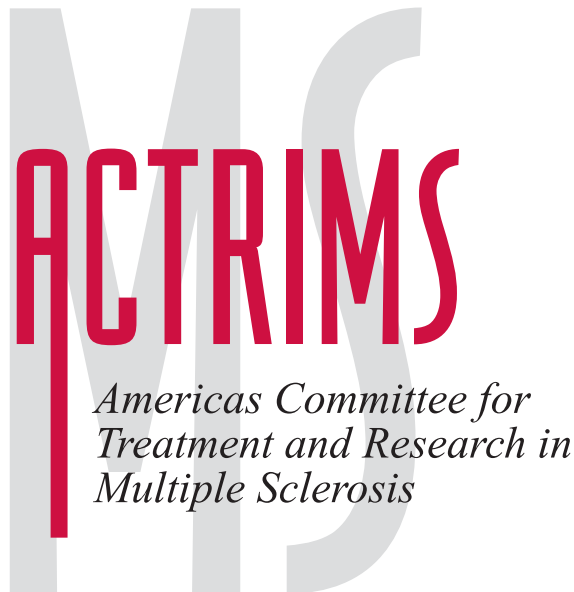


# First Joint Meeting



## **EMERGING THERAPIES IN MULTIPLE SCLEROSIS** Basic and Clinical Issues in Multiple Sclerosis Research

Saturday, June 2, 2007  
Washington, DC

The 12th annual ACTRIMS meeting is jointly sponsored by the University of Maryland School of Medicine and the National Multiple Sclerosis Society in collaboration with the MS Society of Canada



# Welcome

Dear Colleague,

Welcome to the 12th annual meeting of the ACTRIMS (Americas Committee for Treatment and Research in Multiple Sclerosis), jointly sponsored by the National Multiple Sclerosis Society and the University of Maryland, in collaboration with the MS Society of Canada.

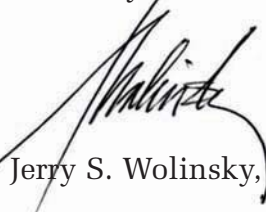
This is an especially exciting year for us, as we move from our annual autumn schedule to offer our first joint meeting with the Consortium of Multiple Sclerosis Centers (CMSC). Together, we are pleased to offer the third annual Donald Paty Memorial Lecture named in honor of Donald W. Paty MD (1936–2004), a compassionate clinician, distinguished neuroimmunologist, and past winner of the John Dystel Prize and the Charcot Award, each recognizing achievements in MS research. Our speaker, Professor Herman Waldman has himself made enormous contributions to the field of immunology, through his examination and manipulation of the immune system for therapeutic benefit. He is a fitting choice to present this lecture.

The Steering Committee and I want to express our appreciation to the industry sponsors who help make these meetings possible. It is remarkable how rapidly basic research in demyelinating diseases has matured to where clinical applications are not only possible but now numerous. We are grateful that the pharmaceutical industry has partnered with the MS community to continue to aggressively seek new means of managing, and hopefully curing, MS and related diseases.

As you know, ACTRIMS was developed to provide a forum where basic scientists, clinical researchers and clinicians interested in the demyelinating diseases could exchange information and network with colleagues to further the science and treatment of MS and related diseases. This is a very dynamic and exciting time for me to be privileged to lead ACTRIMS. However, the continued growth and usefulness of ACTRIMS to the MS professional community is dependent upon your support and active participation.

I look forward to hearing your suggestions for future meeting themes, and particularly to hearing your ideas on how to make the organization even more valuable in the future. I also invite you to put aside the dates of September 17–21, 2008, when ACTRIMS will host a joint meeting with ECTRIMS and LACTRIMS in Montreal, Canada. In the meantime, welcome to today's timely and thought-provoking program. We look forward to your participation.

Sincerely,



Jerry S. Wolinsky, MD

## **Program Support**

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The ACTRIMS Steering Committee acknowledges the following companies for providing education grants in support of the 12th annual ACTRIMS program:

### **GOLD LEVEL**

**EMD Serono**  
**Pfizer Inc**

### **SILVER LEVEL**

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**Genzyme**

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# ACTRIMS Committees

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San Francisco, California

## Program Committee

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Jack Antel, MD

Kenneth Johnson, MD

Robert Naismith, MD

Paul O'Connor, MD

Rhonda Voskuhl, MD, PhD

## National MS Society Organizing Committee

Kristin Summers, PhD, *Chair*

Michael T. Vitale

Deidre Zeigler

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## Program Information

On Friday, June 1, ACTRIMS participants are welcome to attend CMSC programming, the evening poster session and dinner buffet at no additional charge; the ACTRIMS name badge provides admission to these events. Of particular interest to ACTRIMS participants will be the Whitaker Research Track.

### Target Audience

The ACTRIMS program is intended for basic scientists, clinical investigators, and clinicians with an interest in demyelinating diseases.

### Course Objectives

Upon completion of this course, participants will be able to:

- Describe differences among therapeutic monoclonal antibodies in terms of target receptor, potential efficacy in MS, and adverse events of interest
- Evaluate efficacy and safety data for oral treatments currently in development for RRMS
- Recognize clinical trial design issues in MS for single as well as combination therapies

### Accreditation Information

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Maryland School of Medicine and the National Multiple Sclerosis Society. The University of Maryland School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Maryland School of Medicine designates this educational activity for a maximum of 5.5 *AMA PRA Category 1 credit(s)*<sup>™</sup>. Physician should only claim credit commensurate with the extent of their participation in the activity.

# Speaker Disclosures

It is the policy of the University of Maryland School of Medicine to ensure balance, independence, objectivity, and scientific rigor in all of its educational activities. In accordance with the policy of the University of Maryland School of Medicine, faculty are asked to disclose and affiliation or financial interest that may affect the content of their presentation.

## Featured Presenters

### **Bibiana Bielekova, MD**

*The speaker has no conflict of interest to disclose.*

### **Peter Calabresi, MD**

*Grants/Research Support: Biogen Idec, Genentech, Eisai, Novartis, EMD Serono, Teva Neuroscience*

*Consultant: Biogen Idec, Eisai, Genentech, MGI, Novartis, EMD Serono, Teva Neuroscience, Vertex*

### **Fred Lublin, MD**

*Grants/Research Support: Accordia Therapeutics, Novartis, Biogen Idec, Teva Neuroscience, Genentech*

*Consultant: Bayer, Biogen Idec, Genentech, Genmab, Pfizer Inc, Novartis, EMD Serono*  
*Speakers Bureau: Bayer, Pfizer Inc, EMD Serono, Teva Neuroscience,*

### **Olaf Stüve, MD, PhD**

*Speakers Bureau: Bayer, Pfizer Inc, EMD Serono, Teva Neuroscience*

### **Herman Waldmann, FRS, F Med Sci, FRC Path**

*The speaker has no conflict of interest to disclose.*

### **Emanuelle Waubant, MD, PhD**

*Grants/Research Support: Biogen Idec, Genentech*

## Platform Presenters

### **Ann Doan-Do Bass, MD**

*Grants/Research Support: Genzyme*

### **Eliza Gordon-Lipkin, BS**

*The speaker has no conflict of interest to disclose.*

### **Ashutosh K. Mangalam, PhD**

*The speaker has no conflict of interest to disclose.*

### **Kakuri M. Omari, PhD**

*The speaker has no conflict of interest to disclose.*

### **Daniel S. Reich, PhD, MD**

*The speaker has no conflict of interest to disclose.*

### **Jiong Shi, MD, PhD**

*The speaker has no conflict of interest to disclose.*

# Schedule of Events

## FRIDAY, JUNE 1

- 9:00 am – 4:00 pm      **CMSC/Whitaker Research Track**  
*Jefferson Ballroom*
- 7:00 pm – 9:00 pm      **Joint CMSC-ACTRIMS Poster Session and  
Dinner Buffet**  
*Exhibit Hall*

## SATURDAY, JUNE 2

- 7:00 am – 8:00 am      **Continental Breakfast**  
*Exhibit Hall*
- 8:00 am – 8:45 am      **CMSC-ACTRIMS Donald Paty Memorial Lecture**  
*International Ballroom, Center*
- 9:00 am – 12:00 pm      **ACTRIMS General Session**  
*International Ballroom, Center*
- 12:00 pm – 1:00 pm      **Lunch**  
*Exhibit Hall*
- 1:00 pm – 2:00 pm      **Poster Session with Authors Present**  
*Exhibit Hall*
- 2:00 pm – 4:00 pm      **ACTRIMS General Session**  
*International Ballroom, Center*

# June 1—CMSC/Whitaker Research Track Agenda

## WHITAKER RESEARCH TRACK

- 9:00 – 9:10 am**      **Welcome/Introduction**  
Michael Racke, MD
- 9:10 – 9:35 am**      **IL-12 Signaling Protects CD4 T Cells from NK Cell-Mediated Immunoregulation during EAE**  
Mark Kroenke
- 9:35 – 10:00 am**      **Patterns of Disease Activity in MS Patients Undergoing Monthly Brain MRI in the BECOME Study**  
Diego Cadavid, MD
- 10:00 – 10:25 am**      **Myelin Specific Th17 Cells Upregulate CXCR4 and Traffic to the CNS in EAE**  
Praveen Rao, PhD
- 10:45 – 11:10 am**      **Retinal Nerve Fiber Layer Thickness Is Associated with Brain MRI Outcomes in MS Patients**  
Erica Grazioli, DO
- 11:10 – 11:35 am**      **Polymorphonuclear Leukocytes Are Required for Target Organ Inflammation During Experimental Autoimmune Encephalomyelitis**  
Thaddeus J. Carlson, MD/PhD Student
- 11:35 am – 1:00 pm**      **LUNCH AND EXHIBITS**
- 1:00 – 1:45 pm**      **Transcriptional Regulation of Encephalitogenic T Cells**  
Michael Racke, MD
- 1:45 – 2:30 pm**      **Interferon- $\beta$  Gene Therapy in an Animal Model of MS**  
Suhayl Dhib-Jalbut, MD
- 2:45 – 3:30 pm**      **Neuroinflammation in Multiple Sclerosis: Novel Interactions Between Leukocytes, Cytokines, and the Blood-Brain-Barrier**  
Benjamin Segal, MD
- 3:30 – 4:00 pm**      **Does Sex Matter? Multiple Sclerosis and the Gender Divide**  
Clara Pelfrey, PhD
- 4:00**      **Presentation of the Whitaker Prize**  
Michael Racke, MD

# June 2—ACTRIMS Agenda

## CMSC-ACTRIMS DONALD PATY MEMORIAL LECTURE

- 8:00 – 8:45 am**      **Prospects for Reprogramming the Immune System in Multiple Sclerosis**  
Herman Waldmann, FRS  
*University of Oxford, Oxford, England*
- 8:45 – 9:00 am**      **Break**

## FEATURED PRESENTATIONS

- 9:00 – 9:35 am**      **Natalizumab Therapy in Multiple Sclerosis**  
Olaf Stüve, MD, PhD  
*University of Texas Southwest Medical Center, Dallas, Texas, USA*
- 9:35 – 10:10 am**      **Use of Daclizumab in Multiple Sclerosis**  
Bibiana Bielekova, MD  
*University of Cincinnati, Cincinnati, Ohio, USA*
- 10:10 – 10:45 am**      **Studies on Rituximab in the Treatment of Multiple Sclerosis**  
Emmanuelle Waubant, MD, PhD  
*UCSF School of Medicine, San Francisco, California, USA*
- 10:45 – 11:00 am**      **Panel Discussion**  
Paul O'Connor, MD, *Moderator*  
*University of Toronto, Toronto, Ontario, Canada*
- 11:00 – 11:15 am**      **Break**

## PLATFORM PRESENTATIONS

- 11:15 – 11:30 am**      **Inducible Over-expression of CXCL1 by Astrocytes May Be Neuroprotective During Autoimmune Demyelination**  
Kakuri Omari, PhD  
*Albert Einstein College of Medicine, Bronx, New York, USA*
- 11:30 – 11:45 am**      **Functional Epistasis Between MS Associated DR3 (DRB1\*0301) and HLA-DQ8 (DQB1\*0302) Genes Modulate PLPp91-110 Induced EAE in HLA Transgenic Mice**  
Ashutosh Mangalam, PhD  
*Mayo Clinic, Rochester, Minnesota, USA*

# June 2—ACTRIMS Agenda

- 11:45 – 12:00 pm**      **Genetic Predisposition and Cognitive Impairment in Multiple Sclerosis**  
Jiong Shi, MD, PhD  
*Barrow Neurological Institute, Phoenix, Arizona, USA*
- 12:00 – 2:00 pm**      **LUNCH AND POSTER VIEWING**
- 2:00 – 2:15 pm**      **Retinal Nerve Fiber Layer Thickness Correlates With Brain Atrophy in Multiple Sclerosis**  
Eliza Gordon-Lipkin, BS  
*The Johns Hopkins University, Baltimore, Maryland, USA*
- 2:15 – 2:30 pm**      **Corticospinal Tract Abnormalities Associated With Weakness in Multiple Sclerosis**  
Daniel Reich, PhD, MD  
*The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA*
- 2:30 – 2:45 pm**      **Consistent Efficacy of Alemtuzumab in Relapsing-Remitting Multiple Sclerosis Across Major Demographic Subgroups**  
Ann Doan-Do Bass, MD  
*Neurology Center of San Antonio, San Antonio, Texas, USA*

## FEATURED PRESENTATIONS

- 2:45 – 3:20 pm**      **Beyond the Monoclonals: Promising Oral Agents and Neuroprotective Strategies**  
Peter Calabresi, MD  
*The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA*
- 3:20 – 3:55 pm**      **Designing Rational Clinical Trials for New and Emerging Therapies**  
Fred Lublin, MD  
*Mount Sinai School of Medicine, New York, New York, USA*
- 3:55 – 4:00 pm**      **Closing Remarks**

## Disease Modifying Therapy

- P1 Rituximab for Neuromyelitis Optica: Experience With Nine NMO-IgG Positive Patients**  
Andrew David Brown, MD  
*University of Miami, Miami, Florida, USA*
- P2 Continuity in Use of Multiple Sclerosis Immunomodulatory Drugs in a Privately Insured Patient Population: Patterns and Predictors**  
Roberta Constantine, PhD, MBA, RN  
*Research Triangle Institute, Waltham, Massachusetts, USA*
- P3 The Effect of Interferon (IFN) Treatment on Location of Relapsing-Remitting Multiple Sclerosis (RRMS) Relapse**  
Serina Rayhan Deen, BA  
*UCSF MS Center, San Francisco, California, USA*
- P4 Results of a Phase I Trial of Pioglitazone in RRMS Patients**  
Douglas L. Feinstein, PhD  
*University of Illinois at Chicago, Chicago, Illinois, USA*
- P5 Natalizumab Discontinuation Predisposes to Serious Infusion Related Reactions and Antibody Formation**  
John F. Foley, MD  
*Intermountain LDS Hospital, Salt Lake City, Utah, USA*
- P6 Risk Tolerance in Multiple Sclerosis Patients**  
Robert J. Fox, MD  
*Mellen Center, Cleveland Clinic, Cleveland, Ohio, USA*
- P7 Impact of Switching First-Line Disease-Modifying Therapy (DMT) After Failure in Relapsing-Remitting Multiple Sclerosis (RRMS)**  
Alberto Gajofatto, MD  
*University of California, San Francisco, San Francisco, California, USA*
- P8 Efficacy, Safety and Tolerability of 500  $\mu$ g Versus 250  $\mu$ g Interferon Beta-1b Versus Glatiramer Acetate in Patients With Relapsing-Remitting Multiple Sclerosis (the BEYOND study): Baseline Patient Characteristics**  
P. O'Connor, MD  
*St. Michael's Hospital, Toronto, Ontario, Canada*
- P9 Pharmacogenomics of Interferon-b Therapy: Evidence for the Existence of Pharmacodynamic Differences Within Multiple Sclerosis**  
S. Vosslander  
*VU Medical Center, Amsterdam, Netherlands*
- P10 Long-Term Outcome of Minocycline in Relapsing-Remitting Multiple Sclerosis**  
Yunyan Zhang, PhD, MD  
*University of Calgary, Calgary, Alberta, Canada*

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## **Epidemiology/Genetics**

- P11 Clinically Silent Multiple Sclerosis: Description of a Patient Cohort Without Symptoms Typical of MS but Abnormal Brain Magnetic Resonance Imaging**  
Joy Derwenskus, DO  
*Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA*
- P12 Survival Analysis Predicts That Nearly Half of People With MS Become Unemployed Within 15 Years of MS onset**  
Luanne M. Metz, MD  
*University of Calgary, Calgary, Alberta, Canada*
- P13 Clinical Course and Outcome of Transverse Myelitis in Relapsing Neuromyelitis Optica**  
Regina Maria Papais Alvarenga MD, PhD  
*Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, Brazil*
- P14 Integrating Environmental and Genetic Effects on Susceptibility to MS**  
K. Claire Simon, SM  
*Harvard School of Public Health, Boston, Massachusetts, USA*
- P15 Clinical Characteristics of African Americans With MS: The VA Longitudinal MS Study**  
Mitchell T. Wallin, MD, MPH  
*Georgetown University, Washington, DC, USA*

## **Experimental Disease Models**

- P16 Antibody Screen of Insertional Zebrafish Mutants Identifies Novel Genes Involved in Myelination**  
Samuel J. Adams, BS  
*Baldwin Wallace College, Berea, Ohio, USA*
- P17 Pregnancy Modulates Precursor Cell Proliferation in a Murine Model of Focal Demyelination**  
Shirin Haddady, MD  
*University of Massachusetts Medical School, Worcester, Massachusetts, USA*
- P18 Cytokine/Neuroantigen Fusion Proteins as Tolerogenic Antigen-Specific Vaccines: A Novel Therapy for Autoimmune Disease of CNS Myelin**  
Mark D. Mannie, PhD  
*East Carolina University, Greenville, North Carolina, USA*
- P19 Co-administration of AEG35169 and Interferon- $\beta$  Produces a Synergistic Reduction of Clinical Severity in Experimental Autoimmune Encephalomyelitis**  
Craig S. Moore, BSc  
*Dalhousie University, Halifax, Nova Scotia, Canada*

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## Imaging

- P20 HRT Contributes to Neuronal Health in Postmenopausal Women With MS**  
Kathleen Fuchs, PhD  
*University of Virginia, Charlottesville, Virginia, USA*
- P21 Comparison of Lesion Distribution in Children With Clinically Isolated Syndromes Suggestive of Multiple Sclerosis and Adults With Clinically Definite MS**  
Rezwan Ghassemi, MSc  
*McGill University, Montreal, Quebec, Canada*
- P22 Quantitative DCE MRI Suggests Widespread Microvascular Abnormalities in RRMS Brain Tissue**  
Jeffrey Moses Njus, PhD  
*Oregon Health & Science University, Portland, Oregon, USA*
- P23 Sensorimotor Impairments Are Associated With MRI-Defined Tract-Specific Spinal Cord Disease in Multiple Sclerosis**  
Kathleen M. Zackowski, PhD, OTR  
*Kennedy-Krieger Institute/Johns Hopkins University, Baltimore, Maryland, USA*

## Neuroimmunology

- P24 Fibrinogen as a Signaling Molecule and Therapeutic Target for Inflammation and Neuroprotection in Multiple Sclerosis**  
Katerina Akassoglou, PhD  
*University of California, San Diego, La Jolla, California, USA*
- P25 IFN  $\beta$ 1a Induced Changes in Myelin-Specific T Cell Frequency May Serve as a Biomarker Predicting Clinical Outcome**  
Lilyana Amezcua, MD  
*USC Keck School of Medicine, Los Angeles, California, USA*
- P26 NK Cells Inhibit T Cell Expansion and Th17 Priming**  
Jehad H. Edwan, PhD  
*University of Cincinnati, Cincinnati, Ohio, USA*
- P27 Decreased CD1d-Restricted NKT cells in the Peripheral Blood of MS Patients**  
E. L. Hogan, MD  
*Medical College of Georgia, Augusta, Georgia, USA*
- P28 Early Results of the Luciferase Assay to Measure Neutralizing Antibodies to Interferons**  
Joel Oger, MD  
*Neuro-immunology Lab/UBC, Vancouver, British Columbia, Canada*

