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'GERON' THE RIGHT STEM CELL TRACK?

Spinal gap: Neuralstem goes into chronic injuries phase I trial, first ever to be cleared by the FDA

By Randy Osborne, Staff Writer

With encouraging data from a phase I trial in amyotrophic lateral sclerosis (ALS) and a phase II trial under way testing NSI-566, Neuralstem Inc. has begun – with the same candidate – the first human neural stem cell study to be given the FDA's nod for chronic spinal cord injury.

Four patients with thoracic spinal cord injuries (T2-T12) will have NSI-566 transplanted directly into the region of the injury, which has been sustained between one and two years before the treatment. All patients have an American Spinal Injury Association grade A level of impairment, which means complete paralysis with no motor or sensory function at and below the trauma site.

Richard Garr, CEO of Germantown, Md.-based Neuralstem, said the trial is half the size originally planned, and for a good reason. "When we submitted this originally, there were eight patients, but that was before we had treated successfully the high-dose patients in our ALS trial," he told *BioWorld Today*. "We went back to the FDA and asked them to amend the protocol."

Last heard from in the stem cell/spinal cord injury space was Menlo Park, Calif.-based Geron Corp., which last year disclosed in an SEC filing that the assets related to the program were taken over by Asterias Biotherapeutics Inc., a subsidiary of regenerative medicine specialist Biotime Inc., of Alameda, Calif.

The deal involved transfers of common stock and warrants, along with patents, regulatory filings and investigational new drug applications filed with the FDA for Geron's phase I safety study with the oligodendrocyte progenitor cells (OPCs). Geron was investigating the cells' efficacy in acute spinal cord injury, rather than chronic, as with the Neuralstem product. In May of this year, Asterias offered promising safety results with AST-OPC1, a population of cells derived from human embryonic stem cells that contain the OPCs, in five subjects tested during a restarted experiment that Geron began in 2010. (See *BioWorld Today*, Jan. 26, 2009, Jan. 27, 2009, and April 5, 2013.)

"It's hard," Garr said of the research. "For something like this, the FDA won't just let you go in to try. The surgery is very risky. We're the first ones who ever did intraspinal injections with our ALS trial." Neuralstem had to use a special delivery device invented at Cleveland Clinic, and deliver strong preclinical data to U.S. regulators before efforts could move ahead. The firm's approach is "very different from what anybody else, even Geron, has ever done," he said.

Predicting how fast benefit might appear is tricky. "In ALS patients, the maximum window of biological activity for the cells was between four and six months post-surgery," Garr said. "But it was also very clear in four to eight weeks that there was considerable biological functional activity. Will we see that in spinal cord patients? We don't know, but that would be our expectation."

For some ALS patients, the effects turned up much sooner, he added. "What the cells are doing here, in chronic [spinal cord injury] patients, is literally bridging the gap. We're trying to rebuild the circuitry in the gap so that the signal can come through, down the spinal cord. There are also a lot of neurotrophic factors expressed by the cells that can help with healing, but in a chronic patient, it's unknown how much impact that will have."

Garr cited a key difference between spinal cord injury and ALS, "where you are putting the cells in the motor neuron pools to protect and nurture the remaining motor neurons and then hopefully nurture back to health those that haven't hit that tipping point. The early neurotropic factor expression of the cells, even before they are synaptically integrated and matured, could have an effect [in ALS] – clearly has. Maybe in spinal cord injury patients, where the neurotrophic effect isn't the primary reason for benefit, it could take a little longer. We're really waiting for the synaptic connections to happen and for the circuitry to be rebuilt."

RAT MODEL MORE LIKELY TO HOLD: CEO

Recent findings have bolstered Neuralstem's basic thesis. "[You can] use the analogy of a pipe with wires coming down, and there's a break in the pipe," Garr said. "There

was always a question of, 'OK, even if the cells do what they do, and the signal comes through, how do you know the signal going out from the spinal cord to the muscles is still intact and working?'"

Scientists at the University of Louisville and the University of California, Los Angeles, provided an answer.

"There is sort of a junction box in the lower spinal cord that activates the muscles in the legs," Garr said. "Even in paralyzed humans, you can stimulate that junction box and get the legs to move. But nobody knew how far out [from the time of injury] you could do that."

The universities proved it could be done in patients two to four years after their trauma.

Neuralstem raised $19.65 million in a stock offering at the start of this year that left the company with enough money to finish trials in both indications, Garr said.

"Our corporate strategy right now is that we are going to commercialize the ALS therapy and the spinal cord injury therapy in the U.S., and do it through partnering outside the U.S.," he added. (See *BioWorld Today*, Jan. 6, 2014.)

A phase I/II trial with NSI-566 in acute spinal cord injury is expected to start this year or early next year in Seoul, South Korea. CJ Cheiljedang Corp., headquartered there, holds an option in South Korea and five more South Asian countries. "We will have strategic partnerships like that throughout the world," Garr said. "Our goal isn't just to show human data and license it out."

Neuralstem has cause to believe the solid preclinical data in rats will hold true in humans. While in rat models (including those of ALS), the rodents are not infected with the actual disease; "a severed spinal cord is a severed spinal cord," Garr said.

Even considering the different anatomy of the rat, "this isn't a gray area; this is black and white. Animals [were] returned to full walking function," as shown in published data, he said.

The company's stock (AMEX:CUR) closed Thursday at $3.05, down 16 cents. //