

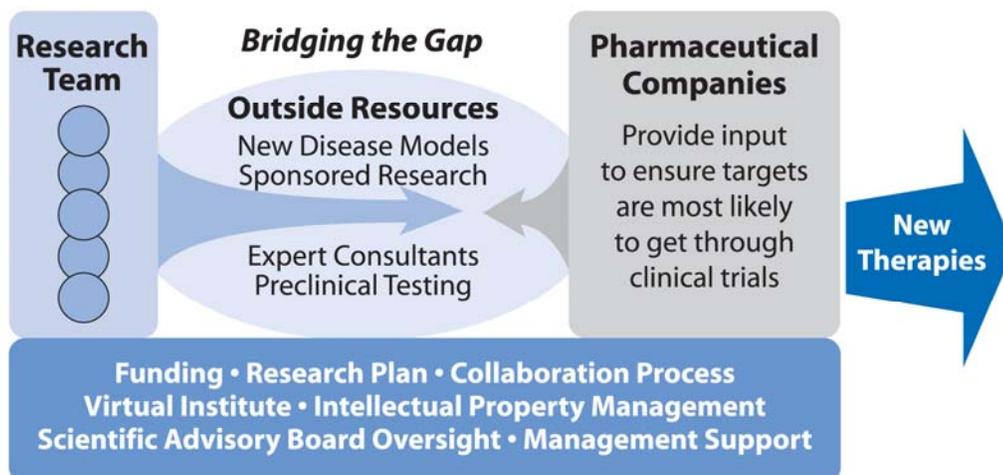
Myelin Repair Foundation Annual Review June 2005 – July 2006

The Myelin Repair Foundation is pleased to present this annual review of our progress toward achieving our goal of discovering and validating effective new treatment targets for multiple sclerosis. We were extremely pleased by the rapid progress of the team both in advancing frontiers of translational scientific research and demonstrating the power of the MRF Accelerated Research Collaboration™ model to achieve results with practical benefits. This report summarizes the key accomplishments of the Myelin Repair Foundation during its second year of research, completed on June 30, 2006.

In the past year, the MRF team achieved the following key milestones:

- Identified nine novel therapeutic targets for myelin repair;
- Identified drug candidates for three targets and a cellular approach for one;
- Initiated validation experiments on two targets;
- Developed ten new database tools, assays or animal models;
- Filed three utility patent applications and three provisional patent applications;
- Began preparation of patent applications for three additional inventions;
- Patents included inventors from four labs;
- Published more than ten scientific publications in peer-reviewed journals;
- Twelve additional publications are in preparation or review
- Research expanded to twenty-three projects with more than 30 participating scientists;
- Exploratory meetings held with six pharmaceutical and biotech companies;
- Shared MRF Accelerated Research Collaboration model with more than 40 disease research organizations.

How the ARC™ Model Drives Discoveries to Treatments



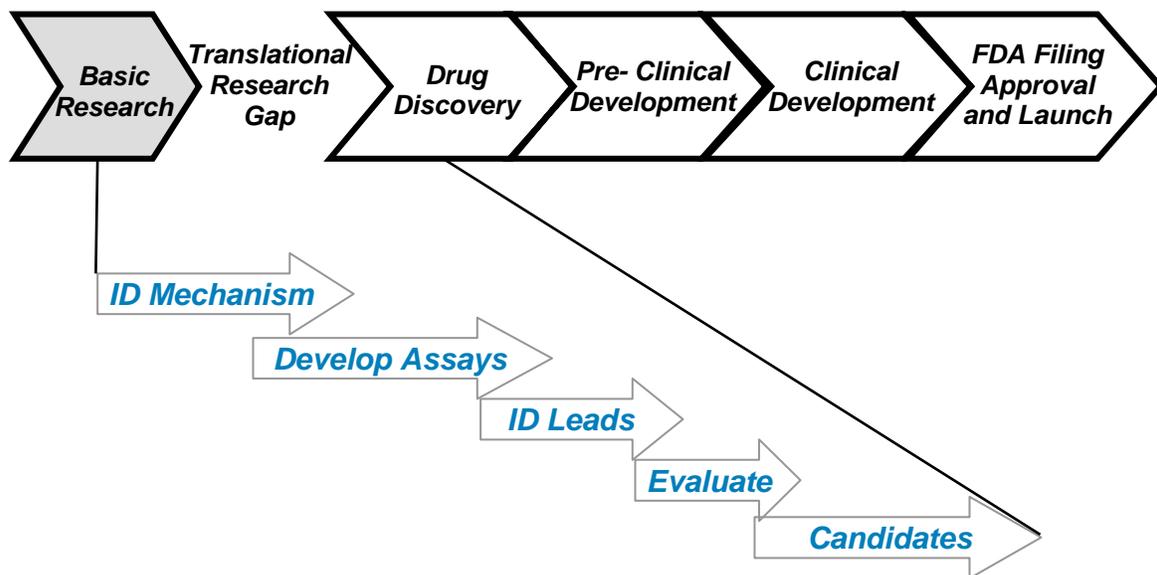
How the MRF ARC™ model is driving discoveries towards treatments

