National
Multiple Sclerosis
Society

AN OVERVIEW OF PROGRESS MADE IN THE NERVOUS SYSTEM REPAIR AND PROTECTION INITIATIVE

EXECUTIVE SUMMARY

In 2004 the National MS Society developed and released an international Request for Proposals with the goal of supporting the first "Translational Partnerships in Nervous System Repair and Protection in MS" awards to propel research that could lead to clinical trials of therapies aimed at repairing or protecting the nervous system in MS. This initiative was spearheaded at a scientific workshop on the topic of nervous system repair convened by the National MS Society and the Foundation for Research on MS in France (ARSEP).

Four international collaborative research teams received an investment of more than $15 million over a five year period from funds raised through the help of generous donors and Society chapters who gave to the Promise: 2010 campaign. The teams eventually engaged more than 100 investigators and postdoctoral research fellows, came together as full teams for three in-person meetings, and collaborated regularly by phone, email and conference calls.

Significant progress was made on each of the initiative goals. The initiative appears to have jump-started the field, trained scores of promising young investigators, produced over 180 research papers, and leveraged millions of dollars in new funding. New therapeutic targets have been identified from extensive screens of tissue culture systems and genes and proteins, and early tests in animal models have been promising. Human clinical trials have now been initiated to test neuroprotective strategies.

INTRODUCTION

Following a 2002 workshop on CNS repair in MS sponsored by the National MS Society and the Foundation for Research on MS in France (ARSEP)[1], the Society convened an international task force of leading scientists and clinicians to further address the issue of applying CNS repair strategies to MS. The group identified several challenges to the development and successful application of potential reparative and protective therapies. Consequently, in 2004 the Society released a Request for Applications for "Translational Partnerships in Nervous System Repair and Protection in MS" awards with these goals:

1) Develop effective **experimental models** for screening potential nervous system repair and protection strategies;
2) Develop and validate methods to **non-invasively monitor** nervous system repair and protection;
3) Develop **clinical trial designs** for nervous system repair and protection strategies in people with MS.

> **"It is expected that the combined research activities of successful partnerships will lead to the design and possible initiation of human clinical trials of neural repair and/or neuroprotective strategies by the end of the funding period." – National MS Society's 2004 Request for Proposals**

After a competitive peer-review process, over $15 million was committed to support four interdisciplinary teams:

- **Peter A. Calabresi, MD** (Johns Hopkins University), searching for better ways to detect and quantify tissue injury in MS and testing agents that may protect the nervous system from further damage. Offsite collaborators located in Philadelphia and Birmingham.
- **Charles ffrench-Constant, PhD, FRCP** (University of Edinburgh and University of Cambridge, UK), focusing on restoring myelin by identifying and amplifying natural repair factors in the brain and by attempting to transplant replacement cells. Offsite collaborators located in London, Paris, Rijswijk, Milan, Montreal, Calgary, Rochester.

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[1] Colman D, Lubetzki C, Reingold S. Trends Neurosci. 2003 Feb;26(2):59-61. "Multiple paths towards repair in multiple sclerosis"

- **Gavin Giovannoni MBBCh, PhD** (Queen Mary University of London, UK), attempting to turn cells into vehicles that will deliver repair molecules to sites of injury in the brain, and screening molecules for their protective properties as a prelude to clinical trials. Offsite collaborators located in London, Stanford NOTE: The MS Society of Great Britain/Northern Ireland provided partial support for this team.
- **Ian D. Duncan, BVMS, PhD, FRCPath** (University of Wisconsin-Madison), developing better imaging technologies such as PET and MRI to visualize myelin and nerve fiber damage and repair, and exploring techniques for transplanting cells to promote repair. Offsite collaborators located in Baltimore, Hines, Ill., Rochester

See Appendix A for a complete list of original team members.

FOCUS OF TEAMS BY ORIGINAL TOPICS SUGGESTED IN RFP

Test therapeutic strategies via in vivo, in vitro models	**Non-invasive monitoring tools**	**Validate surrogate markers for CNS repair/protection**	**Clinical scales of impairment and recovery**	**Clinical trial designs**
Calabresi	Calabresi	Calabresi	Giovannoni	Calabresi
Duncan	Duncan	Giovannoni	Calabresi	Giovannoni
ffrench-Constant	Giovannoni			
Giovannoni				

ADDITIONAL TOPICS PURSUED BY TEAMS

Screen and ID new endogenous repair targets	Develop cells for transplantation, protocols	Biomarker consortium and protocols established	Conduct Clinical trials	Develop in vitro culture systems for screening
Calabresi	Duncan	Giovannoni	Giovannoni	Calabresi
ffrench-Constant	Ffrench-Constant			Giovannoni
				ffrench-Constant

