NATIONAL MULTIPLE SCLEROSIS SOCIETY

Research highlights

A report of recent research progress in MS • • • • • • • • • • • • • • • • • Winter/Spring 2007

Promise: 2010 Update

In Their Own Words:
Nerve Tissue Repair Teams Report Great Progress

The room was buzzing with excitement as some 50 members of the four Nervous System Repair teams, funded by the National MS Society through its Promise: 2010 campaign, met as a group for the first time in November 2006 to share data and foster collaborations. With a Society funding commitment of $15.6 million, the four multinational, interdisciplinary teams are developing paving the way for clinical testing to protect and restore function in people with MS. (Read more about the teams on our Website at http://www.nationalmssociety.org/Research-TargetedRepair.asp.)

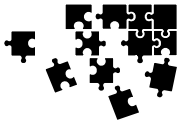
The team leaders share with us now, in their own words, their first years' progress.

Dr. Peter Calabresi's Team (Johns Hopkins)

After meeting with the other teams, Dr. Calabresi remarked, "The first year of the Promise: 2010 grant has been a great success. The news that others are finding similar data is extremely exciting because we can't move on in science if what we find can't be duplicated elsewhere."

Nerve protection: We've discovered how a protein in myelin (the nerve-insulating material which is damaged by immune attacks in MS) called MAG can communicate with the axon (the wire-like nerve fiber inside the myelin coating) and protect it even when MAG is no longer part of the myelin sheath. Understanding how myelin protects axons at the molecular level could lead to novel ways of protecting or repairing nerves without necessarily having to make new myelin. (Dr. John W. Griffin's lab)

We've tested a new model in which axons are damaged at only one part of the spinal cord (as in the disorder transverse myelitis) to determine what happens to axons that pass through areas of injury. This type of research may help us understand the mechanisms of focal injury and how we can rescue partly damaged nerves. (Drs. Calabresi and Douglas Kerr)



inside…

Promise:2010

To encourage innovative research into highly promising areas and to improve MS patient care, the National MS Society launched the Promise: 2010 Campaign. This nationwide effort fueled by local MS chapters will raise at least $30 million to fund four targeted areas that hold great potential, but which have so far been under-explored. If you would like to donate to this campaign, please contact your chapter at 1-800-344-4867.

We've determined that proteins released by immune T cells not only cause damage to nerve cells, but they inhibit nerve precursor (immature progenitor) cells that are trying to repair the brain. By understanding which of these proteins is most important we may be able to better dampen the bad inflammation and allow natural reparative processes to occur more efficiently. (Drs. Avindra Nath and Calabresi)

Drug screening method: We are developing a "high throughput" system to rapidly screen neuroprotective agents in an automated system. This is critical in order to test the thousands of potentially beneficial drugs available, and may allow us to focus on the most promising. (Dr. Nath)

Imaging techniques: We have been able to use new MRI software on stronger MRI magnets to create pictures of fiber tract pathways in MS patients' brains and spinal cords. These pictures may allow us to better image lesions (damaged areas) and discriminate damage to the axon from damage to myelin, rather than just seeing the inflammation. (Drs. Susumu Mori, Seth Smith, and Daniel Reich)

We have shown that a new machine called an optical coherence tomography scanner, or OCT, is a sensitive and easy method to measure the health of the nerve fibers in the back of the eye. OCT shows promise as an outcome measure for neuroprotective clinical trials. We are planning a multi-center clinical trial in patients with acute optic neuritis to test whether a novel neuroprotective drug can limit axon loss in this setting, using OCT as a way to measure axonal loss. (Dr. Laura Balcer, University of Pennsylvania, and Dr. Calabresi)

Dr. Ian D. Duncan's Team (University of Wisconsin, Madison)

"We have made some significant progress toward our long-term goal of initiating a clinical trial in MS."

Experimental models: In the rat, we established a focal model of MS-like EAE in the spinal cord that results in neurologic defects in the hind limbs. We will use this model to explore the anti-inflammatory effects of the antibiotic minocycline, and the restorative capabilities of immature myelin-making cells (oligodendrocyte progenitors) transplanted into, or adjacent to the lesion.