The MRF Accelerated Research Collaboration™ model is designed to bring together all of the resources necessary to achieve maximum results in a coordinated fashion. It relies on using best practices from the academic, business, start-up and non-profit sectors to coordinate and streamline research and minimize impediments. Key elements include:

- World class research team executing a fully integrated, outcome-focused research plan;
- Outside resources (contractors, consultants, etc.) to supplement core team capabilities;
- Professional management and support services to provide funding and coordination;
- Ongoing dialogue with pharmaceutical and biotech companies to facilitate development of new targets.

In developing and executing this model the MRF identified several key steps to bridging the translational gap between basic biomedical research and the commercial drug development process.

MRF's Role in Drug Development



In this report we will highlight some of the key contributions of the MRF research team to this process.

Breaking new ground – Development of new tools, assays and models

Since the MRF research team is driving the frontiers of myelin biology in many areas, the development of new tools, assays and models is critical to our efforts. This section describes the new tools, assays and models developed by the MRF research team over the last year and why they are important to myelin repair and to neurobiology in general.

New Tools

Comprehensive catalog of myelin proteins – A project team headed by Drs. David Colman and Alejandro Roth at the Montreal Neurological Institute completed a comprehensive catalog of the proteins in compacted myelin for mice, rats and humans. The techniques they used overcame the limitations of previous studies and identified more than 70 new proteins, some at very low concentrations. This catalog has several important applications. First, it gives us clues as to unique myelin proteins that may be important in the immune response in MS. Now we can look for fragments of these unique proteins or antibodies to them as an indicator of MS activity. Second, we can develop antibodies to these proteins in order to study their function in myelin formation, maintenance, damage and repair.

Profile of gene expression during myelination – A project team headed by Drs. Ben Barres and Jason Dugas at Stanford University completed a multi-year effort to measure changes in gene expression as myelin-producing cells mature from precursors. In this process they discovered that cellular changes occur in two distinct phases and identified several promising targets for promoting the myelination process. They are now selectively turning these target genes on and off to observe the effect of each target. Finding therapeutic agents that stimulate this process may be critical to myelin repair.

Profile of gene expression in immune demyelinating disease models – The first step in validating any new therapeutic approach is to test in animal models of disease. A project led by Dr. Steve Miller and Wendy Smith-Begulka at Northwestern University has completed comprehensive profiles of gene expression in the three animal models they use. This study provides a critical baseline for understanding how new therapeutic approaches are affecting the expression of genes that are critical to myelination.

Purification method for adult neural cells – Many critical assays require the use of purified neural cells. In most cases these assays have been preformed using immature cells. Since MS is generally an adult onset disease, it is critically important to determine if mature cells respond in the same way to therapeutic agents. A project team headed by Dr. Robert Miller at Case Western Reserve University has developed a process for purifying adult neural cells in order to conduct parallel studies.