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**P29 3G11–CD25+: A New and More Accurate Cell Surface Marker for Regulatory CD4+ T Cells**

Zhao Zhao, MD

*Thomas Jefferson University, Philadelphia, Pennsylvania, USA*

**Neuropsychology/Neuropsychiatry**

**P30 Pediatric MS Patients Exhibit Impaired Processing Speed and Efficiency**

Joseph Ackerson, PhD

*University of Alabama at Birmingham, Birmingham, Alabama, USA*

**Pathology**

**P31 Neurodegeneration of the Retina in Multiple Sclerosis: Relationship to Pathophysiology**

Amber R. Salter, MPH

*UT Southwestern Medical Center, Dallas, Texas, USA*

**P32 Gas6 Activation of the Receptor Tyrosine Kinase Axl Recruits PI3 Kinase and Grb2**

Jason G. Weinger, MS

*Albert Einstein College of Medicine, Bronx, New York, USA*

**Rehabilitation and Quality of Life**

**P33 Mindfulness-Based Stress Management for MS Patients and Caregivers**

Michael J. Baime, MD

*University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA*

**P34 Force Control During Object Manipulation in Multiple Sclerosis**

Vennila Krishnan

*University of Delaware, Newark, Delaware, USA*

**P35 Break in Binocular Fusion During Head Turning in Multiple Sclerosis Patients With Internuclear Ophthalmoplegia Is Exacerbated During Heat Stress: Safety Implications for Driving and Walking**

Douglas A. Mills, BA

*UT Southwestern Medical Center, Dallas, Texas, USA*

**P36 Physical Activity and the Disablement Process in Multiple Sclerosis**

Robert W. Motl, PhD

*University of Illinois at Urbana-Champaign, Urbana, Illinois, USA*

**P37 Mental Practice of Action and Rehabilitation of MS**

Andrew Slifkin, PhD

*Cleveland State University, Cleveland, Ohio, USA*

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## **Surrogate Markers (Non-MRI)**

**P38 Anti Glycan Antibodies in Serum of MS Patients**

Florian Deisenhammer, MD, MSc

*Innsbruck Medical University, Innsbruck, Austria*

**P39 Evaluating the Anterior Visual Pathway in Multiple Sclerosis:  
Structure vs. Function**

Ari Green, MD

*UCSF MS Center, San Francisco, California, USA*

**P40 Sensitivity of Static Stabilometry in Multiple Sclerosis Patients With  
Mild Disability**

Peter N. Riskind, MD, PhD

*University of Massachusetts Medical School, Worcester, Massachusetts, USA*

**P41 Corpus Callosum Volume Correlates With Tactile Temporal Threshold  
in MS**

Yunyan Zhang, PhD, MD

*University of Calgary, Calgary, Alberta, Canada*

## **Symptom Management**

**P42 Validation of Consistent Improvement in Walking Speed on the  
Timed 25 Foot Walk as a Measure of Clinically Meaningful Change**

Andrew D. Goodman, MD

*University of Rochester, Rochester, New York, USA*

**P43 Are Global or Specific Symptoms Better Correlates of Physical Activity  
in Multiple Sclerosis?**

Erin M. Snook, MS

*University of Illinois at Urbana-Champaign, Urbana, Illinois, USA*



## Featured Speaker Biographies

### **BIBIANA BIELEKOVA, MD**

Bibiana Bielekova, MD is an associate professor of neurology at the University of Cincinnati and Director of the Waddell Center for Multiple Sclerosis. Previously she was a staff physician and researcher with the National Institutes of Health, National Institute of Neurological Disorders and Stroke (NIH/NINDS), Neuroimmunology Branch in Bethesda.

Dr. Bielekova's research interests include disease heterogeneity of MS, as it relates to different pathophysiological processes that underlie development of clinical disability; immunoregulation between innate and adaptive immune responses in MS with special emphasis on regulatory role of the natural killer (NK) cells on autoreactive T cells; development of biomarkers that reflect prevailing pathophysiological process in individual MS patients and that have prognostic implications for treatment response with selected therapeutic agents; and the development of new therapies and rational combination of therapeutic modalities for MS.

Dr. Bielekova was awarded her medical degree at Comenius University School of Medicine, Bratislava, Slovakia and completed her neurology residency training at Boston University School of Medicine. She completed a neuroimmunology fellowship at NIH/NINDS, Neuroimmunology Branch.

### **PETER CALABRESI, MD**

Peter A. Calabresi, MD is an associate professor of neurology at the Johns Hopkins School of Medicine and Director of the Johns Hopkins Multiple Sclerosis Center. Dr. Calabresi began his career as Director of the MS Program at Rhode Island Hospital and as an assistant professor of neurology at Brown University Medical School. He later held academic and clinical appointments at the University of Maryland School of Medicine.

As director of the MS Center at Johns Hopkins, Dr. Calabresi is the principal investigator on several clinical trials and also oversees translational laboratory research projects. Dr. Calabresi has designed and directed several clinical trials investigating combination drug therapies in MS and is on the advisory board for three national multi-center clinical trials.

Dr. Calabresi's specific laboratory research interest lies in understanding the mechanisms of T lymphocyte migration into the brain and spinal cord. He has published numerous articles on the adhesion molecules and chemokine receptors responsible for T cell homing to the brain in MS. He is the recipient of a five-year collaborative MS center grant from the National MS Society to study mechanisms of neurodegeneration and strategies for neuroprotection in MS.

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Dr. Calabresi earned his medical degree from Brown University, completed residency training at Strong Memorial Hospital, and completed a research fellowship of the National Institutes of Health, Neuroimmunology Branch. He serves on the clinical care and research programs committees of the National Multiple Sclerosis Society and on the board of trustees of the Society's Maryland Chapter.

**FRED LUBLIN, MD**

Fred D. Lublin, MD is the Saunders Family Professor of Neurology and Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai School of Medicine. He previously held academic and hospital appointments at Jefferson Medical College and at MCP Hahnemann University, where he was Director of both the MS Center and the Neurological Clinical Trials Center.

As a neuroimmunologist, Dr. Lublin has a special interest in immune functions and abnormalities affecting the nervous system. He and his colleagues were among the first in the country involved with studies of interferon beta-1b, which was approved by the Food and Drug Administration in 1993 to treat the relapsing-remitting form of multiple sclerosis. He and his colleagues at the National Multiple Sclerosis Society re-defined the clinical course definitions of MS using data from a survey of the international MS community. Dr. Lublin was also a member of the panel that has re-defined the diagnostic criteria for MS. He is currently involved with several new clinical research protocols on promising agents for treating various aspects of MS and is the national coordinating investigator for a multi-center trial of combination therapy in MS.

Dr. Lublin has served as a consultant to the National Institutes of Health and to many pharmaceutical/ biotech companies. He has served on several committees of the National MS Society and has chaired the Research Programs Advisory Committee, the advisory committee on clinical trials of new drugs in MS, as well as a task force on the ethics of placebo-controlled trials in MS.

Dr. Lublin received his medical degree from Jefferson Medical College at Thomas Jefferson University. He completed his internship in internal medicine from the Bronx Municipal Hospital, Albert Einstein Medical Center, and his neurology residency at the New York Hospital, Cornell Medical Center.

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**OLAF STÜVE, MD, PHD**

Olaf Stüve, MD, PhD is an assistant professor of neurology at UT Southwestern Medical Center in Dallas. Prior to his appointment at UT Southwestern, Dr. Stüve was an assistant professor in the Department of Neurology at the Heinrich Heine University. He received his medical degree from the Free University of Berlin and earned a PhD in immunology in the Department of Clinical and Experimental Immunology at Maastricht University, The Netherlands. He served a transitional internship at the University of Cape Town, South Africa, and a preliminary internship and neurology residency at the University of Washington in Seattle. Dr. Stüve also received postdoctoral fellowship training in neuroimmunology at McGill University and at the University of California, San Francisco.

The research in Dr. Stüve's laboratory focuses on genetic regulation of multiple sclerosis disease activity as well as novel treatment strategies for inflammatory diseases of the central nervous system. He is also an investigator in numerous national and international clinical trials that test the efficacy of novel pharmacotherapies for MS.

**HERMAN WALDMANN, FRS**

Herman Waldmann, FRS is Professor of Pathology and Head of the Sir William Dunn School of Pathology at the University of Oxford. An immunologist, he is best known for his work on mechanisms of immunological tolerance, and its therapeutic generation with monoclonal antibodies. One such antibody Campath-1, is currently licensed as alemtuzumab for the treatment of chronic lymphocytic leukemia.

Dr. Waldmann received his undergraduate and graduate degrees from the University of Cambridge and began his scientific career there in the Department of Pathology. He became Head of the Immunology Division and there was elected to the new Kay Kendall Chair in Therapeutic Immunology. It was at Cambridge that he studied mechanisms by which cells of the immune system could interact to mount immune responses. This early work led him to become interested in immunological tolerance and achieving tolerance for therapeutic purposes.

Since 1980 he has been funded by a Medical Research Council Programme Grant to study mechanisms of transplantation tolerance and strategies to achieve this both experimentally and clinically. In 1985 he published the first studies to show that short courses of CD4 antibody therapy could bring about long-term

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immunological tolerance to foreign proteins, and this work led to the first demonstrations of transplantation tolerance resulting from short-term antibody blockade.

His mechanistic studies of tolerance uncovered a role for regulatory T-cells in infectious tolerance which was published in a seminal paper in *Science* in 1993. The strategies emerging from his laboratory since that time have been based on the use of therapeutic antibodies to enhance regulation over conventional T-cell immunity.

In order to apply antibodies clinically Waldmann developed the first academic antibody therapeutic manufacturing facility. He and his team were able to apply clinical-grade antibodies in a wide range of probing therapeutic studies that enabled them to develop a series of humanized antibodies (CD52, CD3, CD4 and others) which have since been transferred to the pharmaceutical industry. CAMPATH-1H was the first humanized antibody to be introduced into clinical use.

His team's work since 1971 has resulted in more than 450 publications, the majority directed to therapeutic antibodies and their mechanisms of action. These contributions have led to his election to the Royal Society in 1990. Professor Waldmann is the recipient of the Jose Carreras Medal of the European Hematology Society and the Juvenile Diabetes Research Foundation Excellence in Clinical Research Award.

#### **EMMANUELLE WAUBANT, MD, PHD**

Emmanuelle L. Waubant, MD, PhD is an assistant professor of neurology at the University of California, San Francisco (UCSF) and Director of the Nancy Davis Center, UCSF MS Center.

She trained as a neurologist in Toulouse, France and then continued her training as a neuroimmunology fellow at UCSF, focusing on matrix metalloproteinases (MMP) and their tissue inhibitors (TIMP), and their role in migration of lymphocytes through equivalents of the blood-brain barrier. In 1994, Dr Waubant returned to Toulouse to complete her two-year chief residency in neurology, then returned as a clinical fellow at the UCSF MS Center. There she translated her *in vitro* MMP findings that helped to understand the role of MMP-9 and TIMP-1 in patients with MS and their relationship to disease (MRI activity).

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After leading a clinical research center at Salpetriere Hospital in Paris for two years, she returned to the UCSF MS center in 2001, where she currently directs clinical research. She also coordinates clinical research collaborations between seven MS Centers of Excellence throughout the US. With the support of the National Multiple Sclerosis Society, she has started a regional Pediatric MS Center of Excellence at UCSF in January, 2006.

Dr. Waubant's specific interests include the translation of promising agents from the bench to the bedside, the design of clinical trials of promising disease modifying agents for MS, understanding factors that predict the response to interferon therapy, and pediatric MS. Currently, she is the co-lead investigator for three Phase 2 trials: oral interferon tau in relapsing remitting MS; atorvastatin in early MS supported by the Immune Tolerance Network; and rituximab in relapsing-remitting MS supported by Genentech. She just initiated a pilot study of neuroprotection in early MS with riluzole, with the support of the National MS Society.



## Prospects for Reprogramming the Immune System in Multiple Sclerosis

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There are three fundamental processes that prevent the immune system spontaneously attacking self-tissues such as the nervous system. First, the immune system, during lymphocyte development, eliminates lymphocytes with high affinity receptors for self antigens. Second, it generates a set of policing or regulatory T-cells as fail-safes. Third, the tissues in their resting state have the capacity to tune down potential immune reactivity within them. This latter “tissue-privilege” is best seen in the placenta, but is likely present in all tissues to different degrees.

The ideal therapy to reverse unwanted immune reactivity to body tissues would be to empower the regulatory T-cells and to optimise whatever privilege mechanisms are available. This would allow minimization or even elimination of immunosuppressive drugs. If one could do this with short-term treatments then the immune system need only be therapeutically compromised for limited periods.

Recent evidence suggests that regulatory T-cells operate within tissues to encourage privilege. If so, one would expect that strategies which enhance regulation will also enhance tissue privilege.

Acceptance of transplanted tissues has long provided a generic source of information on tolerance mechanisms. Ablation of lymphocytes is an efficient way to halt immune attack and tissue inflammation. Regulatory T-cells have a capacity to recolonise the lymphopenic host more efficiently than their naive T-cell counterparts, and so may be able to gain the upper hand long-term. The disadvantages are the relative immune deficiency, and the uncontrolled expansion of lymphocytes in the lymphopenic host (homeostatic expansion) which may risk other autoimmune syndromes.

An alternative is to use non-ablative strategies using antibodies (CD4, CD3 and others) to temporarily “block”

T-cell function. These can create a ceasefire during which naive T-cells can get recruited into a policing role so ensuring that regulation dominates at the time of drug withdrawal. This conversion of naive T-cells to regulatory T-cells appears to be critically dependent on a source of TGF $\beta$ .

Therapeutic agents which affect T-cell signalling or T-cell migration into tissues may be able to provide immunosuppression during the period of their administration. They may however be non-permissive for conversion of naive T-cells to regulatory T-cells, and for entry of regulatory T-cells into the affected tissues. The conversion process may be sustained indefinitely if tissue antigens continue to be presented in inflammation-free conditions through a process we have coined “infectious tolerance”.

To exemplify these ideas, I will mention clinical studies in multiple sclerosis with alemtuzumab, and in Type I diabetes with a CD3 antibody. I will discuss the possible benefits and disadvantages of the different reprogramming strategies.

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## Natalizumab Therapy in Multiple Sclerosis

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**Background:** Natalizumab (Tysabri®) is a humanized recombinant monoclonal antibody that binds to the alpha  $\alpha$ 4 chain of the  $\alpha$ 4 $\beta$ 1 (very late activation antigen-4; VLA-4) and the  $\alpha$ 4 $\beta$ 7 integrins. Based on the results of two phase III clinical trials (1;2), natalizumab is approved for the treatment of patients with multiple sclerosis (MS) in the European Union and in the United States. We had previously observed that natalizumab decreases the numbers of CD4+ and CD8+ T lymphocytes, CD19+ B cells, and CD138+ plasma cells in the cerebrospinal fluid (CSF) of patients on natalizumab therapy (3;4). We also demonstrated that the cell numbers remained unchanged 6 month after cessation of natalizumab therapy (3). There was a differential effect of natalizumab on lymphocyte subsets, with numbers of CD4+ T cells and B cells in the CSF being predominantly affected (3;4). In the context of a phase II study, it had been demonstrated that three months after discontinuation of natalizumab there was no difference between the treatment group and the placebo groups with regard to gadolinium enhancing lesions on magnetic resonance imaging (MRI) (5). The objective of this study was to assess clinical MS disease activity, surrogate disease markers on MRI, immunological parameters in peripheral blood and CSF, as well as safety in MS patients after discontinuation of natalizumab therapy.

**Methods:** This is a longitudinal prospective study, in which 23 patients who were treated with natalizumab in the context of two phase III clinical trials were followed serially over 14 months. The annual relapse rate, neurological disease progression assessed by the Expanded Disability Status Scale, disease surrogate markers on magnetic resonance imaging (MRI), cellular and humoral immune markers in peripheral blood and CSF, and adverse events of the drug were monitored.

**Findings:** With regard to clinical disease activity, neuroimaging, and immune responses, the majority of patients in our cohort were stable. Decreased lymphocyte cell numbers and altered cell ratios returned to normal 14 months after cessation of natalizumab. No infectious complications were observed.

**Interpretation:** This is the first long-term follow-up of patients who discontinued natalizumab. We did not observe a clinical, radiographic, or immunological rebound phenomenon after discontinuation of natalizumab therapy.

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## Use of Daclizumab in Multiple Sclerosis

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It is believed that multiple sclerosis (MS) is a T cell-mediated autoimmune disease, and therefore the search for new therapies focuses on agents that affect lymphocyte function. Daclizumab, a humanized monoclonal antibody that blocks the IL-2 binding-site on the IL-2 receptor  $\alpha$ -chain (CD25) is among these novel agents. CD25 is present at very low levels in resting human T cells (with the exception of T<sub>regs</sub>), but is significantly upregulated on activated T cells, enabling them to receive a high affinity IL-2 signal. Because it was believed that IL-2 signaling was necessary for T cell function, it was expected that the blockade of CD25 would result in selective functional inhibition of T cell activation. This provided the rationale for the use of daclizumab in autoimmune disorders such as MS.

Two phase II, open-label, baseline-versus-treatment crossover trials of daclizumab in MS patients with incomplete therapeutic response to IFN- $\beta$  have been concluded at NIH (1) and the University of Utah (2). When used in combination with IFN- $\beta$  or as a monotherapy, daclizumab showed a profound inhibitory effect on brain inflammatory activity (>75% reduction) and subsequent stabilization of disability progression. Both the inhibition of brain inflammation by daclizumab and the reappearance of inflammation after cessation of the therapy developed gradually over a period of 2–3 months, consistent with the hypothesis that daclizumab induced gradual and prolonged immunomodulatory changes *in vivo*. A multicentric double blinded Phase II trial of Daclizumab in RR-MS patients with incomplete therapeutic response to IFN- $\beta$  has also been recently concluded and as the news report reflected the daclizumab therapy led to a significant reduction in the number of new or enlarged gadolinium-contrast-enhancing lesions at week 24 as compared to placebo.

We recently reported immunological studies supplementing the two Phase II NIH trials of daclizumab in MS (3). In contrast to the putative mechanism of action of daclizumab, we did not observe any significant inhi-

bition of T cell activation or function during *in vivo* administration of the drug. However, we did observe profound expansion of CD56<sup>bright</sup> natural killer (NK) cells during daclizumab therapy, which correlated with the treatment outcome. CD56<sup>bright</sup> NK cells represent a minute population of lymphocytes (~1%) in human peripheral blood. These cells have been labeled “immunoregulatory” because they are expanded under situations that assume immunoregulation, such as pregnancy or bone-marrow transplantation. Additionally, CD56<sup>bright</sup> NK cells home to lymph nodes and affect T cell priming by production of cytokines and by killing of autologous immature dendritic cells. In our studies, we observed a slow but gradual decline in absolute numbers of CD4+ and CD8+ T cells during daclizumab therapy (by ~10%) and a statistically significant correlation between expansion of CD56<sup>bright</sup> NK cells and reductions in T cell numbers *in vivo*. Extensive *in vitro* experiments demonstrated that daclizumab-expanded CD56<sup>bright</sup> NK cells are capable of killing activated autologous CD4+ and CD8+ T cells in a perforin-dependent manner. This data suggests an unexpected and novel mechanism of action of daclizumab via a regulatory circuit between innate and adaptive immune responses.

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## Featured Presentation

### *Studies on Rituximab in the Treatment of Multiple Sclerosis*

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MS has long been considered to be a T cell-centric autoimmune disease although accumulating evidence has suggested over the years the participation of B cells to disease processes. More recently, the reports of antibody deposition and activation of complement in a significant amount MS lesions, the presence of clonally-expanded, activated memory B lymphocytes and plasma cells in MS lesions, the occurrence of CNS lymphoneogenesis have further pointed out the key involvement of B cells in MS pathogenesis.

B cells could participate in antigen-dependant and antigen-independent manners to MS immune processes. First, B cells are very efficient antigen presenting cells because of their B cell receptor that can internalize antigens and present them to T cells. Second, B cells have co-stimulatory molecules that can promote activation of T cells. Third, B cells release several cytokines such as IL-6, IL-10 and TNF alpha that may in turn modify the local environment of the CNS through their action on microglia, astocytes and other cell types. Fourth, B cells mature in plasmacytes that secrete antibodies which may play a role in myelin damage. Finally, B cells constitute the main reservoir of Epstein Barr virus in the body. EBV infection of B cells results in chronic activation of these cells.