In the "Biozzi" mouse, we have shown a correlation between progressive disability and nerve fiber loss. We can now

Update: The MS Lesion Project

People with MS have known it all along – there is wide variety in this disease. This variety may actually stem from biological differences, and if researchers can determine the nature of these differences – and possibly identify different causes of the disease – it would change the way we diagnose and treat MS.

Dr. Claudia Lucchinetti (Mayo Clinic) is the lead investigator for the Promise: 2010 international research collaboration called The MS Lesion Project. The team is studying damaged areas (lesions) in the brains of individuals with MS for clues to different patterns of destructive immune factors.

Dr. Lucchinetti and a team of renowned researchers from the U.S., Germany and Austria have made excellent progress. (Go to our Web site for more details: http://www.nationalmssociety.org/Research-TargetedLesion.asp.)

Earlier, the team found four distinct types of lesions that differed in the pattern of myelin loss and in the activity of immune cells and proteins. Within an individual, the lesion pattern is the same, but can differ between individuals. This suggests lesion patterns may relate to disease type and to treatment outcomes.

"We are now determining if these different lesion patterns appear differently on MRI," explained Dr. Lucchinetti. "If this proves to be so, then in the future we may be able to determine the lesion pattern through MRI scanning without having to take a biopsy."

Analyses of these tissue samples have already resulted in scores of new findings published in respected, international journals. A recent paper came out with a surprising finding: that a substantial amount of natural myelin repair can occur in people with MS across most types and stages of the disease. Further research is required to uncover factors that determine why some individuals show highly efficient myelin repair while others do not.

compare these findings after attempting treatment to protect tissue or after cell transplantation. We also established an EAE model in marmosets and identified disturbance of the visual system of 100% of those with EAE. As one can now putatively evaluate the loss of nerve fibers in the optic nerve using a technique known as ocular coherence tomography (OCT), we have initiated studies using OCT in the marmoset. We believe that this model offers great opportunities to explore neuroprotective therapies.

Repair cells: We isolated oligodendrocytes (myelin-making cells) from stem cells and succeeded in coaxing them to specialize (differentiate) into oligodendrocytes in increasing numbers and percentage using selective growth factors. We have also shown that these cells make myelin when transplanted into animals that are myelin-deficient, thus proving their functional capabilities.

Imaging: We have been evaluating MRI measures to develop a predictive model of central nervous system tissue

structure and function (myelin growth, axon preservation, scarring, and inflammation). We developed advanced imaging protocols for improving the information obtained with MRI, diffusion transfer and magnetization transfer measurements.

We have been evaluating a PET (positron emission tomography) imaging tracer which is used to label microglia, cells which are present in regions of active inflammation in the central nervous system. We have significantly improved the synthesis of this tracer to obtain increased specific activity. In addition, a new small animal PET scanner has been installed, enabling the detection of smaller lesions in small animal models.

Dr. Charles ffrench-Constant's Team (Cambridge University)

"The goal of our project is to discover new therapies to promote repair by remyelination in MS."

Drug discovery: We identified five signaling pathways present in immature myelin-making cells (oligodendrocyte precursors) of the adult human brain. These pathways may regulate the ability of the precursors to form mature oligodendrocytes and myelin. In keeping with this, inhibitors of one of these pathways, receptor tyrosine phosphatase zeta, do promote oligodendrocyte formation and thus provide our first "target". (Dr. Steve Goldman, University of Rochester)

"Transcription factors" – master regulators that control the expression of genes – also represent promising targets. To discover new transcription factors involved in remyelination we have completed a genome scale screen of the repair process, examining over a thousand transcription factors. This has revealed approximately 25 factors that will now be taken into a secondary screen to establish exactly where and when they are expressed during repair. (Drs. Robin Franklin, Cambridge, and David Rowitch, Dana-Farber Cancer Institute)

Cell transplantation: We need to clarify the ideal cell source for transplantation and the most appropriate route of administration. We have shown that human oligodendrocyte precursors will form new myelin sheaths very effectively when transplanted into the brains of mice, suggesting that they may be suitable for the large amount of repair needed in the brain damaged by MS. (Dr. Steve Goldman)

We have also shown that mouse neural stem cells injected intravenously reach inflamed areas of the central nervous system where they home and reside for months after transplantation and promote both resolution of inflammation and protection of surviving tissue at the site of injury. (Dr. Gianvito Martino, San Raffaele Hospital, Milan)

