Myelination from neural stem cells

By Lauren Martz, Staff Writer

University of California, San Francisco, Oregon Health & Science University and StemCells Inc. have found that neural stem cell transplants could remyelinate axons and treat myelination disorders including Pelizaeus-Merzbacher disease.^{1,2} The biotech is planning a Phase II study of neural stem cell transplantation in the indication.

Pelizaeus-Merzbacher disease (PMD) is a rare X-linked leukodystrophy disorder caused by mutations in proteolipid protein 1 (PLP1). These mutations disrupt the ability of oligodendrocytes to myelinate axons, which leads to neurological deficits and eventually degeneration.

In 2010, a University of California, Irvine team reported that human neural stem cells differentiated into mature oligodendrocytes and neurons and helped restore locomotor function in rodents with spinal cord injury.³

Building on that work, researchers from OHSU and StemCells decided to test whether these cells could differentiate into myelin-producing oligodendrocytes to help treat myelination disorders.

The team also included researchers from UC Irvine, the Stanford University School of Medicine and the Oregon National Primate Research Center.

The group transplanted human fetal neural stem cells into an immunodeficient mouse model of hypomyelination. The neonatal mice given the transplant showed widespread engraftment of the human cells, which differentiated into myelin-producing oligodendrocytes in appropriate brain regions and produced myelin sheaths on axons.

The team repeated the procedure in juvenile mice with extensive demyelination and found similar increases in myelinated neurons, suggesting the strategy could indeed replace lost myelin.

In tissue samples from both the juvenile and neonatal mouse brains, action potentials had higher amplitude in mice treated with neural stem cells than those in vehicle-treated or human liver mesenchymal stem cell-treated controls.

Based on these mouse data, StemCells sponsored a Phase I, open-label trial of the technique in four patients with early severe PMD. The trial was run by David Rowitch, professor of pediatrics and neurological surgery at UCSF and a Howard Hughes Medical Institute investiga-

tor, and Nalin Gupta, associate professor of neurological surgery and pediatrics and chief of pediatric neurological surgery at UCSF Benioff Children's Hospital.

Patients received 3×10^8 human fetal neural stem cells injected through 4 bilateral brain holes followed by 9 months of immunosuppressive therapy.

At 12 months post-transplant, all patients were stable or had modest gains in motor function. Patients also had minor gains in cognitive function.

Diffusion MRI, which maps the diffusion of water molecules to determine the composition of tissues, suggested the presence of myelin in the patients. None of the patients had detectable myelin before surgery.

The human and mouse studies were published as separate papers in the same issue of *Science Translational Medicine*.

According to Gupta, "In general, patients with severe forms of PMD demonstrate a progressively worsening clinical course. The changes we observed in some of the transplanted children amounted to better motor function and improvement in developmental milestones."

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—Nalin Gupta,
UCSF Benioff Children's Hospital

Future trials

The patients from the Phase I trial are being studied by the UCSF team in a four-year follow-up.

"We will be looking primarily for any adverse effects of the cells in the follow-up study, but we will also be monitoring MRI and clinical outcomes," said Rowitch. "We are interested to see how the story continues to evolve and see if the signs that the cells have engrafted and are producing myelin continue to become more obvious with time."

"They do need to determine if the cells are safe in the long term. Tumorigenesis has been caused by neural stem cells in isolated examples," said Spyros Deftereos, VP of drug discovery at Biovista Inc.

Biovista has BVA-101 and the BVA-20x class of compounds with undisclosed mechanisms in preclinical testing to treat multiple sclerosis (MS). The company did not disclose further details.

"Tumors are a risk that we are watching out for," acknowledged Rowitch. "Because this is such an early generation trial, we can't be exactly sure what the potential adverse effects of the cells will be. In the first year of the study, we have had a very favorable safety profile."

Mike Gresser, CSO of the Myelin Repair Foundation (MRF), and Robert Mays, head of neuroscience at Athersys Inc., both were concerned about the duration of immunosuppressant use.

Gresser told SciBX, "In order for the recipient to receive these donor cells, the patient will have to be treated with immune-suppressing drugs to keep their immune systems from rejecting the donated cells, just as organ transplant recipients have to be treated with immune-suppressing drugs. Immune suppression carries the risk of infections and adverse effects."

"Researchers need to understand for how long and at what level immunosuppression would be required for this type of treatment to

have meaningful, long-term benefit,” said Mays. Athersys is developing MultiStem, a multipotent adult progenitor cell–based approach to reduce neuroinflammation associated with CNS injuries and disease. MultiStem cells are in preclinical testing to treat MS and in clinical trials to treat ischemic stroke.

Rowitch told *SciBX* that his team has not seen any changes in immune reaction toward the transplanted cells after ceasing immunosuppressive therapy.

“We noted persistence of the MRI signals after discontinuing immunosuppression. In future studies, it will be important to carefully monitor and manage the potential for cell rejection by the patient,” he said.

Deftereos suggested that a solution to the issue of immunogenicity would be to use autologous stem cells. “The technology exists to dedifferentiate a patient’s cells into pluripotent cells, then redifferentiate them into neural stem cells,” he said.

Jason Hamilton, senior scientist at Athersys, said autologous cells could be a solution to myelination disorders that are not known to be caused by a genetic mutation, such as MS. However, he said, autologous stem cells isolated from patients with PMD or other genetic myelination disorders will have the same mutations as the dysfunctional, myelin-producing cells causing the disease, which may limit their effectiveness as a treatment option.

Other myelination disorders

In parallel with the Phase I extension study, StemCells is planning a Phase II trial.

In addition to the program in PMD, StemCells thinks the transplantation strategy could extend to other neurological disorders, “including certain cerebral palsies, transverse myelitis and even spinal cord injury in certain cases,” said Stephen Huhn, VP and head of the CNS program at StemCells.

He added, “MS is another potential indication. The issue is that it will require unique clinical considerations. MS is an autoimmune disease, and cell therapy could play a role in MS, but it would also be necessary to control the autoimmunity.”

Indeed, MRF’s Gresser was skeptical about the potential for the cell-based approach in MS.

“MS is not associated with a known genetic mutation that may impair their ability to myelinate axons. Due to this lack of genetic variation, we feel that this strategy will most likely not be applicable for MS patients

but instead could be beneficial for patients with a genetic disorder such as PMD,” he said.

Hamilton added, “In the case of an autoimmune disease like MS, in which the demyelination is caused by a systemic autoimmune reaction, this type of cell-based approach would be limited if you don’t use an adjunctive therapy to address the autoimmune component. There would be no way to stop the body from attacking the production of new myelin by the transplanted cells.”

“There could be synergy between the approaches described in these papers and strategies that modulate the negative effects of neuroinflammation. For example, treatment with MultiStem cells may slow or stop neuroinflammation and thereby give subsequently transplanted neural stem cells the chance to engraft and make myelin in a less hostile environment. We are excited about the idea of this synergistic potential,” added Mays.

Huhn told *SciBX* that StemCells holds patents related to both the human and mouse studies. The IP is available for licensing.

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