Most FDA-approved MS therapies have some partial effect on B cell through various mechanisms. Other non-approved treatments for MS seem to have an impact on the disease such as plasmapheresis that helps recovery of severe exacerbations of MS with poor outcome after high dose steroid treatment, and IV immunoglobulins that prevent MS clinical and MRI activity.

The first drug targeting selectively B cells is rituximab. Rituximab (MabThera®/Rituxan®) is a glycosylated immunoglobulin G1 (IgG1) $\kappa$  chimeric mouse/human antibody that binds to the CD20 antigen present on the majority of B cells. Expression of CD20 is restricted to the B-lymphocyte lineage from the pre-B cell stage until terminal differentiation into plasma cells. Treatment with rituximab induces a rapid, selective and prolonged (e.g. 6 or more months) depletion of B cells. Rituximab is approved for the treatment of CD20+ B cell lymphomas and rheumatoid arthritis resistant to

anti-TNF therapy. It is currently evaluated in other autoimmune diseases including lupus. Several groups have started to use off-label rituximab in MS and Devic's disease. In Devic's disease, the medication seems to decrease significantly the number of exacerbations. A large phase III study is on-going for primary progressive MS. A pilot study has evaluated rituximab in RRMS patients doing poorly on IFN or GA, and has reported a significant decrease of B cells and to a lesser extent T cells in the CSF of MS patients. In the past year, a phase II trial of a single course of rituximab showed a rapid and dramatic reduction in the number of new lesions on sequential brain MRI scans obtained over 6 months in rituximab recipients compared to placebo. In a concomitant phase I trial of retreatment with rituximab in RRMS the MRI benefit was reported for 48 weeks. In both studies, there was also a reduction in the number of exacerbations. The medication was well tolerated except for mild to moderate infusion reactions.

The next generation of anti-CD20 antibody is under development and is humanized in order to reduce the rate of HACA development and possibly infusion reactions. In addition to confirming efficacy in well-designed trials of B cell directed therapies, long-term safety and tolerability are important considerations as the threshold of acceptable toxicity over time is different in MS than in the context of patients with lymphoma.

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## Featured Presentation

### *Beyond the Monoclonals: Promising Oral Agents and Neuroprotective Strategies*

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The future of multiple sclerosis (MS) therapeutics is extremely promising. Two major initiatives in MS drug development are: 1) to find better tolerated and more effective immunotherapies; and 2) to develop neuroprotective drugs that preserve neurons and axons that have already been injured. Herein we shall review oral agents, which have shown efficacy in phase II studies and neuroprotective strategies that are on the threshold of clinical translation.

**Oral Immunomodulatory Agents:** FTY-720 (fingolimod) is a sphingosine-1P receptor agonist that is given orally once daily and blocks lymphocyte migration. In a recent phase II clinical trial reported in the NEJM FTY-720 resulted in a greater than 50% reduction in clinical relapse rate and 80% reduction in MRI activity at 6 months (Kappos *et al.*, 2006). Two large phase III trials are underway.

The fumaric acid ester BG-12 is an oral agent that was recently shown in a phase II study of relapsing-remitting MS to have a 44% reduction in the total number of gadolinium-enhancing brain lesions as measured by MRI with six months of treatment (240 mg TID) versus placebo and 32% reduction in annualized relapse rate (ECTRIMS 2006). Common AEs associated with BG12 include; mild increases intransaminases, headache, GI symptoms, and flushing.

Laquinimod (ABR-215062) is related to Linomide, but without toxicity (serositis, myocardial infarction) in dog studies and inhibitory activity on autoimmune and inflammatory diseases in animal models. There was a 44% reduction in MRI activity in a phase II study (Polman *et al.*, 2005) and a subsequent study showed that higher doses may be tolerable and impact positively on relapses.

Teriflunomide is a metabolite of leflunomide, a potent immunosuppressive disease-modifying antirheumatic drug of the isoxazole class, which showed 60% reduction in combined unique active MRI lesions and trend towards reduction in relapses in a phase II clinical trial (O'Connor *et al.*, 2006).

Several other oral agents are in earlier stages of testing. Atorvastatin (Lipitor®), an HMG-coA reductase inhibitor,

has been shown to ameliorate EAE and a pilot open label trial of simvastatin showed a 44% reduction of Gd+ MRI lesions (Vollmer *et al.*, 2004). An Immune Tolerance Network sponsored trial in CIS is in progress. The antibiotic minocycline has both anti-inflammatory and possibly neuroprotective effects. Pilot data suggest an effect in reducing MRI activity, and studies of minocycline are ongoing. The oral diabetes drug pioglitazone, which is a PPAR $\alpha$  antagonist, has shown promising effects in EAE and because of its availability and proven safety in humans is being investigated in MS. Several broad spectrum oral immunosuppressive drugs continue to be examined in MS including cladribine (Cladribine®), mycophenolate mofetil, and azathioprine. Oral methotrexate in combination with weekly interferon beta (IFN $\beta$ ) 1a was recently shown to be no more effective than IFN $\beta$  alone after one year.

**Strategies for Neuroprotection:** Axonal degeneration may occur in MS by direct damage from inflammatory mediators, or indirectly through the effects of demyelination leading to loss of trophic signaling by myelin, and via compensatory up regulation of sodium channels along demyelinated axons leading to increased calcium influx and downstream injury by activation of calpains and cell death pathways. Candidate neuroprotective drugs that might directly increase axonal stability include recombinant human erythropoietin, the non-immunosuppressive neuroimmunophilin ligands, poly-ADP ribose polymerase (PARP) inhibitors and sodium channel blockers (Ehrenreich *et al.*, 2004; Waxman, 2006). In addition, several promising approaches are being developed that may target neurodegenerative pathways in the CNS. These include inhibiting glutamate mediated excitotoxicity using non-competitive AMPA receptor blockers or targeting oxidative stress by interfering with nitric oxide and downstream free radical production. Finally, while stem cells continue to garner much attention for their reparative potential, efforts at enhancing natural repair mechanisms are probably closer to clinical translation. LINGO antagonism has recently been shown to promote remyelination of axons in laboratory models by enhancing

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oligodendrocyte differentiation. Efforts at delineating the normal protective effects of myelin have revealed that the inner lamellar component of the myelin sheath composed of myelin associated glycoprotein (MAG) may have critical axon-protective effects that can be reproduced by administration of soluble myelin peptides.

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### *Designing Rational Clinical Trials for New and Emerging Therapies*

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While MS leads the area of neurotherapeutics in the number and years of experience with disease modifying agents (DMAs), currently available therapies offer partial effect. In the quest to develop better therapies, we are dependent on exploiting the latest understanding of the underlying pathophysiologic mechanisms of MS. Presently, DMAs act through immunomodulation, primarily on the inflammatory aspect of MS. Future therapeutic options include more aggressive and/or easier to administer immunomodulation, neuroprotective agents and repair molecules. The outcome measures currently in use, relapse rate reduction and time to disability, should be suitable for a newer generation of immunomodulatory agents, although increased attention to safety elements may be warranted. For CIS trials, the McDonald criteria have been shown to allow for more rapid assessment of efficacy, due to the shorter time from initial event to McDonald defined MS (1,2). For studies of potential neuroprotective agents, one could use the EDSS, as currently employed, although the MSFC may have advantages, especially in its ability to measure worsening and improvement (3). MRI will serve an important function in screening new therapies. Currently utilized sequences, such as number of enhancing lesions, will continue to be useful in phase II trials of immunomodulating agents. Lesion load, T1 and T2, will be useful in the later stages of testing of these

agents. For neuroprotective and repair strategies, measures of brain volume, especially in concert with segmentation protocols may be useful, although the time to discernable change may impede these techniques. Advanced metrics, such as magnetization transfer imaging/ratios, spectroscopy and diffusion tensor imaging/tractography may also prove to be of value in gauging underlying tissue damage. Success of these metrics may well depend on the ability to port them to multiple sites for large clinical trials. Optical coherence tomography also has potential in studying tissue damage. Lastly, biomarkers in blood, or less desirably in CSF, may provide important diagnostic, prognostic and therapeutic insights.

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## Retinal nerve fiber layer thickness correlates with brain atrophy in multiple sclerosis

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**Keywords:** atrophy; axon; degeneration; MPRAGE; optical coherence tomography; retinal nerve fiber layer

**Background:** Optical coherence tomography (OCT) is a noninvasive, high-resolution technique that uses infrared light to quantify retinal nerve fiber layer (RNFL) thickness. Recent studies show thinning of the RNFL in eyes of patients with multiple sclerosis (MS). MRI has been used to measure brain atrophy in MS to quantify total tissue loss and as a biomarker of disease progression. **Objectives:** Determine if RNFL correlates with brain atrophy in MS. **Methods:** RNFL thickness was measured by Stratus OCT 3 in 40 MS patients and 15 controls. Whole brain MRI scans were obtained. Brain parenchymal fraction (BPF) was estimated with SIENAX. Regression analysis of RNFL vs. BPF and segmentation parameters, controlling for age and duration of disease (DoD), was performed. Expanded disability status score (EDSS) was determined by neurological exam. **Results:** BPF correlated with average RNFL in MS when adjusted for age ( $r=0.45$ ,  $p=0.004$ ) and DoD ( $r=0.40$ ,  $p=0.01$ ), but not in controls. Of the segmentation parameters, only ventricular CSF volume correlated with RNFL when adjusted for age ( $r=-0.38$ ,  $p=0.02$ ) and DoD ( $r=-0.41$ ,  $p=0.01$ ). EDSS correlated with RNFL, when adjusted for age ( $r=-0.38$ ,  $p=0.02$ ), but not when adjusted for DoD. Macular volume analyses will be presented. **Conclusions:** RNFL thickness correlates with brain atrophy in MS. This correlation seems primarily dependent on ventricular CSF volume. OCT, a quick and easy clinical tool to assess anterior visual pathology, may therefore provide global information regarding disease progression in the brain in MS. Because global atrophy is correlated with clinical dysfunction, RNFL thickness may be useful as an outcome measure in clinical trials of neuroprotective/neuroreparative drugs.

**Disclosures:** E Gordon-Lipkin has nothing to disclose.

**Funding:** Nancy Davis Center without Walls, National Multiple Sclerosis Society

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## Functional epistasis between MS associated DR3 (DRB1\*0301) and HLA-DQ8 (DQB1\*0302) genes modulate PLPp91-110 induced EAE in HLA transgenic mice

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**Keywords:** animal model; cytokine; EAE; epistasis; HLA transgenic mice; neuroimmunology

**Background:** Among all the genetic factors associated with MS susceptibility, strongest association has been seen with expression of certain MHC class-II molecules. However, it has been difficult to understand the role of individual class-II genes and interaction between class-II genes in the disease process in human due to high polymorphism and linkage disequilibrium. Both HLA-DR3(DRB1\*0301) and -DQ8 (DQB1\*0302) genes are associated with MS in different ethnic population. However it is not clear, how the interaction between DR and DQ molecule influences the disease. **Objectives:** In this study, we have generated double transgenic (tg) mice expressing HLA-DR3/DQ8 to simulate heterozygous haplotype seen in MS patients and study effect of DQ on DR molecule. Previously, we have shown that DR3 is a disease susceptible gene, while DQ8 is a disease resistant gene in the context of PLP p91-110. **Methods:** Single and double tg mice were immunized with PLPp91-110 and development of EAE was monitored. **Results:** Introduction of DQ8 onto DR3 transgenic mice led to higher disease incidence (100% in DR3/DQ8 vs. 65% in DR3) as well as increased disease severity (average clinical score 4.2 in DR3/DQ8 vs. 2.9 in DR3) on immunization with PLP91-110 suggesting that DQ8 had a synergistic effect on development of EAE. We further characterized that the increased susceptibility in DR3/DQ8 tg mice was due to increased production of pro-inflammatory cytokine IL-17 by DQ8 specific T cells. These double transgenic mice (HLA-DR3/DQ8) with EAE also showed increased inflammation and demyelination in CNS tissue as compared to single DR3 tg mice. We also observed that inflammatory cells inside CNS undergo increased apoptosis in DR3 tg mice explaining milder CNS pathology in these mice. **Conclusions:** Thus our double transgenic mouse model of EAE provides a novel tool to study linkage disequilibrium and shows that HLA-DQ molecule might modulate disease in MS-susceptible HLA-DR allele by functional epistatic interaction.

**Disclosures:** AK Mangalam has nothing to disclose.

**Funding:** National Institutes of Health (NS24180, NS32129, NS38468, NS052173); National Multiple Sclerosis Society (RG1372)

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## Genetic predisposition and cognitive impairment in multiple sclerosis

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**Keywords:** APOE; cognitive; genetic; neurodegenerative; neuropsychological; polymorphism

**Background:** Genetic risk factors for multiple sclerosis (MS) are elusive. Several lines of evidence have suggested that there is no association between apolipoprotein E (APOE) polymorphism and disease onset, severity and phenotypes in MS; however, most symptoms identified at onset involve deficits in sensation and motor systems. Evidence suggests that 40–60% of patients with MS manifest symptoms of cognitive impairment often early in their clinical course. Determining a genetic susceptibility factor for cognitive deficits in MS might be very useful. **Objectives:** To determine whether there is an association between APOE 4 and cognitive deficits in MS. **Methods:** We performed a standardized battery of neuropsychological tests in 197 patients with MS to investigate the four cognitive domains commonly impaired in MS. We then assessed the association of the presence of APOE genotype and its promoter polymorphisms with cognition impairment. **Results:** A strong association was found between the presence of APOE 4 and cognitive deficits in MS patients, particularly in the domains of learning and memory. This association was strongest in our youngest cohort (age 31–40) of patients with MS. **Conclusions:** APOE 4 is significantly associated with cognitive impairment in patients with MS, especially in the youngest cohort. This indicates APOE 4 plays an important role in the pathogenesis of cognitive deficits in the context of central nervous system (CNS) inflammation. Determination of APOE polymorphism might provide important prognostic information regarding the risk of cognitive impairment, particularly in young MS patients. Furthermore, stratifying MS patients according to their genotype may yield more effective means for drug development and therapeutic intervention.

**Disclosures:** J Shi has nothing to disclose.

**Funding:** Pilot Research Award from the National Multiple Sclerosis Society

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## Corticospinal tract abnormalities associated with weakness in multiple sclerosis

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PA Calabresi<sup>3</sup>

**Keywords:** brain atrophy; corticospinal tract; diffusion tensor imaging; magnetization transfer imaging; motor system; pyramidal tract

**Background:** MRI can accurately detect MS lesions, but association of MRI abnormalities with specific disability has been limited. **Objectives:** To assess the relationship between muscle strength in MS and corticospinal tract (CST)-associated abnormalities detected with brain MRI. **Methods:** In 47 individuals with MS (26 relapsing remitting, 13 secondary progressive, and 8 primary progressive), diffusion tensor imaging (DTI) at 3T was used to reconstruct the intracranial CSTs. Tract profiles depicted the variation in multiple MRI parameters—T1 and T2 relaxation times, magnetization transfer ratio (MTR), and DTI-derived indices including fractional anisotropy (FA) and mean diffusivity (MD)—as a function of normalized position along the tract. Brain parenchymal fraction was calculated from high resolution anatomic images as a measure of global atrophy. Stepwise linear regression modeling was used to determine the MRI parameters most closely related to ankle dorsiflexion and hip flexion strength assessed with quantitative dynamometry. **Results:** On average, individuals with MS were significantly weak: average ankle strength fell 1.7 standard deviations below the age-, handedness-, and gender-corrected healthy mean. Small but significant differences in MRI parameters were detected between the stronger and weaker half of subjects. Brain atrophy measures were not strongly associated with weakness. A parsimonious model that includes MTR in the brainstem and MS clinical subtype explains 30–45% of the variance in ankle and hip strength. With similar fidelity, these variables predict strength measured in the same individuals at an earlier time point. **Conclusions:** MRI-detectable abnormalities specific to the intracranial motor tract are modestly associated with clinical dysfunction related to that tract. For the most part, the relevant abnormalities are found in the caudal portion of the intracranial tract, within the brainstem, away from the periventricular zone where inflammatory lesions are most common in MS. This suggests that neurodegeneration, rather than primary inflammation, at least partially explains these findings.

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**Disclosures:** P Calabresi has received research grants and/or has been a consultant for Biogen-Idec, Eisai, Genetech, Millenium, Serono, Shering AG, and Teva.

**Funding:** National Multiple Sclerosis Society

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### Consistent efficacy of alemtuzumab in relapsing-remitting multiple sclerosis across major demographic subgroups

*ADD Bass and the CAMMS223 International Study Group*

**Keywords:** alemtuzumab; demographic subgroups; efficacy; interim analysis; relapsing-remitting

**Background:** Preliminary studies suggest alemtuzumab, a humanized monoclonal antibody against the CD52 antigen expressed on lymphocytes, markedly suppresses disease activity when administered during the early stages of relapsing-remitting multiple sclerosis (RRMS). **Objectives:** Compare two alemtuzumab dose levels with IFN-beta-1a in treatment-naïve RRMS patients. **Methods:** 334 treatment-naïve patients with RRMS were randomized 1:1:1 to thrice weekly SC injections of 44 mcg of interferon beta-1a or annual cycles of IV alemtuzumab at low-dose (12 mg/day) or high-dose (24 mg/day). Alemtuzumab was given intravenously  $\times 5$  days at Month 0 and  $\times 3$  days at re-treatment. Randomization was balanced for site, age, sex, and baseline EDSS score. Key entry criteria included MS onset within 3 years of screening, EDSS 0.0 to 3.0 (inclusive),  $\geq 2$  attacks in the previous 2 years, and  $\geq 1$  enhancing lesion on a screening cranial MRI scan. Co-primary efficacy endpoints were time to 6-month sustained accumulation of disability (SAD) and relapse rate. An independent Data Safety Monitoring Board reviewed pre-specified interim analyses of all data. **Results:** Results of the pre-specified Year 2 interim analysis showed that, compared to interferon beta-1a-treated patients, both groups of alemtuzumab-treated patients had  $\geq 75\%$  reduction in the risk for relapse and  $\geq 65\%$  reduction in the risk for SAD. Both findings were highly statistically significant. Subgroup analysis of the co-primary endpoints by baseline demographic variables

indicates that the treatment effect of alemtuzumab is consistent across sex, age, race (Caucasian and non-Caucasian), and country. Adverse effects of alemtuzumab included infusion-associated events and infections. Autoimmune thyroid disorders, and immune thrombocytopenic purpura may occur late after treatment; additional monitoring is required. **Conclusions:** Alemtuzumab is substantially more effective at suppressing relapses and SAD than interferon beta-1a in treatment-naïve RRMS patients through 2 years of follow-up, regardless of patient sex, age, race, or country. Adverse effects have been treatable and manageable. Overall benefit/risk continues to be evaluated.

**Disclosures:** ADD Bass, on behalf of and as a member of the CAMMS International Study Group, presents the following disclosures: 1) several members of the group received compensation from Genzyme Corporation for participating in a Speaker's Bureau or acting in an advisory capacity; 2) several members of the group received financial support for their MS research studies from Genzyme Corporation; 3) several members of the group received compensation (including stock) as employees of Genzyme Corporation.