Model systems: We have developed a simple test for myelination (myelin growth around nerve fibers) based on cell culture of oligodendrocytes and axons. The simplicity and ease of measurement provided by the test is important, as it will provide a quick first line screen for potential drugs. (Dr. Charles ffrench-Constant, Cambridge)

We have identified techniques that allow us to grow large numbers of human oligodendrocytes, so enabling us to test drugs directly on human myelinating cells. (Drs. Samuel Weiss, University of Calgary and Jack Antel, Montreal Neurological Institute)

Finally, we are developing models of MS lesions, enabling us to model the human disease as closely as possible and also test for restoration of function following treatment. (Dr. Annic Baron Van-Evercooren, INSERM)

Dr. Gavin Giovannoni's Team (Queen Mary University of London)

"In our first year as Promise: 2010 investigators, we have initiated five parallel, but well-integrated, study programs to address our aims," commented Dr. Gavin Giovannoni.

Experimental Models: We have been working with a mouse model of an MS-like disease. These mice experience a period of relapses and remissions, followed by a phase of progressive disability similar to secondary progressive MS. In this phase the mice develop spasticity and tremors that aren't measured with traditional scoring methods. We have therefore started using new methods to assess disability in this phase, which includes activity monitoring. This has led us to plan a pilot study of activity monitoring in people with MS to see if it can be used to assess the effectiveness of nerve-protecting and nerve-restoring therapies. (Dr. David Baker's lab)

Potential Therapies: Two classes of nerve-protecting compounds will be tested in two single therapy clinical trials in the United Kingdom. Lamotrigine (currently used to prevent seizures in people with epilepsy) is being tested to see if it can prevent or slow progressive shrinking of the brain (atrophy) in people with secondary progressive MS. This trial is being run by Dr. Raj Kapoor (National Hospital for Neurology and Neurosurgery, Queen Square, London).

… continued on page 8

"Heat-Seeking Missiles" for Tissue Repair

How can therapeutic molecules be delivered exactly where they are needed to repair tissues? Giovannoni team member Dr. Yuti Chernajovsky is tackling this question by engineering unique delivery cells.

"A good analogy is heat-seeking missiles that target 'hot areas' of inflammation and avoid causing unwanted effects to surrounding healthy tissue," stated Dr. Giovannoni. These delivery proteins consist of two parts, a carrier protein and a cargo protein. The carrier protein will only release its cargo when it is cleaved, or split open, by an enzyme produced in active MS lesions.

The team has designed several different proteins that contain different growth factors as cargo. These factors are known to promote myelin growth. "We plan to test these in our 3-D culture system in the second year of our program," said Dr. Giovannoni.

Fulfilling the Promise for Kids with MS

The picture is getting brighter for children who have multiple sclerosis. With the help of the National MS Society, the management of pediatric MS and research on this hitherto underserved population are gaining ground.

Networking for Kids with MS

Establishing six Pediatric MS Centers of Excellence was the first step, and this was accomplished with funding from the Society's Promise:2010 campaign. However, in order for these centers to set the standard for pediatric MS care and perform critical research to understand both childhood and adult MS, they need to function as a network. These centers in Alabama, California, Massachusetts, Minnesota, and New York have taken major steps toward this goal. Here are the results of some recent meetings:

- Investigators gathered to draft a proposal for a database that would contain information gathered by the pediatric centers. This is a highly technical venture, in which each site will be uploading data in an identical manner; other sites can have access to this data with the permission of a steering committee.
- Centers gathered to develop a protocol for magnetic resonance imaging (MRI) scanning. This is crucial because there can be great variability in reading and interpreting MRI scans. The group also discussed the necessity for collecting the most clinically important data quickly, since getting kids to cooperate may be an issue.
- Social workers from the pediatric centers discussed the issue of how to provide financial assistance when necessary. Some centers are developing relationships with potential donors, such as airlines, to help provide assistance. The group agreed to document cases of financial assistance requests for a couple of months and reconvene to determine what policies can be adapted by all centers.
- Neuropsychological testing is being adapted to children by this group. The standard battery used in adults with MS is being revamped to consider children's needs, such as including a report from parents.

