Emerging Company Profile

QR: Power of positivity

By Michael Flanagan
Senior Writer

QR Pharma Inc. has in-licensed a pair of compounds for cognitive impairment and Alzheimer's disease it believes have suffered from neglect rather than a lack of efficacy or safety.

The more advanced of the two compounds is Posiphen, a positive enantiomer of phenserine that has completed a Phase I/II trial for mild cognitive impairment.

The second product, a preclinical butyrylcholinesterase (BChE) inhibitor, could have utility in later-stage AD patients.

Both compounds were in-licensed from TorreyPines Therapeutics Inc. Posiphen originally came from Axonyx Inc., which reverse merged with TorreyPines in 2006. The compound was a follow-on to racemic phenserine, a next-generation acetylcholinesterase (AChE) inhibitor Axonyx discontinued in 2005 after it failed to show a benefit in three Phase III trials in AD.

According to QR Pharma President and CEO Maria Maccecchini, phenserine was an active agent but ultimately had to be under-dosed because of side effects common to AChE inhibitors, including nausea and vomiting.

While phenserine's negative enantiomer is a potent AChE antagonist, it turns out the positive enantiomer blocks expression of amyloid precursor protein (APP), a membrane-bound protein that gets broken down into neurotoxic fragments believed to play a pathogenic role in AD.

By blocking a translational step during protein synthesis, Posiphen down-regulates expression of APP by roughly 50%, according to Maccecchini.

While APP is often over-expressed in AD patients, it is important not to completely shut down its expression because normal levels of APP are needed for synaptic transmission.

Maccecchini thinks Posiphen may offer a safer approach to preventing the accumulation of amyloid fragments than programs that are designed to inhibit the secretases that process APP into fragments.

So far, secretase inhibitors have not lived up to expectations. Most recently, **Eli Lilly and Co.**'s semagacestat, the most advanced gamma secretase inhibitor, missed the endpoint in a Phase III trial and encountered multiple safety problems, including increased rates of skin cancer vs. placebo *(see BioCentury, Aug. 23, 2010)*.

"These enzymes have many functions, so hitting them" can cause off-target side effects, Maccecchini said. "A secretase enzyme processes 25-50 different membrane proteins, so leaving them in the membrane clogs up the system and causes synaptic transmission problems."

Reducing APP expression, she said, could avoid these problems simply by limiting the amount of protein that is available for processing into toxic fragments.

Posiphen entered Phase I testing just as the racemic phenserine was being dropped, and was de-prioritized after Axonyx merged with TorreyPines.

Maccecchini said TorreyPines completed ongoing studies of Posiphen, including a multiple-ascending dose trial, but back-burnered the program again after the company "ran into difficulties with some of their own programs."

TorreyPines went on the merge with **Raptor Pharmaceutical Corp.** in 2009.

Last year, QR Pharma conducted a 10-day Phase I/II trial in 30 patients with mild cognitive impairment (MCI). The study showed oral Posiphen significantly lowered two different subtypes of APP by 44% and 45% ($p<0.0006$ and $p<0.0001$). It also significantly lowered microtubule-associated protein tau (MAPT; tau; FTDP-17), phosphorylated tau (p-tau) 231 and complement 3 (C3), a marker of inflammation ($p<0.002$; $p<0.0005$; and $p<0.0007$, respectively).

"The inhibition of several toxic fragments should result in less neurodegeneration and cognitive decay," said Maccecchini.

Maccecchini is trying to raise $30 million in series A money that would be used to fund a Phase II/III trial of Posiphen. She hopes to close the round this summer and start the study in 1H12.

With results in hand, QR Pharma will then look for a partner for the compound.

Bisnorcymserine,the second program licensed from TorreyPines, is a BChE inhibitor targeting later-stage AD patients, a population that does not typically respond to AChE inhibitors.

"As people age, the percentage of acetylcholine receptors goes down, and the percentage of butyrylcholine receptors goes up," Maccecchini said. As a result, a butyrylcholinesterase inhibitor should be more effective in older patients.

QR Pharma has a grant from the NIH's **National Institute on Aging** to conduct a Phase I trial that will start next half.

The composition of matter patents covering Posiphen and bisnorcymserine expire in 2022 and 2018, respectively. Maccecchini said QR Pharma also has a provisional patent application for Posiphen that would extend protection until 2031.

Raptor is eligible for milestones and royalties from the two programs.

QR Pharma Inc.

Berwyn, Pa.

Technology: Small molecules for Alzheimer's disease

Disease focus: Neurology

Clinical status: Phase I/II

Founded: 2008 by Maria Maccecchini

University collaborators: Massachusetts General Hospital; Buck Institute; and Medical University of South Carolina

Corporate partners: None

Number of employees: 2 full time, 10 part time

Funds raised: $2.5 million

Investors: Ben Franklin Technology Partners; BioAdvance; and angel investors

CEO: Maria Maccecchini

Patents: 6 issued covering composition, methods of production and use of Posiphen and bisnorcymserine for Alzheimer's disease, dementia and Down syndrome

COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.

National Institute on Aging, Bethesda, Md.

QR Pharma Inc., Berwyn, Pa.

Raptor Pharmaceutical Corp. (NASDAQ: RPTP), Novato, Calif.