New Assays

Culture systems for controlled stimulation of myelination – The MRF team continues to expand its capabilities to create new assays using purified neural cells and a pharmaceutical compound identified by the Barres lab that stimulates myelination. Using these systems the team can now study the effect of various therapeutic agents on purified cells, and combinations of cells, to observe the role of intercellular interactions in promoting and inhibiting myelin repair.

Culture systems for the extended observation of myelin formation – As an extension of the assay above, three of the MRF labs can observe myelin formation over several days. This allows members of the MRF research team to extract cells at specific time points during the process in order to measure gene expression. Using these systems we can introduce immune cells and observe the effect on myelin damage and repair.

Method for simulating the Blood Brain Barrier – Studying how MS or animal models of MS effect the integrity of the blood brain barrier is vital to understanding the disease and repairing the blood brain barrier could be an important therapeutic approach. A project team led by Richard Daneman in the Barres lab has developed a method for stimulating the cells that form blood vessels in other parts of the body to form the tight junctions that characterize the blood brain barrier. This discovery could lead to two critical assays. First, by creating an artificial blood brain barrier we can test the ability of new drugs to penetrate the blood brain barrier in order to reach the CNS. Second, we can now study the effect of various cells and molecules, such as antibodies, to determine how the blood brain barrier is being compromised in MS.

New Animal models

Observing the myelination process *in Vivo* – Dr. Liliana Pedraza at the Colman lab is using transparent zebra fish to study the myelination process in a living organism. By inducing demyelination she can observe the processes of migration, differentiation and repair. By controlling the expression of specific genes she will be able to study the effect of these genes on both early myelination and repair.

New animal models with a disrupted blood brain barrier – The project described above resulted in the identification of a method for disrupting the blood brain barrier in rats and a target for doing so in other animals. With this discovery it may be possible to develop new disease models of MS in animals that more closely model the human disease.

New animal model for measuring remyelination – During the development of the MRF research plan, team members identified a need for an animal model that would allow accurate assessment of the success of myelin repair in demyelinating disease models. In the fall of 2005, a project team headed by Dr. Brian Popko at the University of Chicago developed a unique scheme for creating such a model by incorporating two fluorescent markers into the genes of myelin-producing cells. In January work began on creating transgenic animals that can be cross bred so that the original myelin formed during development can be distinguished from new myelin formed by repair. If this approach is successful, we expect to have our first test animals in late 2006 and be able to perform the first precise measurement of myelin repair in an animal model shortly thereafter.

Identifying New Therapeutic Targets

This section describes potential targets that have been identified by the MRF research team that are in various stages of the validation process.

New tools, assays and models only have value if they help us identify and validate new therapeutic targets for myelin repair treatments. This process begins with understanding the biological mechanisms that drive neural stem cells to become oligodendrocyte precursor cells and:

- Migrate to demyelinated areas in the brain and spinal cord;
- Proliferate to provide adequate local repair capacity;
- Differentiate and mature into myelin producing oligodendrocytes;
- Resist the hostile environment created by the immune system, reactive astrocytes and microglia.

Preventing the migration of immune cells into the central nervous system through repair of the blood brain barrier is an additional strategy for the promotion of repair.

Discovering and validating a new therapeutic target involves several complex steps including:

- Identifying a biological mechanism that influences the process of myelination or myelin repair;
- Developing methods or assays to measure its role in the myelination or repair processes;
- Finding ways to control the mechanism;
- Evaluating its value and importance in the myelination or repair processes;
- If controlling a particular mechanism appears to be beneficial, then the search begins for candidate drug compounds or other therapeutic methods that are appropriate for use in animal models and humans.

This is a complex and time-consuming process that can take several years from the time a potential target is discovered until it has been tested to the point where it is confirmed as a valid candidate for commercial development. Historically there has been a high attrition rate between target identification and validation and an equally high rate of failure during the development and clinical trials processes. The MRF seeks to rigorously validate potential targets to improve their likelihood of success in completing the development and clinical trials processes.