COLLABORATION

Over the course of five years, the teams were brought together for three large-scale meetings to share progress and enhance collaborations. The teams eventually engaged more than 100 investigators and postdoctoral research fellows. Of particular note is the collaboration model of Dr. ffrench-Constant. They engaged a consulting firm to help them establish Web-based conferences and provide administrative support. This was particularly useful in spurring communications between the postdoctoral fellows from far-flung institutions. The investigators were asked to share their thoughts about the collaboration model:

Dr. Calabresi: "The kind of infrastructure that we've established is helping to move things forward more quickly. We can specialize, much in the way a factory does. No one scientist has to think about all the problems that are necessary to move a target, validate it and then get it into clinical trials."

Dr. Duncan: He noted that the collaborations established for his team would not have happened without this grant. "The meetings were very successful. It was useful to hear very early on what people were finding, reducing redundancy and speeding things up."

Dr. ffrench-Constant: "Two things we've done have made a huge difference. We've used the Internet extensively to keep everybody in contact. Also, we've recruited post docs and graduate students who have spent time in all of the different labs. This increases the amount of collaboration, and secondly, it trains the next generation of the scientists that we need in multiple sclerosis."

Dr. Giovannoni: "Collaborating with each other has brought different skills to the table and allowed common themes to emerge. It is important that post-Promise 2010 we continue to collaborate and lead consortia to test our therapeutic strategies."

SUMMARY OF OUTCOMES

Impressive progress was made in each of the three main arms of the initiative. The initiative appears to have jump-started the field, trained scores of promising young investigators, produced over 180 research papers, and leveraged millions of dollars in new funding. New therapeutic targets have been identified from extensive screens of tissue culture systems and genes and proteins, and early tests in animal models are promising.

Goal 1: Develop new disease models to screen repair and protection techniques

New targets for nerve repair and protection therapies have been identified and show promise in early tests with animal models of MS

Details:

- A key pathway called "retinoid x receptor" (RXR) signaling was identified, and administering a molecule that stimulates this receptor resulted in more myelin repair in rodent models (ffrench-Constant team).
- Using an experimental model in which an old mouse is exposed to the blood circulation of a young mouse, exposure to a young environment was shown to reverse age-associated decline of natural myelin repair efficiency. (ffrench-Constant team).
- A molecule that inhibits activity of immune cells in the central nervous system, called microglia, was able to treat MS-like disease in mice (Calabresi team).
- Two myelin components (MAG-Fc and netrin-1) were shown capable of protecting axons from degeneration (Calabresi team)

New tools were developed to better identify and screen more potential repair and protection approaches

Details:

- A novel system of growing human nerve cells with immune cells has allowed exploration of mechanisms whereby various immune factors damage neural cells and axons and provides a new screening mechanism for neuroprotective drugs (Calabresi team).
- The optimization of a cell culture system with nerve cells and myelin-making cells enabled quantitative measures of myelination (ffrench-Constant team).

- A mouse model of secondary-progressive MS was established and used to test potential drug treatments; a mouse model of optic neuritis is undergoing research (Giovannoni team). Followup: Team member (Dr. David Baker) has won Society funding to do pre-clinical testing of engineered glial cells to deliver therapeutic agent to regenerate myelin.
- Genetic screening following a myelin injury in a model of mouse spinal cord at three different time points enabled the identification of 50 factors. This is how the "Wnt pathway" was identified as a key player in inhibiting myelin repair (ffrench-Constant team).
- The "BioMS" European consortium has been leveraged to detect central nervous system biomarkers for disease activity and neuroprotection (Giovannoni team).

Exciting pre-clinical progress was made in cell-based therapies, paving further ground toward human trials in the future

Details:

- Injecting human myelin-making cells into the brains of mice can cause widespread myelin repair and restoration of function (ffrench-Constant team). Follow-up: Team member (Dr. Steven Goldman) has won Society funding to use mouse model to do molecular monitoring responses of human oligodendrocyte (myelin-making cells) to demyelination and remyelination.
- Infusing neural stem cells in blood or spinal fluid of mice with MS-like disease stimulates natural repair and reduces disease inflammation (ffrench-Constant team)
- Most factors that are effective in promoting proliferation of immature myelin-making cells (oligodendrocyte precursor cells, OPCs) in mice are not as effective for promoting human OPC proliferation (Duncan team).
- OPCs can now be generated from human induced pluripotent stem cells (iPSCs) established from adult skin tissues (Duncan team, ffrench-Constant team).
- When OPCs are transplanted adjacent to sites of inflammation in the rat spinal cord, they migrate preferentially toward the site where they can survive, differentiate and myelinate axons (Duncan team).

