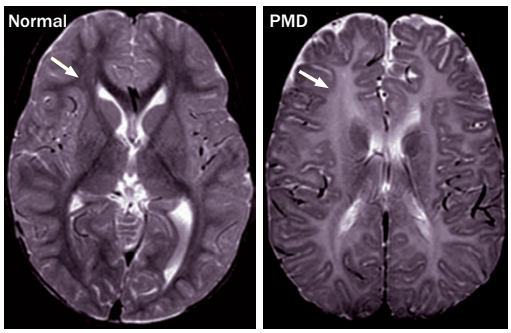
Nature Reviews Neurology **8**, 659 (2012); published online 13 November 2012; doi:10.1038/nrneurol.2012.224

WHITE MATTER DISEASE

Myelination achieved by transplanted neural stem cells

Myelination disorders, which include multiple sclerosis and cerebral palsy in preterm infants, are a major cause of disability and mortality. Now, two studies published together in *Science Translational Medicine* have shown that human CNS stem cells (HuCNS-SCs) differentiate into myelin-producing cells when transplanted into the brains of myelin-deficient mice or humans, providing hope for new treatments for myelination disorders.

The study in humans was a phase I open-label trial involving four young male patients with Pelizaeus–Merzbacher disease, a rare congenital leukodystrophy caused by a mutated myelin protein and involving global hypomyelination.



MRI scans at 2 years show global brain hypomyelination in Pelizaeus–Merzbacher disease (PMD). Image courtesy of A. James Barkovich.

"We used minimally invasive surgical techniques to directly implant HuCNS-SCs into four sites of superficial subcortical white matter," says David Rowitch, senior author of the study. Patients received immunosuppresion for 9 months post surgery, and MRI diffusion tensor imaging was performed at baseline and five times in the following year. "MRI is highly sensitive to the physical characteristics of myelin and seemed, therefore, a feasible approach to look for myelin as a biomarker of persistent stem cell engraftment," explains Rowitch.

The intervention was safe and well-tolerated, and was associated with stable or modest gains in motor and cognitive function at 12 months. Starting at 3 months, MRI signals showing enhanced myelination were detected around implantation sites, but not in other brain areas, and increased in intensity over the study period. "This result represents a scientific advance and reveals certain capabilities of transplanted neural stem cells," says Rowitch. The new MRI signals persisted even after discontinuation of immunosuppresion, suggesting the potential for long-term benefit of this treatment.

In the companion paper, Stephen Back and colleagues transplanted HuCNS-SCs into the brains of newborn and juvenile *shiverer-immunodeficient* mice—a model of myelinating disorders. Immunolabelling revealed the stem cells differentiated into oligodendrocytes (myelin-producing cells) at 2–3 weeks post injection, and were maintained at 25 weeks. Moreover, the HuCNS-SCs migrated extensively along white matter tracts, committing to the oligodendrocyte lineage at appropriate sites. *Ex vivo* high-field MRI signals at 5–7 weeks after transplantation revealed increased myelination in white matter tracts. "This study provides proof of principle that MRI can be used to track the transplants as myelin is being made," claims Back.

A phase II efficacy study of HuCNS-SCs is currently being planned.

Katie Kingwell

Original articles Gupta, N. *et al.* Neural stem cell engraftment and myelination in the human brain. *Sci. Transl. Med.* **4**, 155ra137 (2012) | Uchida, N. *et al.* Human neural stem cells induce functional myelination in mice with severe dysmyelination. *Sci. Transl. Med.* **4**, 155ra136 (2012)