Myelin Repair Foundation

Collaboration. Acceleration. Results.

Myelin Repair Foundation Research Highlights

Fall 2008

In July 2008, the Myelin Repair Foundation completed Year 4 of our five-year research plan to discover and validate new therapeutic targets for myelin repair in multiple sclerosis (MS). When the MRF was founded in 2002, relatively little was known about the underlying biological processes that resulted in myelin formation and how these processes were affected by MS. However, it was becoming apparent that the brain and spinal cord had a capacity for repair and there was some evidence that myelin repair was taking place spontaneously in the early stages of MS. The MRF formed an interdisciplinary research team to identify critical biological questions that would have to be answered before effective myelin repair therapies could be developed. Together we designed a comprehensive research plan to answer these questions in order to identify new biological mechanisms, pathways and ultimately drug targets that would lead to effective therapies to repair damaged myelin.

The MRF's five-year research plan includes developing new research tools and conducting investigations in six key areas:

1. What is the role of neural stem cells in myelin repair?
2. How does myelin form?
3. How is the immune system involved in damaging myelin? How does the immune response prevent myelin repair?
4. Disrupting the immune response and stimulating myelin repair.
5. Repairing the blood brain barrier to promote myelin repair.
6. What new or improved animal or cellular models do we need to ensure this research provides answers applicable to MS in humans?

1. What is the role of neural stem cells in myelin repair?

Myelin Repair Foundation scientists are actively involved in trying to understand the molecules and signals that are involved in directing the migration of neural stem cells to areas of demyelination in MS patients (the MS lesions) and the molecules and signals that are involved in promoting the differentiation of neural stem cells into the myelin-forming cells (oligodendrocytes) of the central nervous system (CNS). These myelin-forming cells, or oligodendrocytes, are constantly being produced in healthy individuals and in patients with demyelinating diseases such as MS. However, for reasons that are still unknown, MS lesions often do not remyelinate or repair.

The Myelin Repair Foundation has identified several of the molecules that play a role in orchestrating the migration of oligodendrocyte precursor cells to MS lesions and/or the differentiation of stem cells into the myelin-forming oligodendrocytes. As the required reagents and tools are generated or become available, Myelin Repair Foundation is systematically evaluating the therapeutic potential of each of these molecules for myelin repair. In recent studies, Myelin Repair Foundation scientists have successfully stimulated myelin repair in a persistent, MS-like lesion by blocking one of these molecules with an inactivating antibody. Based on the success of this experiment, we have gone on to identify small molecule, drug-like compounds that can also bind to and block this molecule. We are in the process of evaluating these compounds for their ability to promote myelin repair in various animal models of demyelination and MS.

In addition to the critical role neural stem cells play in myelin repair, we have also demonstrated that bone marrow-derived mesenchymal stem cells (MSC) can also play a beneficial, though indirect, role in promoting myelin repair. Early studies by the Myelin Repair Foundation and other groups have shown that there is a clear therapeutic benefit when animal MS models are treated with human MSC. The Myelin Repair Foundation has extended these studies by determining that MSC produce their therapeutic effects by inducing resistant neural stem cells to differentiate into myelin-forming oligodendrocytes. The Myelin Repair Foundation has identified the mechanism responsible for this effect, and ongoing efforts are focused on determining the full therapeutic value of these discoveries.

2. How does myelin form?

As part of the experimental tools and models developed by Myelin Repair Foundation scientists in order to better understand the complex process of myelin repair, Myelin Repair Foundation researchers have developed a precise method for culturing neurons and oligodendrocyte precursor cells so that myelination can be studied in a reproducible manner from initiation to the formation of mature, intermodal segments identical to those found in human myelin. Using this co-culture system, the Myelin Repair Foundation has identified molecules critically involved in myelin formation. Using small molecule inhibitors of one of these potential therapeutic targets, the Myelin Repair Foundation has recently demonstrated the therapeutic potential for

this target for promoting myelin formation and myelin repair both in vitro and in vivo. These findings, coupled with studies using small molecules to modulate oligodendrocyte precursor cell migration, demonstrate for the first time that drug-like small molecules that modulate critical aspects of oligodendrocyte cell biology hold promise as novel therapeutic treatments for MS and other demyelinating disorders.