**Funding:** Genzyme Corporation

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### Inducible over-expression of CXCL1 by astrocytes may be neuroprotective during autoimmune demyelination

*KM Omari and CS Raine*

**Keywords:** astrocyte; CXCL1; EAE; IL-6; oligodendrocyte; transgenic mice

**Background:** Mechanisms underlying oligodendrocyte survival and proliferation, features of active multiple sclerosis (MS) lesions, are not understood. In rodents, the chemokine, CXCL1, induces proliferation and inhibits chemotaxis of oligodendrocyte precursor cells. In MS, CXCL1 is expressed by hypertrophic astrocytes which associate with oligodendrocytes bearing the receptor, CXCR2. **Objectives:** Here we set out to investigate whether CXC chemokines affect repair after CNS inflammation. **Methods:** We generated CXCL1/GFAP double-transgenic (Tg) mice which over-express CXCL1 inducibly under the control of the astrocyte specific gene, glial fibrillary acidic protein (GFAP). Double (CXCL1/GFAP)-Tg, single (CXCL1 or GFAP)-Tg and wildtype (wt) animals were sensitized with myelin oligodendrocyte glycoprotein to induce experimental

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autoimmune encephalomyelitis (EAE). After disease onset, CXCL1 production was initiated by intraperitoneal doxycycline injection (500  $\mu$ g/animal). **Results:** Preliminary results show that double-Tg animals displayed much milder signs than single (CXCL1 or GFAP)-Tg and wt controls. While inflammation was similar in all groups, by 15 days post-immunization (d.p.i.), demyelination and axonal pathology (Wallerian degeneration, WD) were more prominent in controls. Interleukin (IL)-6, a cytokine known to prevent oligodendrocyte degeneration and enhance differentiation and remyelination, was more highly expressed in double-Tg mice. By 40 d.p.i. and up to 60 d.p.i., inflammation and demyelination were significantly diminished in double-Tg mice, and WD was markedly less. Interestingly, remyelination was greater in the double-Tg group, together with an increase in oligodendrocytes. Cell proliferation

(BrdU incorporation) within the CNS appeared more widespread in white matter parenchyma of double-Tg animals compared to controls. Efforts are underway to determine the identity of proliferating cell types within the CNS. **Conclusions:** These findings suggest a neuroprotective role for CXCL1 during the course of autoimmune demyelination, mediated via direct interaction with CXCR2-expressing oligodendrocytes, or induction of the pleiotropic cytokine, IL-6.

**Disclosures:** KM Omari has nothing to disclose.

**Funding:** National Multiple Sclerosis Society (RG 1001-K-1), NIH (NS 08952, NS 11920, NS 07098), and the Multiple Sclerosis Foundation

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## Disease Modifying Therapy

### P1 Rituximab for neuromyelitis optica: experience with nine NMO-IgG positive patients

AD Brown, S Delgado and WA Sheremata

**Keywords:** Devic's disease; neuromyelitis optica; NMO-IgG; optic neuritis; relapsing myelitis; rituximab

**Background:** Neuromyelitis optica (NMO) is a rare, often devastating central nervous system (CNS) demyelinating disease for which there is no approved treatment. Autoantibodies binding to the aquaporin-4 CNS water channel (NMO-IgG) have been shown to have 76% sensitivity and 94% specificity for NMO. This biomarker has provided evidence supporting the hypothesis that NMO is antibody mediated. To date only one report of the use of rituximab, a chimeric monoclonal antibody directed at the CD20 antigen found on pre-B lymphocytes, in the treatment of NMO has been published. **Objectives:** To present preliminary observations on the safety and efficacy of rituximab for NMO. **Methods:** Nine patients meeting diagnostic criteria for NMO were selected for treatment with rituximab. All were female, mean age of 31.1 years, and were positive for the NMO-IgG. Rituximab 375 mg/m<sup>2</sup> intravenously was given weekly for 4 weeks. Patients were followed for a mean of 9.7 months (range 3–16 months). **Results:** The treatment was well tolerated. Mean EDSS of the entire cohort was 6.94 prior to initiation of rituximab and 5.78 after treatment ( $p=0.118$ ). A subset of patients responded more favorably to treatment, defined as a decrease in EDSS  $\geq 1$  after treatment. Prior to treatment, mean EDSS of favorable responders, group 1 ( $n=4$ ), was 7.0 vs. 6.9 in group 2 ( $n=5$ ) ( $p=0.933$ ). After treatment, mean EDSS of group 1 was 4.0 vs. 7.2 in group 2 ( $p=0.039$ ). Group 1 had a mean age of 26 years vs. 47.8 years in group 2 ( $p=0.044$ ). The groups did not differ with regard to ethnicity or disease severity. **Conclusions:** Younger patients appear to respond more favorably to rituximab treatment regardless of relapse status, additional treatments or follow up interval. Large scale, randomized controlled trials are warranted.

**Disclosures:** AD Brown has nothing to disclose. S Delgado has received consulting fees or honoraria from Berlex, Biogen Idec, Pfizer, Serono and TEVA. WA Sheremata has received consulting fees or honoraria from Berlex, Biogen Idec, Pfizer, Genentech, Serono and TEVA.

**Funding:** No funding reported

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### P2 Continuity in use of multiple sclerosis immunomodulatory drugs in a privately insured patient population: patterns and predictors

R Constantine<sup>1</sup>, M Trisolini<sup>2</sup>, A Miller<sup>3</sup>, R Baker<sup>2</sup> and J Green<sup>2</sup>

**Keywords:** continuous drug use; drug coverage; drug discontinuation; drug switching; immunomodulatory drugs; privately insured population

**Background:** By 2002, the Federal Drug Administration (FDA) approved four immunomodulatory drugs for the treatment of multiple sclerosis (MS). These drugs have been shown to reduce the number and severity of relapses and may slow the progression of the disease. All four drugs must be taken continuously and indefinitely to be fully effective. **Objectives:** To investigate the patterns of use, discontinuation, and switching among the four immunomodulatory drugs. **Methods:** We analyzed 2001 and 2002 claims data for a privately insured population. A "drug coverage" variable was calculated by dividing the total continuous days of drug therapy by the total continuous days of enrollment in a health plan from the date of the first prescription. Analysis scenarios allowed 14-day and 30-day gaps in drug days supplied in claims for utilization to still be considered effectively continuous. **Results:** Patients with 90% or greater continuous drug coverage totaled 65% of the study population when a 14-day break in coverage was allowed and 71% for a 30-day break. Logistic regression models indicated that a patient was more likely to have 90% or greater coverage if they were older, no depression, resided in Tennessee or Illinois, were in a union or employed. All the models indicated that patients were less likely to have 90% coverage if they had any diagnosis for complications commonly associated with MS, other comorbid diagnoses, or resided in Georgia or Michigan and for some of the models, if they were enrolled in certain insurance plans. **Conclusions:** The majority of MS patients were achieving 90% or greater continuous utilization of immunomodulatory drugs from the time they began taking them. However, many patients did have breaks in coverage. In sum, the patterns in the use of immunomodulatory drugs are generally favorable, but still fall short of the goal of long-term, continuous utilization.

**Disclosures:** R Constantine has nothing to disclose.

**Funding:** National Multiple Sclerosis Society

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### **P3 The effect of interferon (IFN) treatment on location of relapsing-remitting multiple sclerosis (RRMS) relapse**

SR Deen<sup>1</sup>, A High<sup>2</sup> and E Waubant<sup>3</sup>

**Keywords:** blood brain barrier; disease modifying therapy; glatiramer acetate; interferon; relapse location; spinal cord

**Background:** IFN prevents a higher percentage of lesions on brain MRI scans than clinical exacerbations, whereas GA prevents both equally. As brain MRI scans only reflect brain involvement, and clinical exacerbations reflect both brain and spinal cord involvement, the discrepancy seen with IFN could be due to IFN preventing a higher percentage of brain versus spinal cord lesions. If this were true, we would expect a higher proportion of relapses during (versus before) IFN treatment to be located in the spinal cord, but no such difference with GA. **Objectives:** To compare the location of clinical relapse (brain versus spinal cord) before versus during IFN therapy, using glatiramer acetate (GA) as a control. **Methods:** The authors identified RRMS patients from the UCSF MS Center database who underwent  $\geq 6$  months of continuous IFN or GA treatment and had at least one relapse the year before treatment and one relapse during treatment. Relapses were coded as affecting the spinal cord or brain (cerebrum, optic nerve, brainstem/cerebellum). Polyregional relapses were excluded. Relapse locations before versus during IFN and GA treatment were compared (McNemar's analysis). **Results:** The 100 IFN and 33 GA patients did not differ in age at symptom onset (31 years), sex, race, distribution of pre-treatment relapses (59% sc, 41% brain) or average time from symptom onset to treatment start (6.0 years), pre-treatment relapse to treatment start (119 days) or treatment start to during-treatment relapse (1.7 years). The proportion of relapses in the spinal cord was higher than expected during IFN treatment ( $p=0.03$ ), but not GA ( $p=0.8$ ). Results did not change after excluding relapses within the first 3 months of treatment. **Conclusions:** The data, though limited by the smaller number of GA patients, suggest a preferential efficacy of IFN in the brain versus spinal cord. This may be mediated by IFN differentially affecting the blood brain versus blood spinal cord barrier.

**Disclosures:** SR Deen has nothing to disclose.

**Funding:** National Multiple Sclerosis Society

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### **P4 Results of a phase I trial of pioglitazone in RRMS patients**

DL Feinstein<sup>1</sup>, DK Shukla<sup>1</sup>, DD Skias<sup>2</sup>, G Katsamakis<sup>3</sup>, D Stefoski<sup>4</sup>, GT Stebbins<sup>4</sup>, D Jeffery<sup>5</sup> and CC Kaiser<sup>1</sup>

**Keywords:** cytokines; DTI; grey matter atrophy; phase 1 clinical trial; pioglitazone; PPARgamma

**Background:** Actos® is FDA-approved for treatment of type 2 diabetes based on its insulin sensitizing effects. Actos also exerts anti-inflammatory effects in T-cells and glial cells; increases glial metabolism; and is neuroprotective. In EAE Actos reduced disease incidence and severity. In view of its good safety profile, we tested the effect of Actos in a cohort of RRMS patients. **Objectives:** Based on preliminary studies we tested if treatment with Actos (pioglitazone HCl), an agonist of the Peroxisome Proliferator Activated Receptor Gamma (PPAR $\gamma$ ) could provide benefit in RRMS patients. **Methods:** We carried out a one-year, double-blinded, placebo-controlled Phase I trial of Actos (30 mg daily, p.o.) as an add-on in RRMS patients taking Avonex®. Primary outcomes were safety (liver function, Gd enhancement). Secondary outcomes were changes in FLAIR lesion burden, white and grey matter atrophy, and MSFC or EDSS. Other analyses included DTI, fMRI, and measurements of serum cytokine levels. **Results:** Twenty two patients completed this trial. There were no indications of liver toxicity, edema, or increased Gd-enhancing lesions. The average EDSS at baseline was  $3.1 \pm 0.6$  and did not change over 1 year. The average MSFC score increased in both groups; but the improvement was only significant in the Actos group. Total FLAIR lesion volume increased 7% in the placebo group; and was reduced 6% in the Actos group ( $p=0.06$ ). Grey matter atrophy was significantly reduced by Actos (from 5% to 2.5%;  $p<0.05$ ). Results of DTI data for effects on white matter integrity, and of cytokine analyses will be presented. **Conclusions:** Daily Actos (30 mg p.o.) is tolerated in RRMS patients and there are indications that it may reduce disease progression assessed by FLAIR volume and grey matter atrophy. Further testing in MS patients is therefore warranted.

**Disclosures:** GlaxoSmithKline for consulting services, Biogen Idec for speaking.

**Funding:** Takeda Pharmaceuticals North America

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### **P5 Natalizumab discontinuation predisposes to serious infusion related reactions and antibody formation**

*JF Foley*

**Keywords:** adverse event; antibody formation; infusion reaction; natalizumab; natalizumab discontinuation; systemic hypersensitivity

**Background:** Treatment discontinuation of other monoclonal antibodies has been described as predisposing to serious infusion related reaction (SIRR) on rechallenge, with many of these patients found to be antibody positive. A serious systemic hypersensitivity rate of 0.8% to natalizumab was found in the AFFIRM trial. **Objectives:** This analysis was undertaken to assess the effect of natalizumab discontinuation and rechallenge on the subsequent occurrence of serious infusion reactions and antibody formation. **Methods:** Prospective analysis of 128 patients not previously exposed to natalizumab was compared to a series of 34 patients with prior exposure. SIRRs were tabulated. Antibody status was assessed in all patients with serious reactions. **Results:** A total of seven SIRRs were identified. Six of the seven patients had received one to three doses of natalizumab 17 to 20 months prior, yielding a SIRR rate of 6/34 (17.6%). A single patient had not received prior medication (1/128 patients, 0.78%). Antibody positivity was seen in 6/7 patients (85.7%) with a single previously treated patient antibody negative. **Conclusions:** SIRRs were highly correlated to prior transient exposure to natalizumab as well as antibody positivity. Natalizumab antibodies should be obtained in all patients prior to rechallenge. Natalizumab is well tolerated in the population not previously exposed to medication with our SIRR rate nearly identical to that seen in the AFFIRM trial. The relationship of temporary drug discontinuation to SIRR and antibody formation requires further study.

**Disclosures:** J Foley is a consultant for and has received honoraria from Merck Pharmaceuticals, Biogen Idec and TEVA Pharmaceuticals.

**Funding:** No funding reported

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### **P6 Risk tolerance in multiple sclerosis patients**

*RJ Fox<sup>1</sup>, S Kolattukudy<sup>1</sup>, MW Kattan<sup>2</sup> and D Miller<sup>1</sup>*

**Keywords:** death; natalizumab; progressive multifocal leukoencephalopathy; risk tolerance; standard gamble; survey

**Background:** Several approved and developing MS therapies appear very effective but have significant risks. However, there is little understanding of patient acceptance of effective but risky therapies. We studied risk tolerance in MS patients using similar methods to those used in oncology. **Objectives:** Evaluate multiple sclerosis (MS) patient risk tolerance of potentially fatal therapies. **Methods:** We performed a telephone survey of 128 MS patients from our center who planned to begin natalizumab prior to its withdrawal in 2005. We used standard gamble paradigms to assess maximum acceptable risk of death in the following hypothetical therapeutic scenarios: cure MS and related symptoms; cure MS and related symptoms after 1 year of continued disease progression; and expected response to a currently-available treatment (natalizumab, based on Phase III trial results). Wilcoxon test and Spearman rank correlations assessed potential influences to risk tolerance, including current disability, quality of life, time since diagnosis, presence of dependants in the home, and prior receipt of natalizumab. **Results:** Median acceptable risk of death was as follows: cure MS: 1-in-100; cure MS after disease progression: 1-in-10; two-thirds reduction in relapses and 42% slowing of disability (natalizumab trial results): 1-in-1000. 14% of patients would accept a risk of death as high as 1-in-2 in order to cure their MS, while 18% of patients were unwilling to accept any risk of death. Increased risk tolerance was associated with increased disability, worse self-reported quality of life, and the absence of dependents in the home (all  $p < 0.02$ ). A nomogram for predicting MS patient risk tolerance was developed. **Conclusions:** MS patients will often accept a high risk of death in order to treat their disease. Several factors predict this willingness to accept risk. These studies can help guide clinicians in understanding the risk tolerance of their MS patients.

**Disclosures:** R Fox has received speaking and consulting honoraria from Biogen Idec, Genentech, Teva Neuroscience and Serono. D Miller has received speaking honoraria from Biogen Idec.

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**Funding:** No funding reported

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### **P7 Impact of switching first-line disease-modifying therapy (DMT) after failure in relapsing-remitting multiple sclerosis (RRMS)**

*A Gajofatto<sup>1</sup>, E Waubant<sup>2</sup> and A High<sup>3</sup>*

**Keywords:** DMT; glatiramer acetate; interferon beta 1; RRMS; therapy switch; treatment failure

**Background:** DMTs have limited efficacy in a significant proportion of RRMS patients. There is no consensus on the treatment options for non-responders. **Objectives:** To determine whether RRMS course is influenced by first-line DMT switch after failure. **Methods:** RRMS patients who received interferon-beta (IFNB) or glatiramer acetate (GA) monotherapy for at least 12 months as their initial DMT were identified in the UCSF MS Clinic database, where data are prospectively entered. Subjects who failed to respond and switched to another DMT for at least 12 months were selected. Treatment change impact was measured comparing the annualized relapse rate (ARR) before and after the switch. **Results:** Of the 367 RRMS patients on IFNB (n=315) or GA (n=52) for at least 12 months, 111 (30%) were declared non-responders, based on relapse frequency, disability progression or MRI activity, alone or in combination. Seventy-one non-responders switched to another IFNB or to GA, 24 added on or switched to a second-line DMT and 16 discontinued treatment. Forty-four IFNB non-responders switched to another IFNB (IFNB/IFNB') and 15 to GA (IFNB/GA); twelve GA non-responders switched to IFNB (GA/IFNB). These three groups did not differ regarding ethnicity (77% Caucasian, 7% African-American, 6% Hispanic, 3% Asian, 7% other/unknown), mean age (36 years), median disease duration (4 years) and median EDSS score (1.5) when first treated, mean ARR in the two years preceding first treatment (0.68), mean duration of first (1059 days) and second (1169 days) treatment periods or median interval between treatments (1 day). The sex ratio was 1.1 (23F:21M), 2.0 (10F:5M) and 5.0 (10F:2M) for IFNB/IFNB', IFNB/GA and GA/IFNB groups respectively (p=0.09). After switching, the mean ARR decreased in all groups (IFNB/IFNB' from 0.56 to 0.20, p=0.002; IFNB/GA from 0.62 to 0.34, p=0.18; GA/IFNB from 0.50 to 0.11, p=0.01). **Conclusions:** Switching first-line DMT in non-responders may be a successful strategy to impact RRMS course.

**Disclosures:** A Gajofatto has nothing to disclose.

**Funding:** Nancy Davis Foundation

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### **P8 Efficacy, safety and tolerability of 500 µg versus 250 µg interferon beta-1b versus glatiramer acetate in patients with relapsing-remitting multiple sclerosis (the BEYOND study): baseline patient characteristics**

*P O'Connor<sup>1</sup>, M Filippi<sup>2</sup>, BG Arnason<sup>3</sup>, G Comi<sup>4</sup>, S Cook<sup>5</sup>, DS Goodin<sup>6</sup>, HP Hartung<sup>7</sup>, D Jeffery<sup>8</sup>, L Kappos<sup>9</sup>, V Filipov<sup>10</sup>, M Groth<sup>10</sup>, C Kraus<sup>10</sup>, R Sandbrink<sup>10</sup> and T Bogumil<sup>10</sup>*

**Keywords:** baseline characteristics; beyond; clinical trial; glatiramer acetate; interferon-beta 1b; RRMS

**Background:** The BEYOND Phase III study is designed to show whether using a higher dose (500 µg) than the currently approved 250 µg dose of IFNB-1b results in greater efficacy, while still having an acceptable safety and tolerability profile. **Objectives:** To present the baseline characteristics of the patients who have enrolled in the BEYOND (Betaferon®/Betaseron® Efficacy Yielding Outcomes of a New Dose) study. **Methods:** The BEYOND study is a Phase III, multicenter, randomized, parallel-group study that compares the efficacy, safety and tolerability of interferon beta-1b (IFNB-1b) 500 µg versus IFNB-1b 250 µg versus glatiramer acetate 20 mg in treatment-naïve patients with RRMS. **Results:** 2244 patients have been randomized at 198 sites in 26 countries world-wide. Analysis of baseline data revealed that the study population is representative for present multinational trials in RRMS. Patients from North America, Western Europe, and Australia tended to be older yet have a shorter duration of disease and a lower MRI lesion load than patients from Eastern Europe and South America. Baseline disease activity measures (relapses in the year prior to enrolment, proportion with a Gd-enhancing MRI), which can be assumed to be the most important determinants for efficacy outcomes, are very similar across the trial. **Conclusions:** The BEYOND study will provide important comparative data on the efficacy of IFNB-1b and glatiramer acetate. Patients from Eastern Europe and South America appear to have a higher disease burden but similar disease activity compared to those from other geographic areas. Whether this will have any effect on the relative efficacy of the

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study drugs remains to be seen. The study results will become available end of 2007.

