

## FOCUS ON YALE MEDICINE

# Multiple Sclerosis: Can Schwann Cells Wrap It Up?

Antony Merlin Jose

*Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine, New Haven, Connecticut*

### INTRODUCTION

Multiple Sclerosis (MS) is a common, heterogeneous disorder of the central nervous system (CNS). Its causes and the factors that contribute to its heterogeneity are largely unknown. The disease affects about 0.1 percent of the population in temperate climates (approximately 1.4 million people worldwide) [1]. It is a disease of young people (median age of onset is approximately 28 years) but is lifelong and is often disabling.

In multiple sclerosis, the immune system attacks the brain's nerve fibers and strips away the protective myelin sheath around nerve fibers in the spinal cord and brain. The resulting lesions make it difficult for the nerves to transmit messages.

The cause of MS is not known. Epidemiological findings support both environmental and genetic hypotheses, and these forces likely interact to produce individual disease susceptibility and influence disease course.

### CELL REPLACEMENT AS A SOLUTION TO MS

A treatment dilemma posed by MS is how to restore nerve-insulating myelin after it is destroyed by the body's immune system. Because this immune response also induces the death of oligodendrocytes, the myelin-making cells in the brain and spinal cord, spontaneous remyelination is insufficient. One of the most exciting areas of MS research is the effort to transplant myelin-making cells into the central nervous system. These cells may be able to repair damage to myelin, regenerate injured axons and restore nerve signal conduction. The key to cell replacement therapies is finding the right cells — not an easy task. One promising prospect is Schwann cells, myelin-making cells from the peripheral nervous system.

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<sup>a</sup> To whom all correspondence should be addressed: Antony Merlin Jose, Department of Molecular Biophysics and Biochemistry, 333 Cedar Street, P.O. Box 208024, New Haven, CT 06520-8024. E-mail: antony.jose@yale.edu.

<sup>b</sup> Abbreviations: ALD, adrenoleukodystrophy; CNS, central nervous system; MS, multiple sclerosis.

### **CAN SCHWANN CELLS REMYELINATE AXONS OF DAMAGED NEURONS?**

As a first step towards answering the above question, a series of careful animal studies were carried out by the groups of Dr. T.L. Vollmer (Associate Professor of Neurology) and Dr. J.D. Kocsis (Professor of Neurology and Neurobiology) at Yale University. Two important studies are discussed here.

#### *Frozen Schwann cells isolated from humans can remyelinate rat axon*

Sections of sural nerve were removed from amputated legs of patients with vascular disease or diabetes, and Schwann cells were isolated and cryopreserved [2]. Suspensions of reconstituted cells were transplanted into the X-irradiation/ethidium bromide lesioned dorsal columns of the immunosuppressed Wistar rat. After three to five weeks of extensive remyelination, a typical Schwann cell pattern was observed in the lesion zone. The dorsal columns were removed and maintained in an *in vitro* recording chamber; the conduction properties were studied using field potential and intra-axonal recording techniques. The transplanted dorsal columns displayed improved conduction velocity and frequency-response properties, and action potentials conducted over a greater distance into the lesion, suggesting that conduction block was overcome.

This study established that the Schwann cells from the sural nerve could be frozen and then used to remyelinate CNS axons. It further proved that the Schwann cells are functional when transplanted in that they wrap axons, ameliorating neuronal impulse conduction problems.

#### *Quantitative morphometric techniques help assess the extent and pattern of remyelination produced by transplanting allogenic Schwann cells into demyelinated lesions in adult rat spinal cords*

The effects of donor age, prior culturing of donor cells, prior lesioning of donor nerves, and host immunosuppression were evaluated by transplanting suspensions of 30,000 acutely dissociated or cultured Schwann cells from neonatal, young adult, or aged adult rat sciatic nerves into X-irradiation and ethidium bromide-induced demyelinated dorsal column lesions. Three weeks after transplantation, spinal cords were processed for histological analysis. Under all Schwann cell transplant protocols, large areas containing many Schwann cell-like myelinated axon profiles could be readily observed throughout most of the lesion length. Within these "myelin-rich" regions, the vast majority of detectable axons showed a peripheral-like pattern of myelination. However, interaxonal spacing also increased, resulting in densities of myelinated axons that were more similar to peripheral nerve than intact dorsal columns. Freshly isolated Schwann cells remyelinated more axonal length than cultured Schwann cells, and cells from younger donors remyelinated slightly more axon length than cells from older donors, but all Schwann cell transplant protocols remyelinated tens of thousands of millimeters of axon length and remyelinated axons at similar densities. These results indicate that Schwann cells prepared under a variety of conditions are capable of eliciting remyelination, but that the density of remyelinated axons is much lower than the myelinated axon density in intact spinal cords.

