Myelin Repair Foundation

Discovery through Collaboration

Myelin Repair Foundation Research Progress Summary
March 2005

This summary provides an update on the progress of the Myelin Repair Foundation (MRF) research team in the search for new therapeutic targets to repair myelin damaged by multiple sclerosis. The MRF conducts three formal research review meetings during the course of the year in addition to monthly conference calls. In these meetings, the Principal Investigators, working with the Scientific Advisory Board, not only review progress but discuss new ideas and propose adjustments to the research plan determined to be beneficial to accelerating progress. The most recent meeting was held March 7-8 in Chicago, and this summary highlights the progress reported at that meeting. Please keep in mind that this summary only describes a portion of the progress made during the first eight months of a five-year research effort.

This summary is divided into two parts:

1 - Feedback from the MRF Principal Investigators on how they feel the collaboration is progressing and the benefits they are deriving

2 – Summary of recent progress made by MRF Investigators

Feedback from the MRF Principal Investigators

A little more than a year ago we asked five senior scientists and members of their labs to join us on a voyage of discovery into uncharted waters. We asked each to participate in a new collaborative process outside the norms of academic research and beyond their comfort zone. At the most recent research review meeting, we asked the scientists to share their thoughts on the value of the MRF collaboration.

"Being part of the MRF has been a fantastic experience for me and for the members of my lab. By sharing our data way before publication, we have had the tremendous benefit of helpful advice, suggestions, and experience of our team members. These discussions have lead to productive collaborations between the five labs and to interchange of thoughts that lead to new ideas for MS-relevant experiments. By participating in MRF meetings we have all been educated about MS and about how to do translational research." - ***Ben Barres, Stanford University***

"I am extremely encouraged by the progress that all MRF investigators have made towards their research goals during the first year of funding. I am also thrilled by the camaraderie and sharing of ideas and reagents that are occurring between the members of each the research labs. As a result of this collaborative effort, my laboratory has made major advances in new research directions which we would not be involved were it not for the Myelin Repair Foundation. The unique areas of expertise of the individual collaborative investigators and their willingness to share ideas and preliminary data have greatly facilitated progress in all of the participating labs and give encouragement that the five year goal of the

MRF in identifying a drug target for promoting myelin repair will come to fruition." - ***Steve Miller, Northwestern University***

"Participation in the myelin repair foundation has significantly facilitated our research efforts. The interactions that have developed, and which are constantly developing, have allowed for my laboratory to explore new avenues of research and to tackle our ongoing projects in a more comprehensive manner. Access to the expertise and perspective of the four other groups has considerably expanded the nature of the projects that my laboratory feels comfortable addressing. Moreover, the interactions that have developed between the lab members of the groups have been particularly rewarding. It seems highly likely these interactions will spawn new, highly innovative areas of inquiry. The targeted nature of the studies that we are joined in pursuit of has also increased the likelihood that significant advances in myelin repair will result from our efforts. Although specific examples of collaborative ties are import, it could be argued that the general discussions and detailed suggestions provided by our MRF colleagues at our group meetings are equally valuable to our research efforts" - ***Brian Popko, University of Chicago***

"You asked me for my thoughts about what we have achieved thus far. Obviously you can report that the work in the laboratories is being accelerated as a result of the funding received by the group but there is a more intangible advantage that I don't quite know how to describe. My
sense it that by thinking about science together and weeding out of bad ideas moves us much faster as the group than as individuals." - ***Robert Miller, Case Western Reserve University***

"Because of the MRF, our labs are now studying newly identified myelin proteins that may turn out to be very important completely novel therapeutic targets in MS. MRF greatly accelerated the identification process of these potential targets; we now have about 50 candidate molecules that have not been explored before. No one lab could easily or rapidly evaluate all 50. It would take an army of people to do that. The resources of the MRF substantially facilitate these new studies." ***- David Colman, Montreal Neurological Institute***

Recent Progress Made by MRF Scientists

The current projects being conducted by the MRF team are trying to answer the questions of how oligodendrocytes mature into cells capable of producing new myelin and how environmental factors present in MS prevent myelination. Therefore, this report will summarize recent progress made with regard to these two questions.

How oligodendrocytes mature into cells capable of producing new myelin

If you examine the "*Summary of the Myelin Repair Foundation Research Plan"* on our web site you will note that the first three areas of investigation are focused on understanding the processes that drive the transition from neural stem cells into myelinating oligodendrocytes, how these cells produce the proteins and lipids necessary to form normal myelin and how these processes are disrupted by MS.