Stimulation of precursor migration – In order to affect myelin repair, first the precursors of myelin-producing cells must migrate into demyelinated areas. This migration process is controlled by chemical signals that either attract or repel these cells. By blocking a migratory inhibitor the Robert Miller lab has been able to promote migration into demyelinated areas.

Promotion of precursor proliferation – Even if the precursor cells necessary for repair migrate into the damaged area, they must divide until there are sufficient numbers to repair the damage. the Robert Miller lab has also identified a specific receptor that must be blocked to promote the expansion of these cells and is working to test a drug compound that may be effective in promoting proliferation.

Mechanisms for differentiation – The Barres lab has shown that precursors must go through a couple of final stages of development before they can begin to produce myelin. They identified a

specific gene that promotes differentiation during development that may be equally critical to the repair process.

The Robert Miller lab has identified the presence of a developmental inhibitor of myelination that may be blocking the repair process in demyelinated lesions in animals. His lab is currently looking for compounds that will block this signal. Both of these targets are currently being evaluated.

Enzyme inhibitor that stimulates myelin formation – The discovery by the Barres lab of an enzyme inhibitor that stimulates differentiation and myelin formation in culture began the process of evaluating this compound and target for myelin repair. Subsequent studies have been performed in the Steve Miller lab that demonstrate a modest therapeutic effect when used alone in animal models and a more pronounced effect when used in combination with immunomodulatory strategies. Currently these labs are working together to confirm the underlying mechanism for these effects and determine if a more effective molecule can be developed for therapeutic use.

Protecting myelinating cells from inflammatory stress – The Popko lab has demonstrated that a chemical associated with MS inflammation creates an environment that is hostile to new myelin producing cells. During myelin formation, oligodendrocytes must produce 1,000 times the amount of protein that they normally would, creating an enormous stress on the metabolism of these cells. The addition of even a modest amount of inflammatory stress is sufficient to kill these cells. Therefore, it is critical that we find ways to protect the cells that will be repairing myelin from this hostile environment.

Dr. Wensheng Lin in the Colman lab has identified and tested two possible approaches to providing this protection. First, by regulating the protein synthesis process with a drug, the effect of inflammatory stress can be reduced and the cells protected. Second, by artificially stimulating a gene that suppresses sensitivity to these inflammatory chemicals, the cells can also be protected. Both of these approaches have been evaluated, appear promising and are being further validated and refined.

Limiting the autoimmune response by blocking the migration or proliferation of dendritic cells – The Steve Miller lab has shown that in animal models of MS the immune response can be stimulated locally in the CNS by the presence of specialized dendritic cells. This promotes the level of local inflammation inhibiting myelin repair. Thus, preventing these cells from entering the brain and spinal cord would result in a much more hospitable environment for myelin repair. Dr. Miller's lab is looking for ways to prevent these specific dendritic cells from entering the brain and spinal cord.

Restoring the integrity of the blood brain barrier – Ordinarily the cells that form the blood vessels in the brain create a barrier that prevents immune cells and dendritic cells from entering. In MS and several of the animal models used in research, the disease breaks down this barrier allowing these cells to enter the CNS creating inflammation, damaging the myelin and creating a local environment that is hostile to myelin repair. If we can restore the integrity of the blood brain barrier it could dramatically reduce the negative impact of the immune system and restore an environment more conducive to myelin repair. As mentioned above, by investigating the structure of the blood brain barrier, the Barres lab is able to stimulate cells from blood vessels in other parts of the body to act like the blood brain barrier. They are currently identifying the specific molecules involved in this process in order to identify potential therapeutics.

Measuring team effectiveness

Historically there has been a belief that it is impossible to accelerate scientific discovery. Certainly when individual scientists work in relative isolation this is true. However, the MRF research team is proving every day that effective collaboration can achieve remarkable results.

How is the MRF Accelerated Research Collaboration model different from other scientific collaborations?

The short answer is focus and commitment to results. Our mission is unique in that it is focused on achieving a single, specific objective within a short time frame. The desired outcome is unambiguous and provides a constant reminder of the urgency of our mission. That urgency drives everything we do from planning through execution. It is this urgent mission that drives the culture of the MRF.