3. How is the immune system involved in damaging myelin? How does the immune response prevent myelin repair?

MS is a known autoimmune disease. In MS, initiation and progression is due in part to the recognition of normal myelin as being foreign to resident B-cells and T-cells. In fact, the majority, if not all, of the novel therapies under development for MS are targeting different aspects of this autoimmune response. Myelin Repair Foundation scientists have shown that in addition to damaging myelin and axons, the immune response in MS may also be indirectly affecting oligodendrocyte cell survival by exacerbating certain aspects of cellular stress. During periods of myelination, oligodendrocytes must produce vast amounts of myelin protein in order to maintain the active process of myelination. This high protein synthesis rate makes the myelinating oligodendrocytes vulnerable to conditions and factors that enhance cellular stress. In MS, activated immune cells secrete factors, such as interferon-gamma, that promote cellular stress. This results in a vicious cycle in which the more oligodendrocytes are recruited to remyelinate MS lesions, the more vulnerable they are to the detrimental effects of the inflammatory response.

Myelin Repair Foundation scientists have been investigating ways to protect oligodendrocytes from this cycle of inflammation, cellular stress, and ultimately oligodendrocyte cell death. The Myelin Repair Foundation has identified several of the molecules involved in this process and for the last year, Myelin Repair Foundation scientists have been working with the Laboratory for Drug Discovery in Neurodegeneration at Harvard University to identify drug compounds that would act as therapeutics to protect oligodendrocytes from these detrimental effects. Early lead compounds have been identified, and additional studies are being conducted to confirm the effects of these compounds in vivo and in vitro.

4. Disrupting the immune response and stimulating myelin repair.

Since the majority of the existing and emerging therapies for MS target the immune response, Myelin Repair Foundation scientists have begun to explore how inhibition of MS-associated inflammation can unmask the potential for myelin repair in this complex disorder. By utilizing a novel combination strategy to simultaneously block immune responses and promote myelin repair, Myelin Repair Foundation researchers have achieved dramatic recovery in the experimental autoimmune encephalomyelitis (EAE) animal model for relapsing–remitting demyelination. The results achieved by this combination therapy were significantly better than results of experiments using either therapy alone. Myelin Repair Foundation investigations are continuing to

evaluate this combination therapy in other MS models, and in culture, to optimize this synergistic effect.

5. Repairing the blood brain barrier to promote myelin repair.
The role of the blood brain barrier in MS is still not clearly understood. It is thought that the breakdown of the blood brain barrier may play a critical role in initiating and maintaining the autoimmune responses that contribute to this debilitating disease.

Restoring the integrity of the blood brain barrier could significantly retard the disease process in MS. Myelin Repair Foundation researchers have identified several signaling pathways that are highly up-regulated in the blood vessels of the CNS but are absent, or expressed at very low levels, in blood vessels elsewhere in the body. They have begun to identify the key regulatory molecules within each of these pathways in order to identify potential drug targets that could be utilized to restore the integrity of the blood brain barrier and determine if such treatments have therapeutic value for the treatment of MS.

6. What new or improved animal or cellular models do we need to ensure this research provides answers applicable to MS in humans?
In addition to the development of the co-culture system that is allowing us to follow the complete process of myelination in vitro, the Myelin Repair Foundation is actively engaged in the development of novel animal models and tools that will allow us to precisely follow myelin repair in vivo. The Myelin Repair Foundation has recently developed novel methods to selectively eliminate oligodendrocytes or other cells of interest in vivo, and in so doing better understand the role particular cell types play in myelin repair.

The Myelin Repair Foundation is also developing unique animal models that will allow a quantitative assessment of the production of new myelin and the preservation of old myelin after various therapeutic treatments in vivo.

Furthermore, Myelin Repair Foundation researchers have begun measuring changes in gene expression during the course of the disease in the existing EAE models. By using laser dissection to examine gene expression in areas within lesions, near lesions, or in unaffected tissue, we are beginning to compare how thousands of genes behave throughout the clinical disease course. This process has provided new methods for measuring changes in the disease course at a molecular level. In the future, these studies will be validated and expanded by measuring changes in protein and lipid levels within the same tissue samples.