

Product Discovery & Development

Stabilizing fragile X

By Michael Flanagan
Senior Writer

It has long been thought that excessive protein synthesis plays a role in neurological conditions like fragile X syndrome, though little progress has been made in identifying therapeutic targets. **Seaside Therapeutics LLC** thinks it has found one in metabotropic glutamate receptor 5 and on Monday was to announce the start of a Phase I trial of an in-licensed small molecule antagonist.

Fragile X syndrome is a heritable form of mental retardation and one of the foremost known causes of autism, according to Randall Carpenter, president and CEO of Seaside. The condition is characterized by impaired neural and cognitive development caused by transcriptional silencing of the *FMR1* gene, which encodes the fragile X mental retardation protein (FMRP).

While aberrant protein synthesis has been suggested as a cause of a variety of neurological disorders, finding druggable targets has been easier said than done (see *SciBX: Science-Business eXchange*, June 11, 2009).

Seaside now thinks it might have hit on one that works.

According to Carpenter, FMRP normally would act as a negative control on metabotropic glutamate receptor 5 (mGluR5). He said one theory on the pathophysiological underpinnings of fragile X syndrome is that FMRP is absent due to an *FMR1* mutation. This leads to unchecked activation of mGluR5, which in turn causes excessive local protein synthesis and impaired synaptic plasticity, leading in turn to the neurologic and behavioral symptoms characteristic of the disease. These include cognitive impairment, delayed motor development, antisocial behaviors and seizures.

Much of the early research on which Seaside is based was conducted at the Howard Hughes Medical Institute at the **Massachusetts Institute of Technology** by scientific founder Mark Bear, who first showed in *FMR1* knockout mice that mGluR5 and FMRP act functionally as an opponent pair. The results were published in *Neuron* in December 2007.

Carpenter said Bear also was able to show that mGluR5 antagonism rescued abnormal phenotypic behaviors and symptoms in the knockout mouse model of fragile X syndrome.

"We set out looking for the most advanced set of compounds against mGluR5 and ended up being at the right place at the right time," said Carpenter, when **Merck & Co. Inc.** decided to exit the psychiatry space and deprioritized a portfolio of small molecule mGluR5 antagonists.

In mid-2005, Seaside took a license to the compounds.

The single ascending-dose Phase I trial will evaluate the safety and pharmacokinetics of oral STX107 in healthy volunteers, with results expected by the end of IQ10.

"If all goes to plan we hope to be in patients with STX107 in mid-2010," Carpenter added.

Seaside's second program arose from discussions about the mGluR5 program with the autism research community, through which the company became aware of chance observations from clinicians that fragile X patients given generic baclofen for gastroesophageal reflux disease (GERD) exhibited marked cognitive improvements.

Baclofen is a GABA B receptor agonist that has been commercially available for 30 years as a racemic mixture. "We found that the R isomer was much more active in the fragile X mouse and actually rescued a number of the abnormal symptoms similar to the way mGluR5 antagonism does," said Carpenter.

"Because we can pursue a chiral switch approach and link our program to all the

established safety data for generic baclofen, this program has a head start," he added. The lead candidate from the R-baclofen program, STX209, began a double-blind, placebo-controlled, crossover Phase II trial in adolescent and adult patients in December 2008.

Results are expected in late March or early April 2010.

Seaside's primary source of funding for both programs is an undisclosed family investment fund that has so far provided \$60 million, including a \$30 million tranche closed in September (see *BioCentury*, Sept. 21).

The company also has received translational research grants from **NIH** as well as private groups like **Autism Speaks** and **FRAXA Research Foundation**.

The family fund has committed additional capital that could be sufficient to carry Seaside's programs through to market in the U.S., though Carpenter said the company is in discussions about ex-U.S. partnerships.

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Randall Carpenter,
Seaside Therapeutics

COMPANIES AND INSTITUTIONS MENTIONED

Autism Speaks, New York, N.Y.

FRAXA Research Foundation, Newburyport, Mass.

Massachusetts Institute of Technology (MIT), Cambridge, Mass.

Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.

National Institutes of Health (NIH), Bethesda, Md.

Seaside Therapeutics LLC, Cambridge, Mass.

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