Goal 2: Apply advanced MRI and other non-invasive monitoring tools to detect repair

Tools have been developed and tested for their ability to track nerve and myelin health and repair

Details:

- A simple, quick eye test, OCT, has been validated in clinical trials as a method of showing how much nerve fibers in the eye are damaged (Calabresi team); Changes can be observed in people with MS, even without eye inflammation

- Novel imaging technologies (DTI, MT) can specifically detect myelin and nerve fiber damage and track it over time – making them useful for tracking treatment success or failure in clinical trials (Duncan team, Calabresi team).
- A possible biological marker of disease progression was found in spinal fluid tested during a clinical trial of natalizumab (Giovannoni team).
- Simple tests such as vibration sensation, vision tests and others correlate with disease activity and may be useful clinical trial outcome measures (Calabresi team).

Goal 3: Design human clinical trials – Cell Therapies

Guidelines have been developed and early trials have been launched

Details:

- Phase 1 safety study of mesenchymal cells (adult stem cells found in bone marrow and other tissues) in optic neuritis by team members (Giovannoni team). Results nearing publication.
- Phase 1 study underway by team member to study safety of neural stem cell transplantation in children born with a lack of myelin – proof of principle for applying this strategy to people with MS (ffrench-Constant team).
- Guidelines established for design and conduct of clinical trials using cell therapies in MS (International MS Society collaboration including team members)

Goal 3: Design human clinical trials – Neuroprotection

Novel designs have been developed and new trials have been launched

Details:

- UK MS Society Clinical Trials Network has been established. A protocol for a Phase 3 adaptive design has been proposed. Currently in development is a patient-based clinical outcome measure to be validated in a future trial (Giovannoni team).
- Phase 2 study of phenytoin getting launched to determine effects on neuroprotection in optic neuritis -- proof of principle for applying this strategy to people with MS (funded by US Society and UK Society)
  - Trial draws on lessons learned from failed study of lamotrigine in SPMS
  - Taps into UK MS Society clinical trials network
- Results expected later this year from large multicenter study exploring whether cannabis is neuroprotective such that it can slow MS progression (Giovannoni team)
- Team members have launched NIH-funded studies of idebenone for primary-progressive MS and rituximab for secondary-progressives MS; studies will collect much data on these types of MS as well (Calabresi team)

LEVERAGED FUNDING

Most of the teams have been successful using their results to win support for further research. Most notable is the $16 million gift from author J.K. Rowling to establish an MS research center and clinic at the University of Edinburgh, headed by Dr. ffrench-Constant. In addition, team collaborators from the ffrench-Constant team (Drs. Goldman, Rowitch), Calabresi team (Dr. Zakowski), and Giovannoni team (Drs. Baker, Kapoor) have already won research grants from the National MS Society related to their work in the Promise:2010 Nervous System Repair and Protection Initiative.

PUBLICATION METRICS

Another measure of outcomes is the publication of papers stemming from that research. The significance of papers can be evaluated in several ways:

- One is a count of how many times other authors refer to, or cite, a given paper in a subsequent paper. This suggests that other research is building on the results of the first paper.
- The number of citations of a given paper can be weighed against the average number of citations received by the same type of papers published in the same journal in the same year (called "expected cites").
- Another measure is the "Impact Factor" of a particular journal, which is an industry calculation reflecting the frequency with which an average article in a journal has been cited during a particular period of time. As a frame of reference, here are Impact Factors for a few common journals in which MS-related papers appear:

Multiple Sclerosis= 3.279
Journal of Immunology= 5.646
Annals of Neurology= 9.317
Proceedings of the National Academy of Sciences USA=9.432
Lancet Neurology= 18.126
Nature Immunology= 26.00
Nature Medicine= 27.136

As of January 2011, 181 papers had been published and attributed by the teams as outcomes of the Promise:2010 Repair Initiative, and more are expected.