**Disclosures:** P O'Connor has received honoraria for speaking and serving on advisory boards from: Biogen Idec, Teva, Schering, Serono, Novartis, Sanofi-Aventis, Genentech, and Bio-MS. He has also received research funding from: Biogen Idec, Schering, Genentech, Bio-MS, Novartis, and Sanofi-Aventis. M Filippi has received honoraria and research grant support for consulting and speaking from: Schering AG. B Arnason has received honoraria for serving on advisory boards from: Berlex Inc. G Comi has received honoraria for consulting and speaking from: Schering AG, Industria Farmaceutica Serono and Sanofi-Aventis. S Cook has received honoraria for consulting, serving on a scientific advisory board, speaking from: Serono, Pfizer, Teva and Berlex Inc. He has also received personal compensation for serving on the editorial board of Reviews in Neurological Diseases and has received research grant support from: Abbott, Schering AG and Berlex Inc. D Goodin has participated in clinical trials sponsored by: Ares-Serono, Berlex Laboratories, Biogen Idec, Immunex, and Teva Neuroscience. He has also participated in research sponsored by: Ares-Serono, Berlex Laboratories, Teva-Marion Partners, and Biogen. H Hartung has received honoraria for consulting services and speaking from: Schering AG, Biogen Idec, Teva and Serono and has received research grants from: Schering AG, Teva, Biogen Idec and Serono. D Jeffery received honoraria for speaking and consulting from: Berlex Inc., Biogen, Teva, Serono, Pfizer, GlaxoSmithKline and Icagen and has received research grants for conducting clinical trials from: Berlex Inc., Biogen, Teva, Serono, Pfizer and GlaxoSmithKline. L Kappos has served on advisory boards, received honoraria from and participated in research sponsored by: Abbott, Bayer, Bayhill, Berlex, Biogen Idec, Boehringer Ingelheim, Bristol Myers, Centocor, Eisai, Elan, Genzyme, Glaxo Smith Kline, Neurocrine, Novartis, Sanofi Aventis, Schering, Serono, Roche, Teva, UCB and Wyeth. All payments received have been used to support research in his department. V Filipi, M. Groth, C Kraus and R Sandbrink are salaried employees of Schering AG. T Bogumil is a salaried employee of Berlex Inc.

**Funding:** Bayer Schering Pharma AG, Berlex Laboratories Inc.

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### **P9 Pharmacogenomics of interferon- $\beta$ therapy: evidence for the existence of pharmacodynamic differences within multiple sclerosis**

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**Keywords:** biomarkers; genomics; IFN- $\beta$  therapy; microarray; peripheral blood; pharmacodynamics

**Background:** Multiple sclerosis (MS) has a heterogeneous nature, which is reflected in the clinical presentation. Previously we demonstrated that gene expression signatures in MS differ between patients. A subgroup of patients was characterized by an increased expression of an immune defense response gene set, including a type-I INF response signature. **Objectives:** Here we investigated pre- and post-IFN- $\beta$  treatment gene expression patterns in RRMS patients to identify preexisting and/or drug-induced signatures that could explain the clinical response to IFN- $\beta$ . Furthermore we investigated the correlation of the *in vitro* response to IFN- $\beta$  in peripheral blood mononuclear cells (PBMC) from RRMS patients with the *in vivo* gene expression patterns after IFN- $\beta$  therapy. **Methods:** Peripheral blood samples from 16 RRMS patients were collected before (t=0) and one month after treatment (t=1). We used cDNA microarrays to investigate the *in vivo* gene expression profiles in relation to IFN- $\beta$  therapy. PBMC from the same patients at t=0 were stimulated 4 hr with 10 U IFN- $\beta$ . The transcript level of a selection of IFN-response genes was measured by quantitative real-time PCR. **Results:** Patients receiving IFN- $\beta$  treatment showed a marked up-regulation of IFN-response genes. Interestingly, the stimulation index of IFN-response genes differed between patients. The increase in expression of IFN-response genes after IFN- $\beta$  therapy was negatively correlated with the expression level of these genes at t=0 ( $r = -0.67$ ,  $p = 0.005$ ). In addition, the *in vivo* stimulation index of IFN-response genes correlated with the findings from *in vitro* exposure of PBMC to IFN- $\beta$  ( $r = 0.75$ ,  $p = 0.005$ ). Hence, the outcome of the *in vitro* response to IFN- $\beta$  is a good indicator for the *in vivo* IFN- $\beta$

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response. **Conclusions:** The biological response to IFN- $\beta$  therapy is related to the activity of IFN-response genes before therapy. Furthermore, the *in vivo* response to IFN- $\beta$  could be mimicked by *in vitro* stimulation of PBMC prior to treatment.

**Disclosures:** S Vosslander has nothing to disclose.

**Funding:** Dutch MS Research Foundation

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### **P10 Long-term outcome of minocycline in relapsing-remitting multiple sclerosis**

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**Keywords:** long-term; minocycline; MRI; outcome; relapsing-remitting; treatment

**Background:** Current MS therapies are only partially effective, and not all patients respond well. Minocycline has been shown to have a wide range of immunomodulatory properties. Minocycline treatment in experimental allergic encephalomyelitis delays disease course, suppresses disease activity and severity. **Objectives:** To evaluate safety, tolerability, and MRI impact of minocycline in relapsing-remitting MS. **Methods:** Ten patients were treated with minocycline for 36 months after a 3 month run-in period. Monthly 3T MRI was performed during the run-in and first 6 months of treatment, then at 12, 24, and 36 months during a 30 month pre-planned extension. Clinical assessments were completed at 3 month intervals until 6 months on treatment then at 6 month intervals. **Results:** Treatment was safe and well tolerated. The annualized relapse rate was 1.2 during the run-in and 0.25 during 3 years on treatment ( $p=NS$ ). The proportion of active scans was lower during the first 6 months of treatment (5.6%,  $p<0.001$ ) and during the extension (8.7%,  $p=0.002$ ) than during the run-in (47.5%). T2 lesion volume decreased during treatment compared with baseline. To evaluate evolution of contrast enhancing lesions into black holes twelve lesions present at months 0 and one were examined (6 concurrently hypointense, 6 isointense on T1). Three were new as they were NAWM one month earlier; none of these became black holes. Of the 9 old lesions (abnormal T2 on the previous scan) 4 were isointense on T1; 5 were hypointense. Only 3 of the 9 old lesions (all hypointense) evolved into permanent black holes by month 36, all in the same patient. There was a continuous decline in annualized atrophy par-

ticularly during the third year ( $-0.37\%$ ). **Conclusions:** This trial suggests that minocycline is safe and potentially beneficial in relapsing-remitting MS and supports further investigation of its efficacy.

**Disclosures:** Y Zhang has nothing to disclose.

**Funding:** Interdisciplinary Health Research Team (IHRT) grant from the Canadian Institutes of Health Research (CIHR)

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### **Epidemiology/Genetics**

#### **P11 Clinically silent multiple sclerosis: description of a patient cohort without symptoms typical of MS but abnormal brain magnetic resonance imaging**

J Derwenskus and BA Cohen

**Keywords:** abnormal MRI; asymptomatic MS; McDonald criteria; MS natural history; predictors of MS; treatment decision

**Background:** MS remains a clinical diagnosis. The McDonald criteria apply MRI requirements for dissemination in space and time. Rarely do individuals present with an abnormal MRI typical of MS without neurological symptoms. Currently no consensus exists regarding follow-up or treatment of these individuals. **Objectives:** To review patients with an abnormal brain MRI who have not had prior neurological symptoms typical for MS and determine predictors for developing MS over time. **Methods:** 10 patients meeting these criteria from the Northwestern Comprehensive MS Program were identified. Charts were reviewed to determine the reason for the initial brain MRI, development of clinical symptoms, serial neurological examination, and ancillary testing including spine MRI, evoked potentials, and CSF analysis. MRI scans were reviewed to determine if criteria for dissemination in space and time were fulfilled. **Results:** All patients were female with an average age of 42 (range 30–56) at presentation. Reasons for neuroimaging included trauma, migraine, headache, seizure, pituitary microadenoma, hearing loss, control subject in a MRI study, and paresthesias with suspected peripheral etiology. All initial scans met Barkhof's criteria for dissemination in space. Average length of follow-up was 30 (range 0–70) months. Over time, MRI

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scans changed in 3 patients and only one had gadolinium-enhancing lesions visualized. Spinal cord imaging was abnormal in 3 of 4 patients, spinal fluid abnormal in 5 of 8 patients, and evoked potentials abnormal in 2 of 8 patients. Considering only the individuals with at least one year of follow-up, 3/6 were diagnosed with MS. All of these individuals were under 50 years of age at presentation. **Conclusions:** The current study suggests patients with atypical symptoms but typical MRI features under the age of 50 are more likely to develop MS. Consideration could be given to starting a disease-modifying agent in such individuals, while serial imaging and follow-up may be preferred in patients over 50.

**Disclosures:** J Derwenskus has nothing to disclose.

**Funding:** No funding reported

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## **P12 Survival analysis predicts that nearly half of people with MS become unemployed within 15 years of MS onset**

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**Keywords:** cost of illness; education; employment; glatiramer acetate; interferon beta; survival analysis

**Background:** Employment is often lost due to MS. Frequency estimates vary but several factors associated with greater unemployment have been identified.

**Objectives:** Our objective was to characterize the time to onset of unemployment using survival analysis according to disease and socio-demographic factors that influence employment. **Methods:** Date of onset of unemployment was obtained from participants in a study of risk factors and consequences of MS undertaken at two Canadian MS Clinics (Calgary and Montreal). Subjects who stopped working before MS onset were excluded. Survival (continuing employment) was determined using Kaplan-Meier analysis. Subjects were removed from the population at risk on the date they reported stopping work. Observations were censored on the date of the questionnaire. **Results:** Two and a half percent (n=61) of 2489 subjects had never been employed; 5.3% (n=133) were not employed after MS onset, and 3.9% (n=98) had incomplete data. Therefore the survival analyses included 2197 patients. Men comprised 24% (518) of the sample; women comprised 76% (1679). Mean age of MS onset was 32 years (range 6–64).

Mean age at baseline was 45 years (range 16–83). Survival analysis predicted that 45.8% (95% CI: 48.4%–43.2%) will become unemployed within 15 years of MS onset. Survival was decreased with less education, MS onset after age 44, progressive course at onset, and in men without a partner. Gender, otherwise, and site, did not effect survival. Evaluation of the impact of disease modifying therapy (DMT) on survival is ongoing. **Conclusions:** This employment data will improve estimates of the cost of MS and provide better information about the consequences of MS. Clarification of factors that impact employment and partial employment, and assessment of quality of life before and after lost employment, are required. Employment may prove to be a useful outcome to measure the long-term effectiveness of DMT.

**Disclosures:** LM Metz has nothing to disclose.

**Funding:** Canadian Institute of Health Research

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## **P13 Clinical course and outcome of transverse myelitis in relapsing neuromyelitis optica**

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**Keywords:** Brazil; epidemiology; MRI; neuromyelitis optica; relapsing clinical course; transverse myelitis

**Background:** Relapsing NMO is a chronic disease characterized by transverse myelitis (TM) and optic neuritis followed by several acute relapses restricted to the optic nerve and spinal cord. Very few data were published about the characteristics of the motor neurological impairment in different phases of the disease. **Objectives:** To describe the spinal cord involvement in a large cohort of relapsing NMO. **Methods:** An ambidirectional was conducted in a referral center for MS treatment in Rio de Janeiro (Brazil) analyzing 60 patients (6 male:54 female, 25 white:35 African descendents) fulfilling NMO Mayo Clinic (1999) criteria, followed between 1985 and 2004. **Results:** Complete TM was the presenting event in 20 cases characterized by paraplegia (14), tetraplegia (5), hemiplegia (1); 7 patients had sensorial deficits in lower limbs with marked thoracic level. Two patients had TM+ON simultaneously. The median time between the index events was 17

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months (1 day–20 years). In a median time of eight years (0.5–30) 380 acute events occurred (58.9% TM and 10% TM+ON). The median number of events per patient was five (3–18). The motor impairment was analyzed at the first TM and at last evaluation. Severe deficit occurred in 50% at acute phase, 11.6% remained after remission and 23% at the last follow up. The median motor score at acute phase was 3 and at last follow up was 2. There were 14 deaths (12 Afro:2 white). The median survival was 8 years (1–30). **Conclusions:** The most characteristic finding of the TM in RNMO syndrome at onset is a severe and acute motor syndrome at lower limbs, with a high remission rate after treatment and a mild impairment at the last evaluation. The cause of death was related to cervical damage with tetraplegia and respiratory failure. Considering the ethnic characteristics of the population, mortality was significantly greater in Afro Brazilian patients.

**Disclosures:** RM Papais Alvarenga has nothing to disclose.

**Funding:** No funding reported

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#### **P14 Integrating environmental and genetic effects on susceptibility to multiple sclerosis**

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**Keywords:** DRB1\*1501; ebna-1; EBV; Epstein-Barr virus; HLA; infectious mononucleosis

**Background:** High serum titers of antibodies to the Epstein-Barr virus (EBV) are a strong risk factor for multiple sclerosis (MS), but it remains unclear whether this association is explained by genetic factors. **Objectives:** To determine whether the HLA-DRB1\*1501 haplotype, which is the strongest predictor of MS risk among individuals of European origin in the U.S., correlates with anti-EBV titers and whether it explains the association between these titers and MS risk. **Methods:** Nested case-control study among participants in the Nurses' Health Study and Nurses' Health Study II. A total of 143 cases and matched controls, with complete genetic and antibody data, were included in the analyses. The HLA-DRB1\*1501 haplotype was determined by genotyping SNP rs3135391, a previously validated marker of the DRB1\*1501 allele. Anti-EBV and anti-CMV antibodies were determined by indirect immunofluorescence or anticomplement immunofluorescence.

Logistic regression models were used to determine the relative risks (RRs) and 95% confidence intervals (95% CIs) of MS associated with a 4-fold increase in anti-EBV or anti-CMV antibody titers. Additionally, likelihood ratio tests were used to assess a potential interaction between HLA-DRB1\*1501 and anti-EBV antibody titers. **Results:** The risk of MS associated with a four-fold increase in anti-EBNA1 antibody titers was nearly identical amongst HLA-DRB1\*1501 positive (RR=1.59; CI: 1.14, 2.22) and HLA-DRB1\*1501 negative (RR=1.56; CI: 1.15, 2.11) women. The similar RRs amongst those with and without the DRB1\*1501 risk haplotype were consistent amongst all anti-EBV and anti-CMV antibody titers measured. Although there was no significant interaction between anti-EBV or anti-CMV antibody titers and HLA-DRB1\*1501, amongst women with MS, there was evidence of increased anti-EBNA1 titer for those positive for HLA-DRB1\*1501 (p=0.01). **Conclusions:** Plasma titers of anti-EBNA1 antibodies are a risk factor for MS independently of HLA-DRB1\*1501. An interaction between DRB1\*1501 and anti-EBNA1 titers cannot be excluded.

**Disclosures:** KC Simon has nothing to disclose.

**Funding:** No funding reported

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#### **P15 Clinical characteristics of African Americans with MS: the VA Longitudinal MS Study**

*MT Wallin<sup>1</sup>, W Culpepper<sup>2</sup>, W Royal<sup>3</sup>, R Kane<sup>3</sup>, D Bradham<sup>2</sup>, H Maloni<sup>4</sup>, M Koehler<sup>5</sup>, W Tyor<sup>6</sup>, M McCarthy<sup>7</sup>, J Harrow<sup>8</sup>, P Coffey<sup>8</sup>, J Shieh<sup>9</sup> and C Bever<sup>3</sup> and the VALOMS Investigators*

**Keywords:** African Americans; disability; epidemiology; risk factors; treatment; veterans

**Background:** Recent studies have shown that African Americans (AA) with MS are at increased risk for severe disability and increased mortality compared with other race groups. However, few studies have been based on validated longitudinal data. **Objectives:** In this report we compare the clinical characteristics of AA with MS

to Caucasian Americans (CA) with MS enrolled in the VA Longitudinal MS Study (VALOMS). **Methods:** VALOMS is a population-based multi-center study designed to evaluate morbidity and treatment outcomes in patients with MS. Data were collected from baseline assessments of patients enrolled in the VALOMS over the past 18 months (N=69; AA=37, CA=32) at six VA Medical Centers. Patients were recruited from a randomized list of all patients with MS at a particular facility. **Results:** The proportion of males and females was not significantly different by race. Age at first symptom onset was younger for AA compared to CA (36 yr vs. 32 yr;  $p=0.024$ ). There was no significant difference between AA and CA in MS subtype. Time from initial symptom onset to diagnosis was similar between AA and CA, whereas time from diagnosis to treatment with disease modifying drugs was greater for AA vs. CA (47 vs. 29 months) but was not statistically different. Time to conversion to SPMS was shorter in AA vs. CA (7.2 vs. 4.1 years) but only marginally significant ( $p=0.08$ ). A significantly larger proportion of AAs had reached an EDSS of 6.0 by 16 years than CAs (0.607 vs. 0.462,  $p<0.05$ ). **Conclusions:** In this initial report from the VALOMS, AA with MS have a more rapid progression in disease course compared with CA. Earlier initiation of disease-modifying drugs after diagnosis was seen in CA vs. AA. Time to diagnosis after initial symptoms and current use of disease-modifying drugs was similar between groups.

**Disclosures:** MT Wallin has nothing to disclose.

**Funding:** VA MS Center of Excellence—East

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## Experimental Disease Models

### P16 Antibody screen of insertional zebrafish mutants identifies novel genes involved in myelination

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**Keywords:** genetic screen; immunocytochemistry; myelination; oligodendrocytes; wd-repeat; zebrafish

**Background:** Genetic animal models have been effective at identifying genes involved in biological processes. Screens for defects in myelination have identified genes involved in myelination in the zebrafish, an important vertebrate genetic model (Kasakova et al. 2006 Dev Biol, Pogoda et al., 2006, Dev Biol). Studying the myelination process in the model organism can give rise to information involving the demyelination of MS.

**Objectives:** To determine genes necessary for myelination in the zebrafish CNS. **Methods:** Nearly 500 mutant zebrafish lines were created by insertional mutagenesis which includes mutations in 335 identified genes (Amsterdam et al. 2004 PNAS). From these mutant lines, 79 lines were selected based on criteria established in a pilot screen that identified genes involved in protein trafficking (VPS20 and VPS2) and RNA processing (Tho2). Therefore, lines lethal before 4 days post fertilization (dpf; a time myelin is abundant) or that exhibited necrosis in the brain were not collected. Immunocytochemistry for myelin protein zero (P0) was used to determine the presence of myelination and oligodendrocytes in the hindbrain. In addition, total RNA was isolated from wild type embryos in a developmental series (3, 5, 7, 10 dpf) and adult brain for gene expression analysis of identified genes. **Results:** Currently, 7 mutant lines have alterations in the myelination pattern as detected with the P0 antibody. Two of these lines have defects in transcription factors (nrf and sox9a) and two have defects in novel WD40 proteins (2246 and 3630A). The 3630A gene (WDR36) is expressed as early as 24 hours post fertilization (hpf) through 5 dpf, but cannot be detected in the adult brain. Three genes were house-keeping genes involved in RNA processing or protein trafficking. **Conclusions:** Screening insertionally mutated zebrafish lines has determined that two novel WD-40 proteins and the transcription factors, nrf and sox9a are implicated in myelination in the developing zebrafish.

**Disclosures:** SJ Adams has nothing to disclose.

**Funding:** National Multiple Sclerosis Society grant RG 3602-A-2

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### **P17 Pregnancy modulates precursor cell proliferation in a murine model of focal demyelination**

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**Keywords:** gestation; lysolecithin; mitosis; myelination; neural stem cells; oligodendrocyte

**Background:** Recently Gregg et al. (*J. Neurosci.*, in press) have shown that demyelinating lesions are reduced in size in pregnant mice, apparently due to increased oligodendrocyte generation and enhanced remyelination. **Objectives:** To begin to identify the responsible precursor population(s), we analyzed the time course of post-lesion cellular proliferation by immunohistochemistry to phospho-histone H3, the expression of which is tightly correlated with chromosome condensation during mitosis. **Methods:** 1% lysolecithin was stereotaxically injected unilaterally into the corpus callosum of female Swiss Webster mice, animals sacrificed at intervals from 1 to 15 days later, and lesions identified using an antibody to myelin basic protein. **Results:** In non-pregnant mice, the density of peri-lesion mitotic cells peaked 2 days after injection and returned to baseline by day 7. In pregnant mice lesioned on gestational day (GD) 7, a similar proliferative effect was seen at day 2, but this was followed by a larger response, double in magnitude, on day 4. The density of mitotic cells on day 4 after lysolecithin in GD7, GD14, and non-pregnant mice was significantly different ( $p < 0.001$ ; one-way ANOVA), with the density in GD7 significantly greater than in GD14 and non-pregnant mice ( $p < 0.02$  and  $p = 0.0002$ , respectively; Fisher PLSD). In a separate set of GD7 mice, BrdU was injected either on day 2 or day 4 after lysolecithin and co-localized on day 7 to cells immunostained with Olig1; over 70% of day 2 BrdU+ cells were also Olig1+ on day 7, whereas less than 40% of day 4 cells later stained for Olig1. These percentages were similar in non-pregnant mice. **Conclusions:** Our data hint that different precursor cell types may be responding either early or late after lysolecithin, with the late-responding type primarily accounting for the beneficial effect of pregnancy on lesion repair. Oligodendrocyte precursor cells and neural stem cells are two candidate populations for further study.