The above study assessed the effectiveness of Schwann cells as remyelinating

cells of CNS axons. While the Schwann cells did remyelinate, the above quantitative evaluation shows that it was not to the extent of an uninjured CNS axon. However, the substantial improvement in the nerve conduction that can be achieved through Schwann cell replacement would be a boon to MS patients. The findings of this study underscore the need for a monitoring the effectiveness of the Schwann cell replacement in future human trials.

## **SCHWANN CELL REPLACEMENT IN HUMANS**

### *Phase One clinical trials*

The purpose of the Phase One trial is to determine whether cells found in the body's peripheral nerves, in this case, the ankle, can safely repair the damaged cells in the brain and spinal cord that result in neurologic disability in patients with multiple sclerosis and other disorders of myelin.

Dr. Timothy L. Vollmer and colleagues are carrying out a small trial of Schwann cell transplantation in five people with secondary-progressive MS. Dr. Jeffrey D. Kocsis's laboratory is providing technical support. Dr. Kocsis's laboratory has developed highly efficient ways of harvesting these cells from individuals who enroll in the study. Schwann cells will be taken from the sural nerve of the participants, and transplanted into areas of myelin damage in the brain.

This trial is being designed to determine if these cells can survive and to make sure treatment is safe. The procedure will be attempted one person at a time, and if there are any problems, the study will be stopped. If safety and tolerability of this invasive procedure can be shown, clinical trials to test its effectiveness will be planned which involve larger numbers of people and a well-controlled design.

The first central nervous system transplantation to repair the myelin-forming cells in MS was carried out on a woman with MS. The procedure took place on July 17 and 18 of 2001. In the first 24 hours, the team isolated the Schwann cells from the sural nerve, which was removed from the patient's ankle. A neurosurgery team led by Dr. Dennis Spencer (Professor and Chairman of Neurosurgery) then performed stereotactic surgery on the patient, using an magnetic resonance imaging machine to very accurately guide a needle through the frontal lobe and inject the Schwann cells into a previously identified MS lesion.

Dr. Vollmer says the patient was then studied using a number of techniques, including neuroimaging and functional assessments for six months. At the end of that period, the team used a stereotactic procedure to take a small biopsy to determine whether the cells survived and whether they made any myelin.

A 29-year-old man with MS was the second patient to undergo this procedure. The surgery took place on March 6 and 7 of 2002, in two stages.

Both patients are doing fine. The experiment holds promise, not only for the estimated 1.4 million people worldwide with MS, but also for patients affected by other demyelinating diseases, such as the leukodystrophies, a group of hereditary diseases that strike children in infancy.

The results of these experiments have not yet been disclosed.

## **LORENZO'S OIL AND THE MYELIN PROJECT**

### *Funding research in MS*

The replacement therapy attempted at Yale is funded by the Myelin Project.

The story of the Myelin Project begins with Augusto and Michaela Odone and their son Lorenzo. In 1984 Lorenzo came

down with adrenoleukodystrophy (ALD), a rare inherited disease, in which the myelin sheath is destroyed. Doctors said that he would lose all his functions and die within two to three years. Refusing to accept this grim verdict, the Odones set out on a mission to find a treatment for ALD and to save their child (Lorenzo survived and is now 23 years old). In their quest for a treatment, the Odones often clashed with doctors, scientists, and support groups, who were skeptical that anything could be done about ALD, much less by lay people. The Odones haunted medical libraries, reviewed countless animal experiments, badgered researchers, questioned top doctors all over the world, and persisted until a solution came to them in a moment of inspiration. They commissioned a special type of oil (oleic acid and erucic acid) from a British firm, which normalized the accumulation of very long chain fatty acids in the blood of ALD boys. This allowed Lorenzo and others to live on a restricted diet.

In the second chapter of the story, the Odones founded The Myelin Project in the hope of finding a way to restore the myelin sheath, which is destroyed in ALD and a host of other myelin diseases, such as multiple sclerosis.

For the millions affected by MS, the groundbreaking Schwann cell replacement therapy attempted by Dr. Vollmer's team at Yale is a cautious step towards a better life.

#### REFERENCES

1. Wingerchuk, D.M., Lucchinetti, C.F., and Noseworthy, J.H. Multiple sclerosis: current pathophysiological concepts. *Lab. Invest.* 81:263-281, 2001.
2. Kohama, I., Lankford, K.L., Preiningerova, J., White, F.A., Vollmer, T.L., and Kocsis, J.D. Transplantation of cryopreserved adult human Schwann cells enhances axonal conduction in demyelinated spinal cord. *J. Neurosci.* 21:944-950, 2001.
3. Lankford, K.L., Imaizumi, T., Honmou, O., and Kocsis, J.D. A quantitative morphometric analysis of rat spinal cord remyelination following transplantation of allogenic Schwann cells. *J. Comp. Neurol.* 443:259-74, 2002.