181 PAPERS PUBLISHED	
Avg. times each paper was cited	12.4
Avg. journal Impact Factor	7.15
Median journal Impact Factor	5.74
Range journal Impact Factor	0.69-27.14

PAPERS ATTRIBUTED TO REPAIR INITIATIVE 2006-2010

	Calabresi	**Duncan**	**ffrench-Constant**	**Giovannoni**
Average Journal Impact Factor – all collaborators	6.08	5.36	6.81	10.81
Number Co-authors for all PI's papers	171	20	20	66
Top-cited paper for team (as of June 2011)	112 cites Fisher, JB et al. OPHTHALMOLOGY (2006) 113:324-332	33 cites Hu, BY, et al. Proceedings of the National Academy of Sciences USA (2010): 107, 4335-4340	47 cites Kuhlmann,T, et al. BRAIN (2008):131,1749-1758	131 cites Steinman, L. et al. ANN NEUROL (2006) 60: 40898

By most measures, the teams had excellent output of publications, and many of the papers made an impact on research in the field. For example, for the papers published during 2006-2010 by the four repair teams, a significant proportion -- 34% -- were ranked in the top 10 percentile of all papers cited during a particular year in a particular field (ie, neuroscience, immunology, etc.) among 11,000 journals tracked in the Web of Science database; 56% ranked in the top 25 percentile.

NEXT STEPS

In the six years that have elapsed since the Promise:2010 Nervous System Repair and Protection initiative was launched, this field of research has grown substantially. Team members have sought and won additional funding to continue important aspects of their work, and the Society is exploring results and findings that could be transitioned to commercial development through its Fast Forward initiative.

As the research continues and proceeds towards clinical trials of new MS treatment strategies, the Society's leadership is evaluating program outcomes to determine additional ways to sustain the momentum created by these teams. The Society's 2011-2015 Strategic Response sets forth nervous system protection and repair as a major strategy for restoring function in people with MS.

For more on this topic, a webcast (http://nationalmssociety.org/multimedia-library/webcasts--podcasts/index.aspx) can be viewed on "Repairing the Nervous System in MS: Progress and Next Steps." The program features Chief Research Officer Dr. Timothy Coetzee discussing strategies with the Repair Initiative team leaders.

CONCLUSION

The National MS Society's Promise:2010 Nervous System Repair and Protection initiative, launched in 2005, appears to have jump-started the field, trained scores of promising young investigators, produced over 180 research papers, forged new international collaborations, and leveraged millions of dollars in new funding. Significant progress was made on all three original aims, laying the groundwork needed to launch clinical trials. New therapeutic targets have been identified, and human clinical trials have been initiated to test neuroprotective strategies.

APPENDIX A -- ORIGINAL TEAM MEMBERS FROM GRANT PROPOSALS

TEAM 1
Principal Investigator
Peter A. Calabresi, MD
Associate Professor, Neurology (Now Professor)
Johns Hopkins University School of Medicine
Baltimore, MD

Co-investigators
Laura Balcer, MD, MSCE, Associate Professor, Neurology
Division of Neuro-Ophthalomology
University of Pennsylvania School of Medicine
Hospital of the University of Pennsylvania
Philadelphia, PA

Katherine Conant, MD, Assistant Professor, Neurology
Johns Hopkins University School of Medicine

Gary R. Cutter, PhD, Professor of Biostatistics
The University of Alabama at Birmingham
Birmingham, AL

John W. Griffin, MD, Professor and Chair
Department of Neurology
Johns Hopkins University School of Medicine

Norman Haughey, PhD, Department of Neurology
Johns Hopkins University
School of Medicine

Paul Hoffman, MD/PhD, Research Associate, Ophthalmology
Johns Hopkins University School of Medicine

Craig Jones, PhD, Research Associate
Kennedy Krieger Institute
Johns Hopkins University

Douglas A. Kerr, MD/PhD, Assistant Professor, Neurology
Johns Hopkins University School of Medicine

Sanjay Keswani, MBBS, MRCP, Assistant Professor, Neurology
Johns Hopkins University School of Medicine

Justin C. McArthur, MBBS, MPH, Professor, Vice-chair, Neurology
Johns Hopkins University School of Medicine

Susumu Mori, PhD
Associate Professor, Radiology
Johns Hopkins University School of Medicine

Avindra Nath, MD, Professor, Neurology
Director, Division of Neuroimmunology and Infectious Diseases
Johns Hopkins University School of Medicine

Thien Nguyen, MD, PhD, Fellow, Neurology
Johns Hopkins University School of Medicine

Kathy Zackowski, PhD, Instructor
Kennedy Krieger Institute
Motion Analysis Laboratory
Baltimore, MD 21205

Peter Van Zijl, Director, FM Kirby Research Center
Johns Hopkins University School of Medicine
Department of Radiology

TEAM 2
Principal Investigator
Ian D. Duncan, BVMS, PhD, Professor
Department of Medical Sciences
School of Veterinary Medicine
University of Wisconsin Madison
Madison, WI

Co-Investigators
Maria Nikodemova, PhD
Department of Medical Sciences

John O. Fleming, MD
Department of Neurology

Aaron Field, MD, PhD
Department of Radiology

Su-Chun Zhang, MD, PhD
Department of Anatomy

Professor Ian D. Duncan's Team (cont.)

