Stem cell therapy studies for stroke, cerebral palsy prepare for clinical trials

January 29 2008

Finding answers about optimal dosage and timing for stem cell therapy in adults with strokes and
newborns with ischemic injuries is a goal of two new federally funded studies.

The answers are critical before clinical trials can begin, says Dr. Cesario V. Borlongan, neuroscientist at the Medical College of Georgia and Charlie Norwood Veterans Affairs Medical Center. He is principal investigator on the National Institutes of Health grants totaling $6 million that also will explore long-term benefits of cell therapy.

If these additional laboratory studies replicate the promising results of the pilot studies, which indicate about a 25 percent improvement in recovery over controls, MCG and VA researchers hope to begin clinical trials in new ischemic injuries in adults and children within two years.

“We are looking at different procedures that we can adopt from the laboratory for the clinic,” Dr. Borlongan says. “We have at least 10 years of basic research that clearly shows that stem cells have the potential to be a new therapy for adult stroke.”

“This is a whole new paradigm, a totally different way of targeting disease,” says Dr. David Hess, chair of the MCG Department of Neurology and co-investigator. Clot buster tPA is the only drug that is FDA-approved to treat ischemic strokes; an often-delayed diagnosis and a three-hour treatment window mean only a small percentage of patients

get it.

Drs. Hess and Borlongan say cell therapy could eventually be used alone or in conjunction with tPA, if recovery is not sufficient. Pilot studies indicate cell therapy can be of benefit up to seven days after a stroke but that two days out is the optimal time of delivery. “This will allow us to enroll patients who get tPA, give us plenty of time to assess them and prepare the cells,” says Dr. Borlongan.

Their success in an adult stroke model led the researchers to explore the potential for helping babies recover from hypoxic ischemia, a loss of blood and oxygen that can result in cerebral palsy, broadly defined as a brain injury that occurs before or during birth.

Ischemic brain injury accounts for about 10 percent of cerebral palsy and about 80 percent of strokes.

They found young, developing brains more adaptable to injury and better able to recover even without intervention. “Very young patients may be the biggest beneficiaries of cell therapy,” says Dr. James E. Carroll, chief of the MCG Section of Pediatric Neurology and a co-investigator. “Our hope is that cell therapy will speed recoveries of babies who have experienced a brain injury at birth,” he says. “You want to increase the spontaneous recovery, enhance the neurogenesis that is already occurring in the brains of these young patients,” adds Dr. Borlongan. They have models for mild, moderate and severe ischemic injury to reflect damage that can result from scenarios such as an umbilical cord wrapped around the fetus’ neck or placental abruption, which disrupts the fetus’ source of oxygen and nutrients. Researchers expect that cell therapy likely would be used as an adjunct to hypothermia, a new FDA-approved treatment for hypoxic ischemic injury in babies that appears to improve outcomes by reducing metabolic rates, including oxygen requirements, in the hours following an injury.

Given intravenously, the adult, bone marrow-derived stem cell line, developed by Cleveland-based biopharmaceutical company Athersys, Inc., seems to hone in on the area of injury where it works multiple ways. While only a small fraction of the cells actually survive and mature into neurons – more survive in the baby model than the adult – trophic factors they secrete significantly enhance recovery of brain cells injured by lack of oxygen and help grow new blood vessels.

Nothing seems to help the core of the ischemic area in stroke, which is formed within hours of injury; even when cells are placed directly into the core, they do not survive in the area, which is devoid of a blood supply, Dr. Borlongan says. However the cells and their trophic factors can dramatically reduce the penumbra, the area of damaged cells surrounding the core, an area that can continue to grow several days after injury. Interestingly, these undifferentiated stem cells don't seem to interest the immune system, so immunosuppression is not required as it typically is for organ transplants, even when a human cell is placed in a rat, Dr. Borlongan says. Also, pilot studies that have followed rat models for two months after transplant – a long time considering the average rat lives two years – haven't found any signs of tumor formation, which is a concern with stem cells. The new studies will follow transplants for six months, to ensure that efficacy and safety hold up, Dr. Borlongan says.

They'll explore dose ranges between 400,000 and 40 million cells. "We want to see, if we implant more cells, will it be more beneficial?" says Dr. Borlongan. "It may not be the more the merrier."

In preparation for clinical trials, the researchers already have clinical advisory groups for the studies and have begun submitting grant proposals and talking with the FDA. Smaller studies in non-human primate models may also be required before clinical trials begin, Dr. Borlongan says.

Source: Medical College of Georgia