**Disclosures:** P Riskind is a speaker for Biogen Idec, Teva Neurosciences, Berlex and EMD Serono, has consulted for Genentech, Biogen Idec, Teva Neurosciences and Serono, and has received grant support from Biogen Idec and Teva Neurosciences.

**Funding:** National Multiple Sclerosis Society Pilot Grant (pp1158)

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### **P18 Cytokine/neuroantigen fusion proteins as tolerogenic antigen-specific vaccines: a novel therapy for autoimmune disease of CNS myelin**

*MD Mannie and DJ Abbott*

**Keywords:** cytokine/cytokine receptor; encephalitogenic peptide; experimental autoimmune encephalomyelitis; immune regulation; tolerance; vaccination

**Background:** Cytokine/neuroantigen (NAg) fusion proteins may represent a means to develop safe and effective antigen-specific tolerogens for therapy of multiple sclerosis. **Objectives:** The primary objective was to test the concept of cytokine/NAg fusion proteins as tolerogenic, antigen-specific vaccines. **Methods:** Cytokine/NAg fusion proteins were comprised of IL1-RA, IL-2, IL-4, IL-10, IL-13, or IL-16 as the cytokine domain and the dominant encephalitogenic determinant of myelin basic protein as the NAg domain. These fusion proteins were tested for inhibition of experimental autoimmune encephalomyelitis (EAE) in Lewis rats. These fusion proteins were administered to rats every 1–2 weeks for a total of three injections, and then at least one week later, rats were challenged with NAg in CFA. **Results:** Cytokine/NAg fusion proteins exhibited the following rank order of activity for induction of tolerance to encephalitogenic challenge: NAgIL16 > IL2NAg > IL1RA/NAg, IL13NAg > IL4NAg, IL10NAg, GPMBP, encephalitogenic peptide (GP69–88), saline. The two cytokine/NAg fusion proteins exhibiting the strongest tolerogenic activity (NAgIL16 and IL2NAg) also inhibited EAE when administered after encephalitogenic challenge during onset of EAE. In both pre-challenge and post-challenge treatment regimens, NAgIL16 and IL2NAg required covalent linkage of cytokine and NAg for tolerogenic activity. The requirement for covalent linkage was consistent with a mechanism by which the

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cytokine domain targeted the NAg to the MHC class II antigen processing pathway of tolerogenic APC. **Conclusions:** In conclusion, cytokine/NAg tolerogenic vaccines have special promise as antigen-specific therapies for CNS autoimmune disease. These tolerogenic vaccines would be predicted to inhibit pathogenic autoreactive clones without impairing adaptive immune responses against infectious agents.

**Disclosures:** MD Mannie has nothing to disclose.

**Funding:** National Multiple Sclerosis Society

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### **P19 Co-administration of AEG35169 and interferon- $\beta$ produces a synergistic reduction of clinical severity in experimental autoimmune encephalomyelitis**

*CS Moore<sup>1</sup>, ALO Hebb<sup>1</sup>, SJ Morris<sup>2</sup>, SP Narayanan<sup>1</sup>, JW Gillard<sup>2</sup>, JP Durkin<sup>2</sup> and GS Robertson<sup>3</sup>*

**Keywords:** antisense; apoptosis; EAE; inhibitors of apoptosis; interferon-beta; pharmacology

**Background:** Recent evidence suggests that interferon- $\beta$  (IFN- $\beta$ ) may reduce the progression of MS by promoting apoptosis of auto-reactive T cells. By facilitating the resolution of inflammation, this pro-apoptotic mechanism would decrease disease severity by reducing the number of auto-reactive immune cells. The most potent inhibitor of apoptosis (IAP) family member, known as X chromosome-linked inhibitor of apoptosis (XIAP), is elevated in immune cells isolated from peripheral blood of MS patients during relapses. Therapeutics that target XIAP and reduce levels of this protein may therefore prove beneficial in the treatment of MS. **Objectives:** Profile expression of several IAPs in whole blood, T cells, and peripheral blood mononuclear cells (PBMNs), using qRT-PCR and Western blotting, from mice with experimental autoimmune encephalomyelitis (EAE) and healthy controls. Perform dose response studies using AEG35169 (XIAP antisense) and IFN- $\beta$  to determine suboptimal doses of these compounds in the EAE model. Determine if concurrent administration of suboptimal doses of AEG35169 and IFN- $\beta$  synergistically decrease EAE severity. **Methods:** EAE was induced in C57/Bl6 mice using a 1:1 ratio of myelin oligodendrocyte glycoprotein (MOG<sub>35-55</sub>) and Complete Freund's Adjuvant. On Day 21, all mice were sacrificed, and whole blood was collected for RNA and protein analysis. In a separate series of experiments, suboptimal doses of IFN- $\beta$  and AEG35169 were determined for

reducing the severity of EAE. Mice were then either treated with vehicle, murine IFN- $\beta$  (7500 U/day, s.c.), AEG35169 (3 mg/kg/day, i.p.), or both compounds from Days 7–20, and scored daily for clinical signs of EAE. **Results:** XIAP mRNA (whole blood, T cell) and protein (PBMNs) were elevated in mice with EAE compared to healthy controls. Moreover, concurrent administration of suboptimal doses of murine IFN- $\beta$  (7500 U/day) and AEG35169 (3 mg/kg/day) resulted in a synergistic reduction of EAE severity. **Conclusions:** The therapeutic effectiveness of IFN- $\beta$  may be enhanced by treatments that decrease XIAP expression in the immune system.

**Disclosures:** SJ Morris, JW Gillard, and JP Durkin are employees of Aegera Therapeutics Inc. and stockholders with this company. JW Gillard is CSO of Aegera Therapeutics Inc. and JP Durkin is Vice-President of Drug Discovery with Aegera Therapeutics Inc.

**Funding:** MS Society of Canada and Aegera Therapeutics Inc.

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### **Imaging**

#### **P20 HRT contributes to neuronal health in postmenopausal women with MS**

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**Keywords:** estrogen; hormone replacement therapy; menopause; MR spectroscopy; n-acetylaspartate; neuroprotection

**Background:** In women with relapsing-remitting MS, oral estriol treatment is associated with a decrease in number and volume of gadolinium enhancing lesions on MRI. This suggests that estrogen products offer some degree of neuroprotection. To date, it has not been demonstrated if postmenopausal women with MS derive a disease-modifying benefit of hormone replacement therapy (HRT). **Objectives:** In a pilot study of postmenopausal women with MS, <sup>1</sup>H MR Spectroscopy (MRS) was used to compare the level of N-acetylaspartate (NAA)—a putative marker of neuronal integrity—in women with and without HRT. **Methods:** We evaluated 16 women with clinically stable MS—8 on HRT, 8 not on HRT. All localized spectroscopy data (STEAM: TE/TM/TR=20/10/4500 ms, 2048 points, 2000 Hz band-

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width, approx. 8 cm<sup>3</sup> volume, 128 averages) were collected on a 1.5 Tesla Magnetom Sonata whole-body MRI system. A volume of interest involving the corpus callosum and white matter adjacent to the lateral ventricles was used to collect water-suppressed spectra from the participants. MRS data were analyzed using LC Model. **Results:** The groups were comparable in age (mean=50.5 years,  $p=0.07$ ) and disability level as assessed by the MS Functional Composite (mean  $z=0.08$ ,  $p=0.72$ ). There was a significant difference ( $p<0.015$ ) in the NAA/Cr ratio between the women on HRT ( $1.91\pm0.39$ ) and the women not on HRT ( $1.41\pm0.32$ ). When age, level of disability, and use of immunomodulatory therapy were used as covariates in the statistical analysis, the significant difference between the groups remained. **Conclusions:** In this small sample, we demonstrated that use of exogenous estrogen may contribute to neuronal health as measured by MRS. These findings will need to be replicated in a larger sample to determine if the benefits of HRT outweigh the risks in this population.

**Disclosures:** K Fuchs has nothing to disclose.

**Funding:** Pilot Study Grant from the National MS Society

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## **P21 Comparison of lesion distribution in children with clinically isolated syndromes at risk for multiple sclerosis and adults with clinically definite multiple sclerosis**

*R Ghassemi<sup>1</sup>, S Antel<sup>1</sup>, SJ Francis<sup>1</sup>, B Banwell<sup>2</sup> and DL Arnold<sup>1</sup>*

**Keywords:** clinically isolated syndromes; demyelination in children; infratentorial plaques; lesion distribution; pediatric neuropathology; posterior fossa

**Background:** MRI data have contributed substantially to the early diagnosis of MS as well as to the understanding of its pathogenesis in the adult population. Although less well-studied, MRI findings in children with MS differ from the adult MS population. Quantitative MRI data in a pediatric population would allow further insight into these differences. **Objectives:** We compared the spatial distribution of demyelinating lesions in children with clinically isolated syndromes suggestive of MS (CIS) and adult patients with clinically

definite MS. **Methods:** T2- and T1-weighted lesions were segmented on MRIs from 58 children with CIS suggestive of MS, and 58 adults with relapsing-remitting multiple sclerosis. For each patient group, the incidence of supratentorial and infratentorial lesions was determined, lesion volumes were measured, and maps of average lesion distribution were generated. **Results:** Compared to the pediatric CIS group, adult MS patients were significantly more likely to exhibit a) supratentorial T2-weighted lesions (100% vs. 44.8%); b) infratentorial T2-weighted lesions (44.8% vs. 24.1%); and c) supratentorial T1-weighted lesions (93.1% vs. 22.4%). Supratentorial T2-weighted lesion volume was greater in the adult MS group than in the pediatric CIS group as a whole. However, among patients who had lesions, pediatric CIS patients exhibited significantly greater infratentorial T2-weighted and T1-weighted lesion volumes, and among patients who had T2-weighted infratentorial lesions, pediatric CIS patients were significantly more likely to exhibit intrapontine lesions compared to adult MS patients (78.6% vs. 38.5%). **Conclusions:** Pediatric patients with CIS are much more likely to develop pontine demyelinating lesions than adults with MS. This could reflect differences between children and adults in myelin maturation or in the immunobiology of MS.

**Disclosures:** R Ghassemi has nothing to disclose.

**Funding:** Multiple Sclerosis Scientific Research Foundation

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## **P22 Quantitative DCE MRI suggests widespread microvascular abnormalities in RR MS brain tissue**

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**Keywords:** blood volumes; brain tissue; DCE; lesions; quantitative MRI; sex

**Background:** Abnormal microvascular properties are likely to be the earliest expression of MS pathology detectable by imaging techniques. Recent histopathological findings suggest widespread tight-junction abnormalities in MS brain tissue. **Objectives:** To investigate MS disease- and sex-related differences in fractional blood volumes ( $v_b$ ) and rate constants ( $K^{\text{trans}}$ ) for contrast reagent (CR) extravasation. **Methods:** 12 healthy control (HC) subjects (7 women, 5 men) and 16

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RR-MS subjects (9 women, 7 men) provided informed consent before participating in this study. All MR data were collected at 4T.  $R_1$  maps were collected before, and at multiple times after, CR injection. ROIs were carefully selected from interior areas of non-acute MS lesions (WM lesions), and bilaterally from three internal NAGM and five NAWM structures.  $v_b$  and  $K^{\text{trans}}$  were determined from an equation for (transendothelial) two-site-exchange. MANCOVA was used to estimate the effects of disease and sex on  $v_b$  and  $K^{\text{trans}}$  values. **Results:** Comparisons between the MS and HC groups revealed increased mean  $v_b$  and  $K^{\text{trans}}$  values in MS NAWM and NAGM; the only statistically significant ( $p < 0.05$ ) finding was an increased mean MS NAGM  $v_b$  value. Comparisons between MS NAWM and MS lesions revealed significantly increased mean  $v_b$  and  $K^{\text{trans}}$  values in MS lesions. Furthermore, our results suggest that the increase in the mean  $K^{\text{trans}}$  value was due to the women. **Conclusions:** Our results suggest a slight increase in the  $v_b$  and  $K^{\text{trans}}$  in MS NAWM and NAGM. On the other hand, we find a significant increase in the  $v_b$  of the MS lesions compared to MS NAWM, suggesting the possibility of microscopic angiogenesis and/or vasodilatation. In addition, significant BBB disruption in non-acute MS lesions was observed only for the women. Our data suggests that disease-related microvascular changes in MS brain tissue may involve an increase in  $v_b$ , and that the extent of BBB leakage in non-acute MS lesions may depend on sex.

**Disclosures:** JM Njus has nothing to disclose.

**Funding:** National Multiple Sclerosis Society (RG 3168A1); National Institutes of Health (NS 040801)

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### **P23 Sensorimotor impairments are associated with MRI-defined tract-specific spinal cord disease in multiple sclerosis**

*KM Zackowski<sup>1</sup>, SA Smith<sup>2</sup>, DS Reich<sup>3</sup>, E Gordon-Lipkin<sup>4</sup>, AJ Bastian<sup>5</sup> and PA Calabresi<sup>4</sup>*

**Keywords:** corticospinal tract; dorsal columns; magnetization transfer imaging; sensation; strength; white matter

**Background:** It is hypothesized that the accumulation of sensorimotor impairments in multiple sclerosis (MS) comes to a greater extent from diseased spinal cord

rather than from purely cerebral involvement. However, this has been difficult to prove because of technical issues in imaging the spinal cord. High resolution magnetization transfer (MT)-based MRI can overcome these obstacles and provides the resolution needed for accurate spinal cord assessment in MS. **Objectives:** We hypothesize that MT imaging in the spinal cord will be associated with specific sensorimotor impairments to a greater extent than combined MT and conventional (T1w, T2w) imaging in the brain. **Methods:** We performed MT imaging using a 3T Philips Gyroscan-NT (Best, The Netherlands) system with 19 MS subjects and 8 controls. We obtained axial MT weighted images covering C2–C6 of the spinal cord and calculated the CSF-normalized MT (MTCSF) signal intensity in the dorsal and lateral columns. As a metric of damage, we calculated the area under the MTCSF exceeding 1SD from the control mean, as a function of slice. We evaluated sensorimotor impairments using quantitative walking, vibration sensation, and strength tests. **Results:** Our data show that MTCSF imaging is highly sensitive to white matter pathology in the spinal cord, *in vivo*. In our cohort of MS patients there are significant relationships in the spinal cord (MTCSF area under the curve) between dorsal columns and sensation ( $r = 0.64$ ,  $p < 0.01$ ) and between lateral columns and lower extremity strength ( $r = -0.57$ ,  $p < 0.001$ ). There are not significant correlations between sensation and lateral columns or strength and dorsal column. **Conclusions:** Our data supports a link between spinal cord imaging abnormalities and quantitative measures of sensorimotor dysfunction in MS. This is a first step in relating spinal cord structure with function in MS. The linking of this information is important for better defining pathophysiology of disability and tracking recovery or progression.

**Disclosures:** KM Zackowski has nothing to disclose.

**Funding:** NIH-NCMRR, The Dana Foundation, The Montel Williams Foundation, The National Multiple Sclerosis Society, NINDS, and Philips Medical Systems

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## Neuroimmunology

### P24 Fibrinogen as a signaling molecule and therapeutic target for inflammation and neuroprotection in multiple sclerosis

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**Keywords:** axonal regeneration; blood-brain barrier; experimental autoimmune encephalomyelitis; fibrinogen; integrin receptors; microglia

**Background:** Microglia activation and axonal damage are pathologic hallmarks of multiple sclerosis (MS), but a strategy to inhibit microglia activation and repair axonal damage in MS has not yet been developed. Fibrin, which is derived from the blood protein fibrinogen, is deposited in MS plaques as a result of blood-brain barrier (BBB) disruption. **Objectives:** We sought to examine whether fibrinogen contributed to the development of inflammatory demyelination by altering pathophysiological properties of CNS cells. **Methods:** We examined both the cellular and molecular effects of fibrinogen in primary cultures of microglia and CNS neurons, as well as the effects of genetic or pharmacologic depletion of fibrinogen in the progression of Experimental Autoimmune Encephalomyelitis (EAE). **Results:** We show that fibrinogen functions both as an activator of microglia as well as a potent inhibitor of neurite outgrowth of mammalian CNS neurons. Fibrinogen signals through the Mac-1 (CD11b/CD18) integrin receptor expressed by microglia to induce their differentiation to phagocytes via activation of Akt and Rho. Targeting of the interaction of fibrinogen with Mac-1 either genetically in fibrinogen- $\gamma$ 390–396A knock-in mice or pharmacologically through intranasal delivery of a fibrinogen-derived inhibitory peptide ( $\gamma$ 377–395) is sufficient to suppress EAE in mice that retain full coagulation function. Moreover, fibrinogen signals through the  $\alpha$ v $\beta$ 3 integrin receptor expressed by neurons to inhibit neurite outgrowth in a concentration-dependent manner in two neuronal cell types examined, cerebellar granular neurons and superior cervical ganglia. **Conclusions:** These results identify fibrinogen as a potential molecular link between vascular damage, inflammation and inhibition of axonal regeneration in the CNS. Since blocking fibrinogen signal transduction via its CNS integrin receptors affects only the inflammatory and not the coagulation properties of fibrin, pharmacologic targeting of the interaction of fibrinogen with its microglia and/or neuronal receptors could represent novel targets for therapeutic intervention in inflammatory demyelination.

**Disclosures:** K Akassoglou has nothing to disclose.

**Funding:** German Research Foundation (DFG) postdoctoral fellowship to C Schachtrup; National Multiple Sclerosis Society (NMSS) postdoctoral fellowship to RA Adams; NMSS grant RG-3782 and NIH/NINDS R01 grant NS052189 to K Akassoglou.

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### P25 IFN- $\beta$ 1a induced changes in myelin-specific T cell frequency may serve as a biomarker predicting clinical outcome

L Amezcua<sup>1</sup>, HQ Ta<sup>1</sup>, R Berkovich<sup>1</sup>, D Tsao-Wei<sup>2</sup>, D Bandari<sup>1</sup>, NJ Kachuck<sup>1</sup> and BT Lund<sup>1</sup>

**Keywords:** clinical outcome; EDSS; interferon; myelin; T cell frequency; Th1/Th2 bias

**Background:** The clinical course of MS, an autoimmune disease of the CNS, most typically follows an initial relapsing-remitting pattern (RRMS) in which immunosuppressive therapies such as intramuscular interferon- $\beta$ 1a (IFN-IM) have been shown to slow disease progression. IFN-IM has also been shown to have both *in vivo* and *in vitro* effects on myelin antigen-specific proliferative responses and cytokine production. Indeed, we have previously shown that within 12 months following initiation of IFN-IM therapy there were significant reductions in most myelin antigen-specific T cell frequencies and marked changes in the Th1/Th2 bias of these peripheral blood mononuclear cells (PBMC). **Objectives:** The objective of this study was to determine if the changes in frequency and Th1/Th2 bias of myelin antigen-specific PBMC which occur following initiation of IFN-IM therapy can predict future clinical outcome in RRMS patients. **Methods:** A retrospective analysis of a cohort of patients with RRMS who initiated IFN-IM therapy in 1998–2000 and who remained on IFN-IM therapy for at least 6 years. Changes in clinical measures of disease progression over 6 years were compared to changes in myelin antigen-specific T cell frequencies and Th1/Th2 bias which were observed in the 12 months following initiation of therapy. **Results:** Preliminary analyses suggest that changes in MBP (myelin basic protein) and whole myelin-specific T cell frequencies may predict clinical stability over the following 6 years. Patients showing a reduction in MBP or myelin-specific T cells following commencement of IFN-IM therapy progressed at a slower rate than patients

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with no reduction in T cell frequency. Increased production of IL-5 by PBMC following initiation of therapy similarly correlated with clinical stability. **Conclusions:** Changes in myelin and MBP specific T-cell frequencies and Th1/Th2 bias may predict clinical outcome over 6 years after the initiation of intramuscular interferon- $\beta$ 1a.