Andrew L. Alexander, PhD
Department of Medical Physics

Zsuzsanna Fabry, PhD
Department of Pathology and Laboratory Medicine

P. Charles Garell, MD
Department of Neurological Surgery

James E. Holden, PhD
Department of Medical Physics

Alexander Converse, PhD
Waisman Center

Mary Elizabeth Meyerand, MS, PhD
Department of Medical Physics

Collaborators
Thomas Cook, PhD
Department of Biostatistics and Medical Informatics

Jeff W.M. Bulte, PhD, Associate Professor
Dept of Radiology and Institute for Cell Engineering
Johns Hopkins University School of Medicine
Baltimore, MD

Steve Goldman, M.D., Ph.D., Dean Zutes Professor and Chief
Division of Cell and Gene Therapy
Department of Neurology
University of Rochester Medical Center
Rochester, NY

George DeVries, PhD, Research Career Scientist
Hines Veterans Hospital
Hines, IL

TEAM 3
Principal Investigator
Charles ffrench-Constant, Professor of Neurological Genetics,
Dept. of Pathology
University of Cambridge
(Now also at University of Edinburgh)

Collaborators
Dr. Robin J.M. Franklin, Reader in Experimental Neurology,
Cambridge Centre for Brain Repair & Centre for Veterinary Sciences,
University of Cambridge

Dr. Anne Baron Van-Evercooren, Director
INSERM
Paris, France
With Dr. Baron:
Dr Brahim Nait-Oumesmar

Dr. Bert A 't Hart, Chairman Dept. Immunobiology
Biomedical Primate Research Centre
RIJSWIJK
The Netherlands

Gianvito Martino, MD, Head, Neuroimmunology Unit
Dept. of Neuroscience
DIBIT - San Raffaele Hospital
Milan, Italy

Dr. Bernard Zalc (Boris), Director, Biologie des Interactions Neurones/Glie
INSERM
Hopital de la Salpetriere
Paris, France

With Dr Zalc:
Dr Catherine Lubetzki
Dr Jean-Leon Thomas
Dr Bruno Stankoff

Professor Charles ffrench-Constant Team (cont.)

Steve Goldman, M.D., Ph.D., Dean Zutes Professor and Chief
Division of Cell and Gene Therapy
Department of Neurology
University of Rochester Medical Center
Rochester, NY
With Prof Goldman:
Benjamin Segal, MD
Dr. Fraser Sim

Jack Antel, Professor
Department of Neurology and Neurosurgery
Montreal Neurological Institute
Montreal, Quebec

Dr. Samuel Weiss, Professor and Director
Hotchkiss Brain Institute
University of Calgary
Calgary, Alberta, Canada

David H. Rowitch, M.D., Ph.D.
Department of Pediatric Oncology
Dana-Farber Cancer Institute, Dana 640D
Boston, MA

TEAM 4
Principal Investigator

Dr. Gavin Giovannoni
Neuroimmunology Unit
Department of Neuroinflammation
Institute of Neurology
University College London
Queen Square
London
(Now at Queen Mary's School of Medicine and Dentistry, University of London)

Co-investigators
Prof. Larry Steinman, Chair, Interdepartmental Program in Immunology
Dept. of Neurology and Neurological Sciences
Beckman Center for Molecular Medicine
Stanford, CA

Prof. William Robinson
Dept. of Neurology and Neurological Sciences
Beckman Center for Molecular Medicine
Stanford, CA

Prof. David Baker
Neuroinflammation Group
Department of Neuroinflammation
Institute of Neurology
University College London
Queen Square
London

Prof. Yuti Chernajovsky
ARC Chair of Rheumatology,
Bone and Joint Research Unit, St. Barts and The London, Queen Mary's School of Medicine and Dentistry
University of London
London, United Kingdom

Prof. David H Miller
Department of Neuroinflammation
Institute of Neurology
University College London
Queen Square

Dr. Lara Diemel
Neuroinflammation Group
Department of Neuroinflammation
Institute of Neurology
University College London
Queen Square

Prof. Alan Thompson
National Hospital for Neurology & Neurosurgery
Queen Square

APPENDIX B -- List of All Papers Attributed to Repair Initiative Funding

Through 1/2011

CALABRESI TEAM

1. Beeton C, Pennington M, Wulff H, Singh S, Nugent D, Crossley G, Khayton I, **Calabresi PA,** Chen C-Y, Gutman G, Chandy G. [2005] Targeting effector memory T cells with a selective peptide inhibitor of Kv1.3 channels for therapy of autoimmune diseases. Mol Pharmacol., Apr; 67(4):1369-81.
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