

BIO 2010

Stimulating Neurogenesis Offers Hope for Depression

By Nuala Moran

BioWorld Today Correspondent

CHICAGO - The 1998 discovery that - contrary to all previous teaching - the brain continues to generate neurons throughout life, is now being translated through to new drugs for treating depression and neurodegenerative diseases, attendees at the Biotechnology Industrial Organization annual conference were told Thursday.

Those are small steps as yet, but the ability to stimulate neurogenesis offers the prospect of revitalizing pharma's interest in psychiatric disorders and of providing effective treatments in an area of huge unmet medical need.

The leader in the neurogenesis pack, BrainCells Inc., of San Diego, was able to show a statistically significant effect on depression in a clinical proof-of-concept trial of a neurogenesis stimulator BCI-952 that reported in July last year.

Meanwhile NeuroNova AS, of Stockholm, Sweden, is about to move up to the highest of three doses in a Phase I trial of its small-molecule drug sNN0031, which is intended to stimulate endogenous stem cells in the hippocampus to form new neurons and influence the production of dopamine in Parkinson's disease patients.

The results of the six-week study of BCI-952, a formulation of the generic antidepressant buspirone and melatonin, showed it had a positive effect on depression symptoms in multiple clinical endpoints.

"This was quite a remarkable outcome, because it was a very robust signal," Carolee Barlow, chief science officer of BrainCells, told delegates. This was the first clinical validation of neurogenesis as a target for treating mood disorders like depression.

One of the investigators in the trial, Donald Garcia, of Future Search Trials, of Austin, Texas, said the trial result was all the more remarkable given the difficulty of demonstrating efficacy in treating depression. "The challenge we have in testing psychiatric drugs is that the placebo effect has been growing over the past 20 years," he added. At the same time these diseases are extremely heterogeneous and it is impossible to identify likely responders.

"It's frustrating because we know these drugs work in the right patients - people are putting money into compounds, but the end result of trials is that there is no demonstration of difference from placebo," Garcia said. He added, "It's extremely exciting when you get a novel platform like BrainCells' and you get such a big signal."

Like BrainCells, NeuroNova has developed a proprietary platform for identifying compounds that stimulate stem cell progenitors in the brain.

While the company has shown its lead compound stimulates neurogenesis in animal models, it does not have direct proof that results in the generation of dopaminergic neurons. However, in the animal models the drug cures dopamine deficiency, and if the de novo proliferation of neurons is interrupted, the animals again exhibit Parkinson's disease symptoms.

"We've got effects, but we can't show [the animals] are making dopaminergic cells. We don't know what the neurons turn into," said Anders Haegerstrand, NeuroNova's vice president and chief science officer.

Frank Yocco, vice president and head of CNS and pain discovery at AstraZeneca plc's research laboratory in Wilmington, Del., echoed Garcia's views on the difficulties of carrying out depression studies, saying that is leading big pharma to abandon the field. "Companies like GlaxoSmithKline and AstraZeneca are stepping away from doing this work. One of the reasons is we can't identify the patients we need to use in trials where we have a specific mechanism of action," he said.

That is very unfortunate, not just because of the huge disease burden. However, Yocco said, "We now see small companies picking up the gauntlet and starting to run with it."

Yocco has been discussing the significance of neurogenesis for drug discovery with his colleagues, to assess whether AstraZeneca should get involved. "If we want to get in, is it only for depression, where you are stimulating neurogenesis, or is it possible in some [diseases] there is too much neurogenesis and you want to

hinder it?"

Neurogenesis may also have potential in treating deficits in cognition, memory and learning; aberrant neurogenesis may be a feature of Alzheimer's disease; and stimulating neurogenesis could form the basis of a treatment for stroke. That underlines the extent to which the discovery of neurogenesis and the first attempts to modulate the process is opening up possible avenues to new ways of tackling a range of intractable diseases. Psychiatry, in particular, is a field that is "married to outdated pharmacological models," Yocco said, asking, "So can we use BrainCells' platform to create new models?"

For example, there could be value in using high content screens to identify compounds that are active across different stages of neurogenesis. "Many targets are active in other aspects of neuronal plasticity, suggesting the potential for broader applications," Yocco added.

Although Barlow agreed that finding biomarkers to segment patient populations is a significant issue, she pointed out that BrainCells has an efficacy measure - cerebral blood volume - that the company has demonstrated is correlated directly with neurogenesis. "This is an objective measure, and we hope it will correlate with benefit."

Published May 7, 2010