Based on work in Dr. Barres' lab described in a previous update, his team has determined that oligodendrocytes must undergo a previously unknown step in their development before they can become myelin producing oligodendrocytes. Dr. Barres' lab has identified a class of investigational drugs that stimulate this newfound development step in cell culture *(in vitro)*, resulting in strong formation of myelin that appears to have normal characteristics (thickness, compaction, rate of formation). The next step was then to test these drug compounds in animal models.

Dr. Steve Miller's lab has now tested these drug compounds from Dr. Barres' lab in his EAE* animal model of Relapsing – Remitting MS, with encouraging results. Dr. Steve Miller's lab has shown by testing these compounds on mice, that myelin proteins are indeed expressed at higher levels in the remission phase (versus the relapsing phase). This is exciting because it provides further evidence that animals are making an attempt to repair myelin damaged during the previous relapse. Furthermore, these results may lead to a quantitative way to measure myelin repair in living animals (*in vivo*).

Why Further Investigation is Necessary

While these early results from Dr. Barres' lab and Dr. Steve Miller's lab are significant steps forward in understanding the development steps of an oligodendrocyte, there are several significant challenges that must be addressed before new therapies can be developed. First, the class of drugs being used in these experiments has some undesirable side effects. Thus it is critical that we understand the specific molecule that controls this final development step of an oligodendrocyte cell so that a highly targeted therapeutic agent can be developed. Uncovering the specific pathway and an appropriate agent to control it will require a concerted team effort over several years.

Secondly, stimulating this development step alone may not be sufficient to induce myelin repair. It is likely that it will still be necessary to overcome environmental factors in the central nervous system (CNS) such as those described in further detail in the next section of this summary.

Thirdly, as Dr. Steve Miller realized, while this discovery may be a beneficial tool in developing a quantitative way to measure new myelin formation, there are numerous technical hurdles that must be overcome before we can identify new myelin from the old myelin, as a result of this agent.

Therefore, the MRF research team is continuing to investigate the environmental factors present in MS in order to determine the specific mechanism that triggers this final step in the development of an oligodendrocyte so that it can produce myelin. If the proper chemical signal is missing, or the pathway to receive the signal is being blocked, it could account for the presence of apparently mature oligodendrocytes in MS lesions that do not produce myelin. It will require significant additional investigations before suitable therapeutic pathways and targets can be identified.

Environmental factors present in MS that prevent myelination

This area of investigation in the MRF research plan deals with environmental factors in the CNS that may inhibit myelin repair. These factors may be produced by cells normally present in the CNS, such as Astrocytes and Microglia, which are reacting abnormally due to MS. Factors that inhibit new myelin formation may be foreign to the CNS, like T cells, which migrate through the blood brain barrier during the course of the disease.

Dr. Popko's lab has just demonstrated one direct damaging impact of T cells in the CNS to myelin repair. They have identified a specific chemical signaling molecule released by T cells that, even in very low concentrations, causes excessive stress in myelinating oligodendrocytes. This stress is sufficient to cause rapid death of those cells and this effect appears to be unique to those cells that are just beginning to produce myelin. Thus the persistence of T cells in MS lesions may be one explanation of why myelin repair does not take place during or after acute inflammation in MS.

The most obvious approach to using this information would be to suppress the production of this chemical signal. Unfortunately the same signaling molecule plays a variety of beneficial roles throughout the body, including the CNS. Thus a more appropriate, and complex, therapeutic approach may be needed to reduce the sensitivity of oligodendrocytes to this particular signal. The entire MRF research team is now engaged in developing ideas about new therapeutic approaches that utilize this finding.

Other Experimental Updates

Dr. Popko's lab is taking a transgenic mouse (a transgenic mouse, or any other species, is simply an organism that has had DNA introduced into one or more of its cells artificially) approach to identifying new genes critical to the myelination process. These studies are nicely complimented by a molecular approach in Dr. Barres' laboratory and a biochemical effort in Dr. Colman's lab, which have similar underlying goals. Already the sharing of data among the groups, which would not have occurred without the MRF, has allowed Dr. Popko's lab to identify the genetic defect present in a mutant strain of mice with myelin abnormalities.

At the recent MRF group meeting, discussions with Dr. Bob Miller have resulted in the planning of a new research project designed to better understand the underlying cause for the remyelinating incapacity of adult myelinating cells from a mutant strain of mice that Dr. Popko's lab developed.

Based on discussions with Dr. Popko and Dr. Robert Miller, Dr. Steve Miller's lab has begun productive collaborations aimed at promoting myelin repair via various approaches involving stem cell therapy and they have initiated a collaboration with Dr. David Colman to examine immune responses to unique myelin proteins identified in his lab.

**Experimental autoimmune encephalomyelitis (EAE) is an animal model of MS which can be produced by immunization with myelin antigens.*