**Disclosures:** L Amezcua has nothing to disclose.

**Funding:** Biogen Idec (NJ Kachuck and BT Lund); Nancy Davis Centers Without Walls (NJ Kachuck and BT Lund); National Multiple Sclerosis Society Fellowship (L Amezcua)

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## **P26 NK cells inhibit T cell expansion and Th17 priming**

*JH Edwan<sup>1</sup>, H McFarland<sup>2</sup> and B Bielekova<sup>1</sup>*

**Keywords:** dendritic cells; IL-17; IL-17 cells; NK cells; T cells; Tsh17 cells

**Background:** Multiple Sclerosis (MS) is a T-cell mediated autoimmune disease. Recent studies indicate that NK cells may play a crucial role in regulating the balance between innate and adaptive immune responses. Our laboratory previously demonstrated that NK cells participate in the termination of adaptive immune responses by killing activated T cells. **Objectives:** In this study, we sought to evaluate the role of NK cells in the development of effector T cell responses. Since the known deleterious role of Th17 cells in autoimmunity, we focused on evaluating the effect of NK cells on Th17 priming. Because we hypothesized that NK-mediated immunoregulation may be defective in untreated MS patients and restored by daclizumab therapy, we evaluated this pathway in healthy donors (HD) and in those MS patients whose clinical disease activity has been successfully controlled with daclizumab. **Methods:** Negatively-selected CFSE stained autologous T cells were primed by antigen (Ag)-loaded dendritic cells (DC) in the presence or absence of autologous negatively selected NK cells for 7 days. Cells were then briefly restimulated with PMA/Ionomycin in the presence of Brefeldin A. Intracellular cytokine staining was performed for IL-17 production, and surface staining to identify CD4+ and CD8+ T cells. CFSE dilution served to identify proliferating T cells. Cells were proportionally enumerated between the conditions by using APC-microbeads. **Results:** We observed that NK cells

significantly suppress CD4+ and CD8+ T cell proliferation to Ag-loaded DC. In addition, proliferating CD4+ T cells from daclizumab treated MS patients expressed less IL-17 than T cells from HD and MS subjects upon activation with Ag-loaded DC. This IL-17 expression was further diminished when T cells were co-cultured with NK cells. **Conclusions:** Our results confirm the immunoregulatory role of NK cells on T cell responses and indicate that NK cells may be an especially relevant population for maintaining immune tolerance.

**Disclosures:** JH Edwan has nothing to disclose.

**Funding:** University of Cincinnati Millenium Scholar Award to B Bielekova; intramural NINDS/NIH

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## **P27 Decreased CD1d-restricted NKT cells in the peripheral blood of multiple sclerosis patients**

*J O'Keeffe<sup>1</sup>, C Gately<sup>2</sup>, AP Moran<sup>2</sup> and EL Hogan<sup>3</sup>*

**Keywords:** CD161+; CD1d-restricted T cells; CD3+; MKR; NKT; regulatory T cells

**Background:** T cells expressing NK cell receptors (NKR) display rapid MHC-unrestricted cytotoxicity and potent cytokine secretion and are thought to play roles in regulating immunity and in prevention of autoimmune diseases. **Objectives:** To quantify NKR+ T cells (including invariant NKT cells as defined by CD1d loaded tetramers) in freshly isolated peripheral blood from patients with multiple sclerosis. **Methods:** Phenotype study: (MS) (n=23) (classified as relapsing-remitting, secondary progressive, and primary progressive MS), and other neurological disease controls (n=24) subdivided into non-inflammatory (NI-OND, n=18) and inflammatory (I-OND) subgroups. Peripheral blood mononuclear cells (PBMC) were obtained, purified, and isolated by flow cytometry markers: CD3, CD56, CD161, CD94, V $\alpha$ 24-J $\beta$ 18 and PBS57 loaded CD1d tetramers. **Results:** CD161+T cells were expanded in all MS categories compared to NI-OND but not I-OND group: no differences in the numbers of CD94+ T cells or CD56+ T cells. When compared with HS, reduced numbers of CD161+ T cells and CD94+ T cells but not CD56+ T cells were found in the MS subgroups especially in the primary progressive for CD161+ T cells and in the secondary progressive for CD94+ T cells. There were reduced numbers of invariant NKT cells as defined by

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CD1d loaded tetramers found in the MS group compared HS. The predominance and heterogeneity of NKR+ T cells may be central in regulating immune responses in multiple sclerosis. **Conclusions:** 1. CD1d-restricted T cells are reduced in MS PBMCs indicating a decrease in regulatory function for glycolipid-reactive T cells in MS suggesting an important inhibitory decrease of autoreactivity via non-pleomorphic lipid antigens in MS. 2. NKT cell phenotypes implicate NKTs—particularly CD3+CD161+ - (express C-type lectin hNKR-P1) are increased in MS PBMC relative to NI-ONDs. Functional analyses of these CD3+CD161+ and other glycolipid-reactive NKT cells are ongoing.

**Disclosures:** EL Hogan has nothing to disclose.

**Funding:** National Multiple Sclerosis Society (RG#3473) and NINCDS (NS51666)

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## **P28 Early results of the luciferase assay to measure neutralizing antibodies to interferons**

*J Oger<sup>1</sup>, R Lam<sup>2</sup>, T Aziz<sup>2</sup> and E Gibbs<sup>3</sup>*

**Keywords:** interferon; luciferase; measurement; neutralizing antibodies; technique; validation

**Background:** Neutralizing antibodies (NABs) are accompanied by reduced bioavailability and different assays are used; all are cumbersome and expensive. **Objectives:** To present preliminary results of the luciferase assay to detect NABs. **Methods:** We used the cell line HT-1080, stably transfected with the luciferase gene linked to the interferon stimulated response element (gift of G.Uzé, Montpellier France). When IFN $\beta$  binds to its receptor, luciferase is expressed. After addition of substrate, the amount of luciferase is proportional to the chemiluminescence signal. An initial screening test is performed in which diluted serum (1:20) is pre-incubated with IFN $\beta$ -1b (20 U/mL) and added to cells. After 5 hr the substrate is added and chemiluminescence measured. An IFN dilution curve is included on the plate. If the calculated inhibition (using the Kawade method) is <50%, the sample is NAB<sup>-</sup>. If the inhibition is >50%, the result is NAB<sup>+</sup>. **Results:** The IFN $\beta$  dilution curve is linear between 5 and 50 Units. Coefficients of variation for the different dilutions vary between 4 and 12%. We compared our results to that obtained on the same 33 samples by the CPE assay (Dr S. Grossberg): The Luciferase assay did not fail to identify any of the

26 NAB<sup>+</sup> by CPE assay (sensitivity=100%); there were 3 “false-positive” samples which were negative by CPE (<20 TRU) but positive by ELISA; The Luciferase assay is more sensitive than the CPE assay of Grossberg. 9/42 (21.4%) of the Binding antibody positive samples were negative with Luciferase a result similar to the CPE (7/33, 21.2%). **Conclusions:** Our preliminary experience reveals that the Luciferase assay is easy to run, can be run daily with a single technician and it has a large throughput. We evaluate that it will have a lower cost. Our goal is to make it available to Canadian MS centres by July 2007.

**Disclosures:** J Oger has received education grants, research grants, speakers fees and honoraria from Serono, Berlex, Biogen-Idec and Teva Neurosciences.

**Funding:** Supported by grants from Biogen Idec, Berlex-Shering AG, Serono Canada, and Teva Neurosciences

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## **P29 3G11-CD25+: a new and more accurate cell surface marker for regulatory CD4+ T cells**

*Z Zhao, GX Zhang, S Yu, B Ciric and AM Rostami*

**Keywords:** 3g11; anergic; CD25; EAE; MOG; Treg

**Background:** 3G11 is a sialylated carbohydrate antigen on the disialoganglioside molecule and is expressed predominantly on the membranes of CD4+ T cells. Our previous studies suggested that loss of the 3G11 molecule could be a new cell surface marker for anergic/regulatory CD4+ T cells and is highly relevant to intravenous tolerance against experimental autoimmune encephalomyelitis (EAE). **Objectives:** In the present study, we found that, upon anti-CD3/CD28 stimulation, 3G11-CD4+ T cells expressed significantly higher levels of foxp3 and IL-10, but lower IL-2 compared to the 3G11+CD4+ population. The 3G11- population largely overlaps with CD25+ T cells as up to 75% of CD25+ T cells are 3G11-. **Methods:** Using FACS sorting, we purified four subpopulations of CD4+ T cells: 3G11+CD25+, 3G11-CD25+, 3G11+CD25- and 3G11-CD25-, and their immunological phenotype was assayed. **Results:** Among these 4 subpopulations, the 3G11-CD25+ population expressed the highest levels of Foxp3 and IL-10 and most efficiently inhibited

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both anti-TCR- and autoantigen-induced immune responses. 3G11+CD25+ and 3G11-CD25- T cells possessed weaker immunoregulatory capacity, while 3G11+CD25- T cells were effector cells. **Conclusions:** Thus, 3G11-, combined with CD25+, could be a new and more accurate cell surface marker for Treg than CD25+ alone or 3G11- alone.

**Disclosures:** Z Zhao has nothing to disclose.

**Funding:** NIH; National Multiple Sclerosis Society

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## Neuropsychology/Neuropsychiatry

### P30 Pediatric MS patients exhibit impaired processing speed and efficiency

*J Ackerson<sup>1</sup>, S Middleton<sup>1</sup>, K Bashir<sup>2</sup> and J Ness<sup>1</sup>*

**Keywords:** efficiency; executive function; IQ; neurocognitive; pediatric; processing speed

**Background:** MS onset before age 18 is uncommon but increasingly recognized. There is limited data about neurocognitive function in pediatric MS. **Objectives:** Characterize the neuropsychological profile in pediatric MS patients. **Methods:** A standardized neuropsychological assessment was performed in 13 pediatric MS patients. The protocol included Wechsler Abbreviated Scale of Intelligence (WASI), Digit Span, Connors Continuous Performance Test (CPT), California Verbal Learning Test (CVLT), Expressive One-Word Picture Vocabulary Test (EOWPVT), Trailmaking Test, Contingency Naming Test and Verbal Fluency Test from the Dellis-Kaplan Executive Function system (DKEFS). Patients and parents also completed the Behavior Rating Inventory of Executive Function (BRIEF) and the Behavior Assessment System for Children (BASC-II). **Results:** This pediatric MS cohort had a mean age $\pm$ SD of 14.1 $\pm$ 3.2 years (range 8–18 years) and was 77% female, 69% African-American. Mean time between initial demyelinating episode and neuropsychological testing was 22.1 $\pm$ 20 months with 2.8 $\pm$ 1.7 relapses by the time of evaluation; 46% were on disease modifying therapy but none were tested while on steroids. This group demonstrated average cognitive abilities as measured by WASI, Digit Span, CPT, EOWPVT, Verbal Fluency Test and BRIEF. In contrast, deficits in aspects of executive functioning were detected by the Contingency Naming Test which measures processing speed and efficiency. This pediatric MS population also scored 1–2 standard deviations below the mean for trials that assess

parallel processing and mental flexibility (67.7 $\pm$ 35 for the timed score and 79.1 $\pm$ 8.7 for efficiency). Furthermore, the DKEFS identified deficits with number but not letter sequencing. Parental ratings on the BASC-II indicated significant concerns regarding internalizing problems and somatic preoccupation. **Conclusions:** Children and adolescents with MS demonstrate significant deficits in processing speed and efficiency despite having a normal IQ. These findings can be used to help tailor appropriate educational interventions. Sequential assessments will be critical to determining whether there is accumulation of cognitive deficits.

**Disclosures:** J Ackerson has nothing to disclose.

**Funding:** National Multiple Sclerosis Society; Pediatric MS Center of Excellence

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## Pathology

### P31 Neurodegeneration of the retina in multiple sclerosis: relationship to pathophysiology

*AR Salter<sup>1</sup>, AL Conger<sup>1</sup>, T Frohman<sup>1</sup>, F Costello<sup>2</sup> and EM Frohman<sup>1</sup>*

**Keywords:** laser polarimetry; optical coherence tomography; pupillometry; retinal nerve fiber layer; unilateral optic neuropathy; visual function

**Background:** The retinal nerve fiber layer (RNFL) contains myelin-free ganglion cell axons which transmit information within the optic nerves to the brain for visual processing, sleep wake cycles, and pupillary light reflexes. RNFL values have been shown to predict visual field recovery and low contrast letter acuity. We studied a cohort of fourteen patients with unilateral thinning of their RNFL, in order to characterize the relationship between axonal degeneration within the retina and its impact upon measures of visual function and the dynamics of pupillary light reflexes. **Objectives:** To study the relationship of retinal neurodegeneration to clinical and physiologic measures of visual function in patients with MS and unilateral optic neuropathy. **Methods:** MS patients with unilateral thinning of the RNFL (n=14) were assessed with high and low contrast measures of visual acuity, Humphrey automated perimetry, optical coherence tomography (OCT), and laser polarimetry (GDx). We utilized infrared pupillometry

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(with defined flash specifications) for the purpose of analyzing the dynamics of the pupillary light reflex. Measures derived from the affected eye were compared to the unaffected fellow eye of the same patient, and to control subjects. **Results:** In contrast to the unaffected MS and normal subject eyes, as the RNFL thickness decreased in the affected MS eye, we observed corresponding and significant abnormalities in total macular volume, low contrast letter acuity, visual fields and pupillary reflexes (including percent change in diameter and velocities). **Conclusions:** Our findings confirm the hypothesis that axonal and ganglion cell degeneration within the retina of MS patients represents a biomarker for both patient reported and neurophysiologic measures of the anterior visual system. These findings have implications for the identification of novel therapies that can exert neuroprotective and potentially even restorative capabilities for patients with visual loss in particular, and perhaps for the MS disease process in general.

**Disclosures:** AR Salter has nothing to disclose.

**Funding:** Cain/Denius MS Support Fund

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### **P32 Gas6 activation of the receptor tyrosine kinase Axl recruits PI3 kinase and Grb2**

*JG Weinger<sup>1</sup>, P Gohari<sup>1</sup>, K O'Guin<sup>1</sup>, J Backer<sup>2</sup>, B Varnum<sup>3</sup> and B Shafit-Zagardo<sup>1</sup>*

**Keywords:** Axl; Gas6; Grb2; oligodendrocytes; PI3 kinase; survival

**Background:** Axl belongs to the Axl, Rse, Mer family of receptor tyrosine kinases. Axl is expressed in the immune, reproductive and central nervous systems, where it is implicated in cell survival following cell starvation and other stressors. We previously determined that in human oligodendrocyte cultures insulin withdrawal and TNF $\alpha$ -induced cell death are significantly reduced upon growth arrest-specific protein 6 (gas6) stimulation of Axl. Gas6 ligand stimulation and autophosphorylation of the Axl receptor signals to phosphatidylinositol-3 kinase (PI3 kinase) resulting in activation of the Akt survival pathway. **Objectives:** In this study, the interaction of Axl and its signaling partners was explored. **Methods:** Mutagenesis of Axl followed by pull-down assays and immunoprecipitations were performed on Cos7 cells. In addition, immunoprecipitations were performed on day 10 mouse brain

homogenates immunopanned for O4+ oligodendrocytes. **Results:** Pull-down assays and immunoprecipitations using wildtype and mutant Axl transfected cells determined that Axl binds the SH2 domains of the p85 subunit of PI3 kinase and growth factor receptor-bound protein 2 (Grb2). Mutational analysis defined the sites on Axl essential for direct and indirect association with these molecules. When the Axl YVN site was mutated to YVQ, Grb2 binding to Axl was eliminated. Co-transfection of p85, plus wildtype or Axl mutant constructs determined that p85 binds to either pYXXM motif beginning at phosphotyrosine (pY) 779 and pY821. Grb2 and p85 can compete for binding at the pY821VNM site, and p85 can bind the YALI, YVQM Axl mutant. By immunoprecipitation analysis, an interaction between Axl, p85 and Grb2 was confirmed in enriched populations of O4+ oligodendrocytes. **Conclusions:** These data demonstrate that in oligodendrocytes, gas6 stimulation of the Axl receptor recruits PI3 kinase and Grb2.

**Disclosures:** JG Weinger has nothing to disclose.

**Funding:** National Multiple Sclerosis Society (RG3020); CMBG training program: NIH, NIGMS (T32 GM 07491)

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### **Rehabilitation and Quality of Life**

#### **P33 Mindfulness-based stress management for MS patients and caregivers**

*MJ Baime<sup>1</sup>, LJ Ladden<sup>2</sup>, AJ Levan<sup>2</sup>, M Hoffman<sup>2</sup> and CE Markowitz<sup>3</sup>*

**Keywords:** caregivers; cognitive-behavioral; meditation; mindfulness; quality of life; stress, psychological

**Background:** Mindfulness-based stress management (MBSR) combines cognitive-behavioral techniques with structured mindfulness meditation training. Research has suggested that MBSR programs result in meaningful improvements in psychological well-being and physical health. **Objectives:** To demonstrate the feasibility and acceptability of a modified MBSR program for patients with MS and their caregivers, and to determine the effects of the intervention on mood, symptoms, and quality of life. **Methods:** Patients with relapsing-remitting MS and their caregivers were recruited. The intervention was an eight-week MBSR program customized for MS patients and caregivers. All subjects were given

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standardized surveys prior to the start of the intervention, at the end of the program, and four months later. MS patients and caregivers completed the Profile of Mood States (POMS) and the Brief Symptom Inventory (BSI). MS patients also completed the Multiple Sclerosis Quality of Life Inventory (MSQLI). Repeated-measures ANOVA was used to assess the significance of changes. **Results:** Twenty individuals (10 patients and 10 caregivers) were enrolled in two intervention groups. Adherence to the protocol was good. Both caregivers and patients reported improvements in POMS subscales (decreased anxiety,  $p=0.02$  and fatigue,  $p=0.032$ ) and BSI scores (mean global severity score decreased from 0.581 to 0.385,  $p=0.006$ ). The MSQLI documented significant improvements for MS patients in the Perceived Deficit Questionnaire, the Bowel Control subscale, and the Mental Health Inventory. The most significant changes were seen in the positive affect ( $p=0.016$ ), retrospective memory ( $p=0.027$ ), and attention/concentration ( $p=0.037$ ) subscales. Trends persisted, but statistical significance was lost, at 4 months. **Conclusions:** An exploratory study of MBSR for patients with MS and their caregivers demonstrated meaningful improvements in subjective mood, quality of life, and cognitive function. A larger prospective randomized trial controlling for attention, expectancy and group support is justified to verify these findings.

**Disclosures:** MJ Baime has nothing to disclose.

**Funding:** National Multiple Sclerosis Society

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### **P34 Force control during object manipulation in multiple sclerosis**

*V Krishnan, PB de Freitas and S Jaric*

**Keywords:** control; EDSS; feedback; grip; hand; manipulation

**Background:** Force coordination is essential for performing everyday manipulation tasks. **Objectives:** The aim of this study was to evaluate a method for assessment of hand function in mildly affected MS patients. **Methods:** Sixteen MS patients (EDSS 1–4.5) and sixteen age and gender matched healthy controls were examined on simple manipulation tasks using an instrumented rod-like device. The device consisted of two

handles that could be either fixed or detached from the base. Two transducers measured grip force (G; acting normally at the contact area) applied against the handle, while two additional transducers measured the load force (L; tangential force) that was exerted along the handle. In the dynamic manipulation task, subjects lifted and held the handles, using either one or both hands. In the static manipulation tasks subjects either traced a depicted ramp pattern or exerted a sinusoidal pattern by exerting L under both visual and non-visual feedback condition. **Results:** When compared with healthy individuals, MS patients revealed a deteriorated task performance regarding the accuracy of exertion of the prescribed L pattern. Excessive G/L ratio (i.e., ‘over-gripping’) was also observed in MS patients under all task conditions. The force coupling observed through the cross correlations between G and L revealed similar results in two groups except in the dynamic manipulation where MS patients demonstrated lower correlation coefficients. However, switching from visual feedback to no feedback conditions revealed similar effect in both groups. **Conclusions:** The results suggest that the applied methodological approach is sensitive enough to distinguish between the mildly involved MS patients and healthy individuals. Taking also into account a lack of objective quantitative test of hand function in neurological patients, as well as the importance of hand function per se, one could conclude that the applied method could be developed into a standard protocol for testing hand function in MS and, possibly, other neurological diseases.

