly neurodegenerative disorders – including positions at Neuralstem Inc., Centaur Pharmaceuticals Inc. and Cortex Pharmaceuticals Inc.

She is the primary inventor on more than 50 U.S. and global patents in small-molecule therapeutics.

Kelleher-Andersson next tapped Kathleen Mattis, who served as vice president of finance at Neuralstem, to run the financial side of NeuroNascent, and the firm raised initial funding from friends and family. In 2005, NeuroNascent – whose name refers to new neurons – launched operations.

The company's discovery platform starts with human neuronal progenitor cells from the adult hippocampus, which are constantly being replenished through the process of neurogenesis. Even when assailed by certain neurodegenerative conditions, the brain attempts to compensate for the neuron loss by promoting further proliferation and differentiation into new neurons, which migrate to regions of the brain exhibiting the neurodegeneration, Kelleher-Andersson explained.

Drugs that accelerate the neurogenesis process could potentially halt and even reverse disease progression, she reasoned.

To find such compounds, NeuroNascent needed an oral small molecule that could easily cross the blood-brain barrier. The company licensed several focused small-molecule libraries, screened the libraries to identify agents with the ability to produce adult neurons from progenitor cells and examined whether the neurogenic agents also were neuroprotective.

The company then began to optimize the agents in vitro and move them into animal models.

"We have to prove the neurogenesis we saw in cell cultures also occurs in animals and these new neurons actually correlate with improved behavior," characteristics such as enhanced memory performance, reduced anxiety and heightened motor function, Kelleher-Andersson told *BioWorld Today*. "We're not chasing a single target but looking to enhance cellular function."

Unlike other neurodegenerative drug candidates, NeuroNascent's program isn't seeking to affect symptoms.

"We're actually trying to reverse a deficit, not just inhibit it," Kelleher-Andersson said. "We're setting the bar extremely high."

Meeting that goal requires greater effort in animal models than the typical preclinical study, she added. NeuroNascent's lead compound, NNI-362, demonstrated the ability to reverse a cognitive deficit in aged mice as well as the capacity to halt motor deficits in a neurodegenerative model of Huntington's disease.

In potentially game-changing work, NeuroNascent also examined a Down syndrome model in transgenic mice, using its technology to reverse cognitive deficits associated with the disorder.

"That finding correlated with the increase in neurogenesis in those animals," Kelleher-Andersson said.

The lead indications for that therapeutic candidate, NNI-351, are depression and post-traumatic stress disorder (PTSD). But NNI-351 also inhibits a protein, Dyrk1a protein, that is overproduced in individuals with Down syndrome, perhaps enabling NNI-351 to increase the production of new neurons in the hippocampus and subsequently increasing learning and memory in Down syndrome transgenic mice. Importantly, those beneficial effects modified the disease, rather than simply masking symptoms, in the mouse model, according to Kelleher-Andersson.

NeuroNascent's AD compound is now in investigational new drug (IND)-enabling studies. NNI-351 has advanced to preclinical studies in depression and PTSD, and a Parkinson's disease (PD) drug is in the optimization phase. All of the compounds are covered for composition of use in patent filings.

"We think the only way really to affect the 30 million Alzheimer's disease patients worldwide is to be neurorestorative as well as neuroprotective," Kelleher-Andersson emphasized. Thus, the company's platform seeks not only to enhance the growth of additional neurons

but also to protect those neurons "so they don't die off in the same way," she said.

"Having agents that are truly neurogenic – producing new neurons, not just new connections – as well as neuroprotective by enabling those neurons actually to survive is critical for many neurodegenerative diseases," Kelleher-Andersson added. "We're in a good place here, if we can get into the clinic."

To that end, NeuroNascent is using roughly a 50/50 mix of translational grants and angel funding to complete pre-IND studies for NNI-362. With the two principals the only full-time employees, "we can survive on very little money," Kelleher-Andersson said.

Once the IND is filed, the company hopes to attract additional angels and, perhaps, pharmaceutical venture funding.

"We've spoken with every major neurology player, and we're still in communication with a number of these companies," Kelleher-Andersson said. "We believe there are enough funding sources out there to help us with this."

The push toward treatments for rare diseases may expedite the path for NNI-351 in Down syndrome, as a growing body of research suggests many intellectual disabilities may be treatable. (See *BioWorld Insight*, Feb. 13, 2012.)

Long term, NeuroNascent hopes to partner the AD program and use those resources to move the earlier-stage PD and depression candidates forward on its own. Kelleher-Andersson is loath to push each asset into a separate company, as "we do intend to be acquired," she said. "Even though there's a trend toward pre-AD therapeutics, there are still enough pharmaceutical companies out there that are interested in helping patients with existing Alzheimer's disease." ■