



Feb 15 2008 (Vol. 28, No. 4)

BrainCells Bets on Small Molecule Therapies

Firm's Screening Device Provides Fingerprint of a Compound's Neurogenic Profile

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Experts estimate that brain-related illness afflicts more than 1.5 billion people worldwide, and 10% of all adults have some sort of mood disorder. Approximately one-third of patients do not respond to currently available therapies to treat anxiety and depression. Current treatments typically have a three to six week delay for onset of action, and patients often suffer from gastrointestinal or sexual side effects.

“Psychiatry has been thought of as a mysterious black box,” says Carolee Barlow, M.D., Ph.D., CSO, and one of [BrainCells](#)’ (BCI) founders. “Now we know that we can treat mood disorders by means of a biological process.”

Currently, the worldwide market for pharmaceuticals that treat depression and anxiety exceeds \$30 billion. Companies selling neuropharmaceutical products generated over \$93 billion in global revenues in 2005. These therapies represent the top-selling drug category in the world.

Since its inception in 2004, BrainCells has focused on the development of small molecule therapeutics for diseases of the central nervous system (CNS). The biopharmaceutical company has merged two academic findings into a predictive screening platform to understand the biology of mood disorders and to identify new drugs based on that information.

Neurogenesis and CNS Diseases

BCI's technology platform is based on research in the field of neurogenesis in the adult brain and recent discoveries linking neurogenesis to CNS disease states.

Neurogenesis is a complete cellular process that includes proliferation of neural stem cells; migration of those cells to an appropriate location in the brain; differentiation of neural stem cells into cell lineages including neurons, astrocytes, or oligodendrocytes; and survival of the appropriate cell type in its location. It has recently emerged as a fundamental process underlying CNS physiology and disease.

“Fred Gage, Ph.D., a cofounder of the company, and his colleagues at the Salk Institute discovered that neurogenesis occurs in the adult human brain and that adults continue to make neurons throughout their lifetime,” Dr. Barlow explains. “Stress suppresses the process, while good nutrition and exercise help it.”

Researchers at Columbia University discovered that drugs designed to relieve mood disorders also stimulate neurogenesis. “They found that when the process of neurogenesis is blocked, the drugs no longer work,” she adds.

In mammals, the production of new brain cells occurs primarily at the time the nervous system is developing although certain brain areas generate neurons throughout adulthood. One such area is the hippocampus. Hippocampal cells are continuously produced in adults as well as in young animals.

“When we think about the hippocampus, we think of memory,” explains Dr. Barlow. “Now we know that neurogenesis is critical to emotional memory. We can boost neurogenesis to reconfigure emotional memory and help people out of difficult situations.”

BrainCells is using its neurogenesis technology platform to screen for candidate drugs for depression and anxiety and to identify clinical-stage compounds as well as novel targets optimal for CNS indications. The company is building a pipeline of clinical-stage programs to address unmet medical needs in the treatment of mood disorders, psychoses, cognition, brain repair syndromes, and other CNS disorders.

BCI’s neurogenic platform technology encompasses both in vitro and in vivo assays. The in vivo assays include measurements for the growth of new neurons as well as traditional and leading-edge behavioral studies for CNS indications. When combined, the assays provide a complete fingerprint of a compound’s neurogenic profile, measuring all aspects of the neurogenesis process, according to the company.

The neurogenesis platform is being used to profile compounds as well as targets and compare them to both successful and failed CNS compounds. BCI believes that compounds with neurogenic profiles similar to successful drugs that treat CNS disorders will have an increased probability of clinical success.

After testing more than 500 compounds in its neurogenesis assays, BCI has determined that the profiles of marketed drugs for treating classes of CNS indications are distinct from one another. The company is using this information to select and find new uses for clinical-stage compounds with established safety databases and to discover novel targets

and compounds for treating CNS disorders.

First Pipeline Candidate

Although BrainCells is focusing its initial efforts on the treatment of mood disorders, it believes that its technology has applications in other neuropharmaceutical markets such as cognition, schizophrenia, and brain repair.

In 2006, BCI in-licensed its first mood disorder drug candidate, BCI-540, from **Mitsubishi Pharmaceutical** for the treatment of major depressive disorder combined with anxiety.

The company elected to develop BCI-540 because its favorable neurogenic profile is similar to currently available antidepressants. In addition, the drug appears to have a dual mechanism of action, with a profile that could be used to treat both diseases.

BCI has now repositioned BCI-540 using its neurogenesis platform technology and has selected the treatment of depression and anxiety, where BCI believes there is a strong market need and high likelihood of clinical success. BrainCells expects to enroll the first patient for its Phase II trial in the first quarter of 2008.

“BCI-540 has a different mechanism of action from other antidepressants,” says Dr. Barlow. “Some patients can’t tolerate or don’t respond to other drugs on the market. This presents an alternative that may be efficacious but doesn’t work through serotonin, epinephrine, or dopamine.”

BrainCells continues to seek high-quality products with neurogenic profiles optimal for the treatment of various CNS disorders. Since the importance of the role of neurogenesis in the treatment of CNS diseases is relatively new and BCI has established a screening platform and related database, the company hopes that there are many opportunities to identify compounds addressing unmet CNS market needs.

Finding the Fingerprint

Future products can come from in-licensing clinical-stage compounds, screening qualified libraries to reposition clinical assets, identifying novel drug combinations that act synergistically, and developing in-house discovery programs.

BrainCells is currently partnering with other companies to search for additional agents that could be useful in treating mood disorders. Meanwhile, it is “looking for the fingerprint of the successful antidepressant,” Dr. Barlow says.

“We’re harnessing neurogenesis to create a paradigm shift in psychiatry,” she concludes. “It’s exciting biology and it’s exciting to think that the brain has the ability to rewire itself.”