Today that culture is manifested in many different ways.

First is the commitment of the research team to working together in ways that are far different from the norm. The five principal investigators, and the members of their labs, have developed a sense of team spirit that puts the achievement of the team's mission above the personal interests on any single individual. They have come to rely on the creative input of their colleagues from the beginning of the planning process through the execution of experiments, evaluation of results and validation of targets. They have learned how to function effectively as a team, tapping the expertise of fellow team members and asking MRF management for assistance from outside resources when the necessary expertise is not resident within the team.

They have begun to think in a more "industrial" fashion. They have accepted the need to update project plans and budgets on an annual basis based on results. This process combines a unique level of flexibility and accountability that is not common in the academic research world. Commitment to delivering results is driven by personal and professional pride and team spirit. Team members now think in terms of the fastest and most efficient ways to maximize the team's intellectual assets and expertise, along with MRF's financial support, to achieve results. Progress is motivated by the desire to expand the limits of therapeutically relevant knowledge rather than writing the next publication that will lead to the next grant.

Along the way, MRF management has focused its efforts on providing the support and facilitation services necessary to maximize the productivity of the research team. Unencumbered by writing lengthy grant proposals, endless grant review meetings and other administrative tasks, the MRF's principal investigators can focus their time on achieving our scientific goals. This process also enables them to be creative in the avenues they explore. Because the research plan is a team effort that maximizes their ideas with the best input from experts on the scientific advisory board, even projects that do not result in new targets or tools provide useful information. It is the continuous, real-time learning that maximizes the productivity of the MRF research team.

There are two key measures of team productivity.

The scientific collaboration and MRF's management oversight have created a number of unexpected efficiencies that have translated into the saving of time and money in the execution of various experiments. For example, when the first annual research plan was created, the scientific team expected the series of experiments to take three years at a cost of \$750,000. This same set of experiments was completed in 2006 – one year ahead of the original anticipated timeline at a cost of less than \$300,000. In addition, several investigations that were unlikely to result in therapeutically relevant results were terminated at the recommendation of the investigators, freeing time and resources for more promising avenues of investigation.

The number and scope of the projects in the annual research plan has grown by more than 37% from 12 in 2004-05 to 32 in 2006 – 2007. For the first time four projects are using human MS tissue.

A second barometer of productivity is the number of patents resulting from the MRF research plan. Prior to 2004, collectively, the five participating labs had filed only two patents. In our second research year the MRF filed six patent applications and identified inventions that will result in three additional applications. In addition since 2004, the team has published 12 papers in highly regarded scientific journals and will publish another 12 by the end of 2006. This is an exceptional level of productivity by any standard.

Expectations for the future

In the MRF strategic plan we expected to file our first patent application in mid-2007 and to have validated our first therapeutic target by 2009. Our hope was that the discoveries and inventions of the MRF research team would be of interest to biotech and pharmaceutical companies and that we could initiate licensing discussions by early 2009.

Based on the rapid progress of the team we now believe that MRF will have assays and animal models that will be of licensing interest to any company working on neurodegenerative disease by July 2007. As a result we began exploratory discussions with Biogen, Serono, Novartis, Wyeth, Sanofi Aventis, Genentech and Eli Lilly this past spring. These meetings provided an overview of the current assays and models used by the MRF research team as well as a preview of those we are currently developing. The goal of these meetings was to determine which validation assays are considered most important in evaluating targets and drug candidates for development. We expect to continue these discussions over the next year and expand the number of companies we are evaluating as potential development partners for new therapies.

This brief snapshot of the MRF and its results cannot do justice to the talent, dedication and professionalism of the MRF's research team, management team and growing team of volunteers, and especially to our donors, all of who made critical contributions directly to these results. It is hard to believe that we have learned so much in such a short period of time. I hope that in reading this information you share our enthusiasm and expectation that we can make effective myelin repair treatments a reality in just a few years.