Third Rock Start-up Sage Debuts with $35M Series A

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Third Rock Ventures LLC launched a new company, Sage Therapeutics, with a $35 million Series A financing to develop new therapies for schizophrenia, depression, pain and traumatic brain injury based on modulation of GABA and glutamate neurotransmitters.

Central nervous system (CNS) disorders are an area of great unmet need, but those indications also are regarded as highly challenging for drug development.

“This isn’t easy, but I don’t know an area in drug discovery that is easy,” Third Rock Ventures founding partner and Sage interim CEO Kevin Starr told BioWorld Today.

The Boston-based company said imbalances in the brain from over- or underactivity of GABA and glutamate neurotransmitters are believed to cause many CNS disorders. Its positive and negative allosteric modulator (PANAM) chemistry platform is designed to identify receptor modulators that can bring balance to disrupted neuronal activity.

The company is focusing on nonbenzodiazepine and nonglycine modulators.

“Nature has provided certain allosteric binding sites that ... finely tune upward or downward glutamate and its receptors or GABA and its receptors,” said Steven Paul, a Sage co-founder, adding that mimicking the transmitter is “too crude” an approach to be effective.

“A lot of drugs that companies go after directly agonize or antagonize. In these particular receptors. agonism and antagonism disrupt normal brain rhythm in those circuits,” Starr said.

“What we found and hope will prove out in the clinic is that allosteric modulation restores those rhythms to normal function and normal signals so the brain can interpret it the right way,” he said.

The company already has supporting data in animals and in humans showing proof of concept.

The $35 million financing will fund two sets of programs at Sage. Formulation-based programs will advance work already done on prototypical molecules. Starr said those molecules could enter the clinic within two years.

A second program will focus on lead optimization, and is expected to reach the investigational new drug application stage in two to three years.

Currently marketed therapies for CNS disorders fail a majority of patients, according to Sage. It said that two-thirds of patients with depression fail to respond to medications. Schizophrenia medications also have low response rates, plus some serious side effects.

Additionally, drugs for schizophrenia only address psychotic symptoms, but do not treat the highly disabling negative and cognitive symptoms of the disease.

Sage estimated the market for brain injury includes 1.7 million people per year due to accidents, sports and combat. There are no drugs approved to protect the injured brain.

Addex Pharmaceuticals Inc. is developing a number of positive allosteric modulators (PAM) and negative allosteric modulators (NAM) in the CNS area, generating some high-dollar deals, but some of its programs have experienced setbacks.

In July, Merck and Co. Inc. handed back rights to ADX63365 and other PAMs targeted at the mGluR5 receptor for schizophrenia that it had acquired in 2008 for $22 million up front. If successful, that deal could have been worth up to $702 million for Addex. (See BioWorld Today, Jan. 4, 2008.)

In September, Merck dropped the other shoe, exiting from a license agreement with Addex for a modulator of the mGluR4 receptor, for which it paid $170 million up front in 2007. (See BioWorld Today, Dec. 4, 2007.)

Addex continues to work on those programs internally.

Paul said Sage is expecting challenges, but the firm contended its programs are strong and its leadership experienced. “We like where we are with respect to our chemical scaffolds. We believe they have already built in safety,” he noted.

“We’ve thought this out very very carefully,” Starr said. “We thought this through in terms of getting to the
finish line. We felt we brought the team on board and various partners on board that can help get there.”

Third Rock is not the only organization that is looking for an opportunity in CNS and schizophrenia, in particular. Takeda Pharmaceutical Co. signed two deals with biotech companies this year for schizophrenia drugs.

In April, it signed a deal worth up to $106.3 million with Heptares Therapeutics Ltd. to characterize the structure and deliver early leads against a G-protein coupled receptor involved in schizophrenia. (See BioWorld Today, April 12, 2011.)

And in March, it signed a deal worth up to $750 million with Intra-Cellular Therapies Inc. for worldwide development and commercialization of Intra-Cellular’s preclinical selective phosphodiesterase type 1 (PDE1) inhibitors for cognitive impairment associated with schizophrenia. (See BioWorld Today, March 4, 2011.)