These efforts are breaking new ground, providing standards for managing the care of children with MS, and for collecting data that will prove invaluable to understanding their experience with the disease, as well as adults.

Recent Research on Kids' Concerns

The feelings of children and teenagers living with MS were recently explored by Jennifer R. Boyd, MHSc, RN, CNN, MSCN and Lynn J. McMillan, RN, CNN, MSCN (Hospital for Sick Children, Toronto). They interviewed 12 kids between the ages of 8 and 18 to learn what it was like for them to live with the diagnosis of MS (*Journal of Neuroscience Nursing* 2005;37;334-342). Here are just some of their findings:

- Upon learning of their diagnosis, most felt scared and feared dying, particularly if they were hospitalized at the time and recalled their parents' reactions. Some felt pressured by family members to expand their knowledge of MS, but indicated that they were not interested in learning more.
- All talked about wanting to disclose their diagnoses very selectively, and perceiving that more people knew than they would prefer. They felt embarrassed and vulnerable to possible teasing or pity.
- Most said that MS had a limited effect on their lifestyle, but readily noted its effect on school participation and learning. Relapses and appointments made them miss school, and many described increased problems with memory and concentration.

Acknowledging that this study represents a very small sample, the authors cite several recommendations for nurses caring for young people with MS:

⇒ Reassure them that they will not die from MS.
⇒ Respect their right to limit the information they obtain.
⇒ Explore concerns related to school, relationships and peers.
⇒ Review the benefits of treatment and the importance of making it part of their routine.
⇒ Discuss concerns about disclosing the diagnosis of MS.

The National MS Society provides resources for children and teens with MS, such as the magazine Teen InsideMS. Find out more about these resources online at http://www.nationalmssociety.org/Pediatric_and_Childhood.asp ■

Sonya Slifka Longitudinal MS Study Renewed

Six years of success have led to the recent renewal of the Society's commitment to the Sonya Slifka Longitudinal MS Study. Results thus far have helped the Society paint a realistic picture of the true impact MS has on peoples' lives.

This first study of its kind in the U.S. is a repository of in-depth social, medical and economic information about the lives of people with MS. Investigators led by Sarah Minden, MD (Abt Associates, Cambridge, Mass.) have been collecting data every six months from a national sampling of 2,000 individuals.

Data from the study have been used to inform important advocacy issues. In a recent example, the study provided data for the Society's Long-Term Care Caucus, suggesting that some 30% of people with MS need home care assistance. Echoing the general population, about 80% of that care is provided by unpaid helpers, usually family members.

A second national sampling of 2,500 participants will now be recruited. Specific subgroups will be over-sampled to enhance the database, including people newly diagnosed, those more severely disabled, and minorities.

Some 10 outside investigators have been granted access to the database to investigate questions about quality of life, rehabilitation, prognostic indicators, the cost-effectiveness of therapies and others. ■

Dr. Gavin Giovannoni's Team
… continued from page 5

The second is a large, multi-center study to see if the active compound in cannabis, THC (tetrahydrocannabinol) can slow the progressive phase of the disease, as has been suggested in EAE. This is being coordinated at the Peninsula Medical School in Plymouth.

Another part of our team is using animal models of MS to assess several novel drugs. One of these is 3,4-DAA (Tranilast or Rizoben, which is licensed to treat various allergies). This drug may reduce the severity of EAE by shifting the profile of inflammatory cells from a bad to a good profile. We plan to test combinations of compounds to see if we can find synergism between them at doses that will be well tolerated in people with MS. (Dr. Larry Steinman, Stanford University)

Testing Drugs in Lab Dishes: We are using a complex, three-dimensional cell culture model of the nervous system to test potential therapies. In this model the nerve cells produce extensions called axons. These are then insulated by myelin produced by cells called oligodendrocytes. Importantly, the nerve cells in this system become electrically active. This 3-D culture system is allowing us to explore combinations of drugs for their ability to protect nerves from damage.

Biomarker study: A biomarker is an objective measure of a specific biological process that occurs in MS. We are evaluating a panel of biomarkers in the blood and spinal fluid to measure different biological processes in MS. It is hoped that these markers will allow us to select patients for clinical trials and to use a change in these marker to assess therapeutic efficacy of our target compounds. ■

NATIONAL MULTIPLE SCLEROSIS SOCIETY