**Disclosures:** V Krishnan has nothing to disclose.

**Funding:** Grant HD-48481 from the National Institutes of Health

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### **P35 Break in binocular fusion during head turning in multiple sclerosis patients with internuclear ophthalmoplegia is exacerbated during heat stress: safety implications for driving and walking**

*DA Mills<sup>1</sup>, SL Davis<sup>1</sup>, DA Woo<sup>2</sup>, AR Salter<sup>1</sup>, EM Frohman<sup>3</sup> and TC Frohman<sup>1</sup>*

**Keywords:** accident; eye movement; head turning; heat sensitivity; INO; internuclear ophthalmoplegia

**Background:** The most common eye movement disorder associated with MS is internuclear ophthalmoplegia (INO), characterized by adduction slowing during hori-

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zontal saccades. Many patients with INO report brief visual distortion during head turns. This observation is germane to understanding why such patients are at higher risk of accidents when performing activities of daily living such as turning while walking or changing lanes while driving. **Objectives:** To demonstrate that elevations in core body temperature increase break in binocular fusion in MS patients with INO during head turning. **Methods:** Horizontal saccadic eye movements were characterized using 2D infrared oculography (Eye-link) in MS patients with INO (n=10) and healthy controls (n=5). From this group, two of the MS-INO patients and two of the controls were actively heated  $\sim 0.8^{\circ}\text{C}$  above their baseline temperature and subsequently cooled using a water perfused body suit. Body core temperature was recorded continuously using an ingestible temperature telemetry pill. During the heating and cooling process, binocular eye-movement recordings were performed during active head and body turning maneuvers using 2D infrared oculography and video oculography. **Results:** With head or body turning, MS-INO patients exhibited dysconjugacy during saccadic eye movements characterized by a decrease in velocity and amplitude wave forms in the adducting eye, compared to the abducting eye. MS-INO patients demonstrated greater dysconjugacy at peak heating when compared to baseline and cooling values. Using the same paradigm, normal subjects showed no evidence of break in binocular fusion at baseline, peak heating, or cooling. **Conclusions:** Our study represents the first observation linking INO with head turning abnormalities. These findings have important safety implications for patients while driving and walking, especially in hot climates. Physicians should be aware of this phenomenon and educate their patients on strategies (cautious head movements) for minimizing the impact of ocular dysconjugacy and the associated risks of car accidents and falls.

**Disclosures:** DA Mills has nothing to disclose.

**Funding:** Irene Wadel & Robert Atha Research Fund for MS and the Kenney Marie Dixon Pickens Research Fund for MS, Department of Neurology, University of Texas Southwestern Medical Center

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### **P36 Physical activity and the disablement process in multiple sclerosis**

*RW Motl and EM Snook*

**Keywords:** disability; exercise; functional limitations; health promotion; physical activity; symptoms

**Background:** MS is a chronic neurological disease that involves progressive and unpredictable episodes of axonal demyelination and transection. The axonal damage is associated with loss of function and feeling in limbs, fatigue, loss of balance and coordination, pain, cognitive dysfunction, and depression. Ultimately, the symptoms can lead to functional limitations and disability. Physical activity may be beneficial for symptom management among those with MS, and symptoms have been considered as a possible step in Nagi's disablement process. **Objectives:** This study examined the relationship between physical activity and the disablement process in individuals with MS. We expected that physical activity would be associated with disability and that the relationship would be indirect and operate through a pathway that involved symptoms and then functional limitations. **Methods:** Participants (n=133) were individuals with MS who wore an accelerometer for a seven-day period and completed the Godin Leisure-Time Exercise Questionnaire, Multiple Sclerosis Symptom Checklist, Symptom Inventory, Expanded-Disability Status Scale, Performance Scales, and abbreviated Late-Life Function and Disability Inventory. The data were analyzed using structural equation modeling with physical activity, symptoms, functional limitations, and disability as latent variables in AMOS 6.0. **Results:** The structural model with latent variables provided an excellent fit for the data ( $\chi^2=25.92$ ,  $df=18$ ,  $p=0.10$ , NNFI=0.96, CFI=0.98). Interpretation of the standardized path coefficients indicated that (a) those who were more physically active had fewer symptoms ( $\gamma=-0.62$ ), (b) those with fewer symptoms had better function ( $\beta=-0.86$ ), and (c) those with better function had less disability ( $\beta=-0.89$ ). **Conclusions:** Our findings are encouraging from the perspective that physical activity is a modifiable behavior that is associated with reduced disability through a pathway that is consistent with Nagi's disablement process in individuals with MS.

**Disclosures:** RW Motl has nothing to disclose.

**Funding:** No funding reported

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### **P37 Mental practice of action and rehabilitation of multiple sclerosis**

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**Keywords:** cognition; exercise; mental practice of action; motor control; neural plasticity; rehabilitation

**Background:** Much of the current research on the rehabilitation of individuals with MS has focused on engagement in physical exercise programs. While physical exercise has been shown to have benefits to MS patients, a serious drawback is that it may result in the acute worsening of common symptoms of the disease. Consequently, there has been low compliance in studies on exercise in MS patients. **Objectives:** Given such constraints, the current research evaluates an alternative approach—mental practice of action (MPA) to improve motor function in MS patients. Since no actual movement occurs during MPA, risk for the worsening of neurologic symptoms and injury should be removed, and compliance should increase. **Methods:** In our ongoing study, MS patients practice a manual aiming task [Visually Guided Pointing Task (VGPT)] in one of three groups: Mental Practice Group (MPG), Actual Practice Group (APG), No Practice Group (NPG). Patients in the MPG and APG come to the laboratory to mentally or actually practice twice a week, over an eight-week period. Those assigned to the NPG do not practice. During Pretest and Posttest sessions, patients in all groups actually perform the VGPT, along with a range of other tests [e.g., MSFC]. **Results:** The results from the initial patients in our study show that the average Pretest-to-Posttest change in VGPT movement speed is +4.00%, +21.15%, and +33.59% for the NPG (n=3), MPG (n=3) and APG (n=4), respectively. Other analyses indicate that MPA (VGPT) may relate to improvements in other upper extremity function (9-HPT), lower extremity function (T25-FW), and even cognitive function (PASAT). **Conclusions:** Thus, the preliminary results suggest that prolonged MPA is superior to no practice, and approximates the benefits of actual practice. We will present data from additional patients that will have completed our ongoing study.

**Disclosures:** A Slifkin has nothing to disclose.

**Funding:** National Multiple Sclerosis Society (PP 1148)

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### **Surrogate Markers (Non-MRI)**

#### **P38 Anti glycan antibodies in serum of MS patients**

*F Deisenhammer<sup>1</sup>, N Dotan<sup>2</sup>, R Altstock<sup>2</sup>, A Millonig<sup>1</sup>, T Berger<sup>1</sup> and M Reindl<sup>1</sup>*

**Keywords:** biomarker; carbohydrates; diagnostic; glycans; IgM antibodies; prognostic

**Background:** There is an unmet need to develop specific serum based biomarkers for the diagnosis and prognosis of MS. Elevated levels of serum anti-Glc(alpha1,4)Glc(alpha) (GAGA4) IgM antibodies were reported to exist in RRMS patients in comparison to patients with other neurological diseases (OND). **Objectives:** To further validate increased levels of anti-GAGA4 IgM, and other anti glucose based glycans antibodies (AGAb), in MS patients. **Methods:** Two hundred and thirty (230) MS patients, 150 healthy controls, 40 patients with HIV infection, and 80 patients with OND (viral meningitis (n=45), bacterial meningitis (n=23), dementia (n=12)) were included. Serum IgM antibodies against 4 glucose based glycans: GAGA4, Glc(alpha1,6)Glc(alpha), polysaccharide of (Glc(alpha1,4)Glc(alpha))n chains, cross linked with Glc(alpha1,6)Glc, and alpha-GlcNAc, were measured by a solid phase, enzyme linked immunoassay. The ratio of AGAb levels to square root of total serum IgM was calculated because AGAb levels depended strongly on total IgM values. **Results:** Mean GAGA4 EU/total IgM(0.5) ratios were significantly (p=0.03) elevated in MS patients compared with all control groups (17.9±8.7 in MS, 15.6±5.9 in OND, 16.0±7.2 in HC 13.2±8.9 in HIV). Using a cut-off value of >22 the sensitivity for MS vs. all other groups was 24.3% with a specificity of 84.8%. Other antibodies did not show a significant difference between MS and all control groups. Total IgM levels [mg/ml] (0.5) differed significantly between HIV (4.2±1.6), MS (3.6±1.1), and HC (3.2±0.8) groups. None of the variables were age dependent. **Conclusions:** A relatively high specificity for MS and higher levels of anti GAGA4 antibodies in a subgroup of MS as compared to control groups was validated. Anti-GAGA4 might indicate a specific subtype of MS. Both, elevated total IgM and anti GAGA4 antibodies could reflect an activated immune response/alertness against infectious agents.

**Disclosures:** F Deisenhammer has nothing to disclose.

**Funding:** No funding reported

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### **P39 Evaluating the anterior visual pathway in multiple sclerosis: structure vs. function**

*A Green<sup>1</sup>, MK Menz<sup>2</sup>, MD Menz<sup>3</sup> and EE Sutter<sup>2</sup>*

**Keywords:** multifocal ERG; OCT; optic nerve; retinal ganglion cell; VEP; visual pathway

**Background:** Assessment of the anterior visual pathway has been proposed as an important method for studying axonal injury and demyelination in MS. **Objectives:** Comparison of optic nerve function with retinal anatomy in MS using multifocal visual evoked potentials (mfVEP), the optic nerve head component (ONHC) of the multifocal electroretinogram (mfERG), and optical coherence tomography (OCT). **Methods:** MfERG and mfVEP were recorded from 8 normal subjects and 6 MS patients. Stimulation and analysis were performed with the VERIS 5 system. To provide better coverage of the visual field, we used an mfVEP stimulus with 120 sectors and then applied spatial averaging. In mfERG recordings the global flash paradigm was used to emphasize and evaluate signal contributions originating at the transition from membrane to saltatory nerve conduction at the lamina cribrosa. We compared these electrophysiological tests with Stratus OCT measures of macular volume and RNFL thickness. **Results:** One patient with MS but no ON history, showed significant local unilateral mfVEP delays. In the same area, the ONHC was reduced or absent suggesting retrobulbar demyelination. OCT nerve fiber layer thickness was normal while the macular volume in this eye was slightly reduced. In another patient without ON history, the mfVEP showed significant local delays in some areas as well as significantly reduced amplitude unilaterally. The ONHC suggested areas with retrobulbar demyelination in both eyes. OCT results were normal. In an MS patient who had a clinically resolved unilateral ON 18 months prior, we found areas of delayed mfVEP responses. MfERG and OCT results were in the normal range. **Conclusions:** While both mfERG and mfVEP present substantial evidence of demyelination, OCT showed no conclusive evidence of fiber loss. Interocular comparison of mfVEP results appears to be the most sensitive test in unilateral or asymmetric disease. ONHC-ERG may be particularly useful in patients who have relatively symmetrical ON injury.

**Disclosures:** EE Sutter works for and has a financial interest in EDI, the company that produces the Veris system for multifocal electrophysiological tests.

**Funding:** National Multiple Sclerosis Society

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### **P40 Sensitivity of static stabilometry in multiple sclerosis patients with mild disability**

*PN Riskind<sup>1</sup>, A Abou-Elias<sup>2</sup>, K Kane<sup>1</sup>, J Weaver<sup>1</sup>, K O'Leary<sup>1</sup> and R Beyroutey<sup>3</sup>*

**Keywords:** ataxia; balance; disability; EDSS; progression; stabilometry

**Background:** Imbalance is not rigorously assessed in multiple sclerosis (MS) clinical trials, despite the clear impact of disequilibrium upon disability and morbidity. **Objectives:** In order to determine whether static stabilometry (SS) might be a useful and simple quantitative technique to detect subtle imbalance, we have compared stabilometric outcomes in healthy young controls (n=21), minimally-disabled MS patients having EDSS 1–2 (n=26) and mildly-disabled MS patients having EDSS 2.5–3.5 (n=25). **Methods:** Root Mean Square Sway (RMS sway) was determined in each of five different static foot-positions (each with eyes open and closed) using a computerized force platform (AMTI). Data acquisition duration was 60 seconds, data rate was 50 Hz. Abnormal scores were defined as RMS sway >3 standard deviations above controls. **Results:** Acquisition of data from took about 25 minutes per patient to complete. Abnormal scores were detected in up to 20% of the minimally disabled patients and in up to 44% of mildly disabled patients, including 6 patients with normal cerebellar Functional Status Scores. Significant correlations between mean RMS sway, EDSS, and 9HPT were found for some test conditions. A composite RMS mean sway score was significantly worse for patients with ataxic-spastic gait than for MS patients with normal gait. Mean RMS sway was significantly higher in mildly disabled patients than minimally-disabled patients in some test conditions. **Conclusions:** These results suggest that SS can detect subtle imbalance in patients that have minimal disability from MS, and support the utility of SS as an outcome measure for MS clinical trials.

**Disclosures:** P Riskind is a speaker for Biogen Idec, Teva Neurosciences, Berlex and EMD Serono, has consulted for Genentech, Biogen Idec, Teva Neurosciences and Serono, and has received grant support from Biogen Idec and Teva Neuroscience.

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**Funding:** Teva Neuroscience

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#### **P41 Corpus callosum volume correlates with tactile temporal threshold in MS**

*Y Zhang<sup>1</sup>, LN Brown<sup>1</sup>, LM Metz<sup>1</sup>, RK Zabad<sup>1</sup> and JR Mitchell<sup>2</sup>*

**Keywords:** corpus callosum; livewire; MRI; outcome; progression; tactile temporal threshold

**Background:** The tactile temporal threshold (TTT) represents the longest time interval between the onsets of two tactile stimuli when they are judged as simultaneous. Judgments for bimanual stimulations require inter-hemispheric impulse transfer via the corpus callosum (CC). The TTTs are increased in people with MS suggesting compromised conduction capacity in axons across the CC. **Objectives:** To determine the relationship between CC volume and bimanual tactile temporal threshold (bTTT) in patients with MS. **Methods:** The bTTTs were measured in thirteen MS patients and eleven matched controls. Pairs of tactile stimuli were delivered to index fingers of both hands. The mean bTTT from each subject was calculated. A set of 3-plane localizing MR images was acquired on a 3T MR system within 48 hours of clinical assessment and measurement of bTTT. The CC volume was measured on a mid-sagittal slice using a liveWire program, an intelligent algorithm capable of finding the best-fit contour of structures measured. A MANOVA was used to compare group differences. Pearson correlation was performed to assess the relationship between CC volume and bTTT in MS patients. Significance was set at 0.05. **Results:** The CC volume was smaller (by 21% on average,  $p < 0.01$ ) and the bTTT was higher (by 49% on average,  $p < 0.05$ ) in MS patients than in controls. A significant correlation ( $r = -0.661$ ,  $p = 0.01$ ) between CC volume and bTTT was present in MS patients. **Conclusions:** This study revealed a relationship between CC volume and bTTT in MS and confirmed the presence of CC atrophy and conduction impairment in MS patients compared with controls. This suggests that bTTTs may be a useful measure of CC function and may be a useful index of progression in MS. Further studies are needed to determine the relationship between cognitive function, CC volume, and TTT.

**Disclosures:** Y Zhang has nothing to disclose.

**Funding:** MS Society of Canada, Hotchkiss Brain Institute

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#### **Symptom Management**

#### **P42 Validation of consistent improvement in walking speed on the Timed 25 Foot Walk as a measure of clinically meaningful change**

*AD Goodman<sup>1</sup>, TR Brown<sup>2</sup>, JA Cohen<sup>3</sup>, L Krupp<sup>4</sup>, R Schapiro<sup>5</sup>, SR Schwid<sup>1</sup>, R Cohen<sup>6</sup>, L Marinucci<sup>6</sup> and A Blight<sup>6</sup>*

**Keywords:** 4-aminopyridine; activities of daily life; ambulation; fampridine; MSWS-12; symptomatic treatment

**Background:** A multi-center trial (MS-F203) of sustained-release fampridine (4-aminopyridine) in MS used, as its prospectively defined primary outcome, a response criterion for consistent improvement in walking speed on the Timed 25 Foot Walk (T25FW). The criterion for a responder was a subject whose walking speeds for at least three of four on-treatment visits were faster than the fastest speed across any of their four pre-treatment visits and one follow-up visit. This criterion was derived from a post hoc analysis of a similar trial (MS-F202). In both studies, fampridine treatment was associated with significantly increased probability of response compared to placebo ( $p < 0.001$ ). **Objectives:** To validate the consistent response criterion as a measure of clinically meaningful change. Clinical impact was assessed by comparing responders and non-responders for changes during treatment on the 12-Item Multiple Sclerosis Walking Scale (MSWS-12) and, secondarily, scores on a subject global impression (SGI) and a clinician global impression (CGI). **Methods:** Both trials were randomized, double-blind, placebo-controlled, parallel group, multi-center studies, with a 14-week double-blind period, in MS patients with ambulatory deficits. A total of 501 patients were included in the analyses (205 from MS-F202 and 296 from MS-F203) with a randomization ratio of 3:1, drug: placebo. **Results:** Responders had significantly greater average improvements from baseline in the MSWS-12 score than the non-responders ( $-7.8$  and  $-1.5$  respectively,  $p < 0.001$ ). The validation was highly consistent across the studies as well as the patient subgroups examined. Responders also showed significantly better

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SGI scores and CGI scores than non-responders ( $p < 0.001$ ). **Conclusions:** The consistent response criterion identified a group of patients that experienced clinically meaningful improvement in ambulatory activities of daily-life, as self-assessed using the MSWS12 and as assessed by the SGI and CGI.

**Disclosures:** AD Goodman and JA Cohen have been consultants to Acorda Therapeutics. TR Brown, L Krupp, R Schapiro, and SR Schwid have received research funding for the conduct of these studies from Acorda Therapeutics. A Blight, R Cohen and L Marinucci are full-time employees of and have stock holdings in Acorda Therapeutics.

**Funding:** Acorda Therapeutics, Inc.

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### **P43 Are global or specific symptoms better correlates of physical activity in multiple sclerosis?**

*EM Snook, JA Scott, RC Gliottoni and RW Motl*

**Keywords:** depression; fatigue; pain; physical activity; symptom inventory; symptoms

**Background:** Accumulating evidence indicates that multiple sclerosis (MS) is associated with a dramatic reduction in physical activity behavior. By comparison, there is limited research on determinants in physical inactivity in this population. Global and specific symptoms of MS have been associated with reductions in multiple activities of daily living and might similarly influence participation in physical activity. **Objectives:** The present study examined overall and specific symptoms as determinants of physical activity in persons with MS. We expected that global symptoms would exhibit a stronger correlation with physical activity behavior than the individual symptoms of fatigue, depression, pain, and cognitive dysfunction. **Methods:** The sample consisted of 80 individuals with a definite diagnosis of MS from the Midwest region of the United States. Participants completed the Symptom Inventory (SI), Fatigue Severity Scale (FSS), Center for Epidemiologic Studies Depression Scale (CES-D), McGill Pain

Questionnaire (MPQ), and Perceived Deficits Questionnaire (PDQ) and then wore an accelerometer for a 7-day period for measuring physical activity. **Results:** There was a strong inverse correlation between the overall SI score and physical activity ( $r = -0.56, p = 0.0001$ ). Scores from the individual symptom questionnaires were all significantly and inversely correlated with physical activity, and the correlations were moderate-to-weak in magnitude: FSS ( $r = -0.34, p = 0.002$ ), CES-D ( $r = -0.32, p = 0.004$ ), MPQ ( $r = -0.28, p = 0.01$ ), and PDQ ( $r = -0.26, p = 0.02$ ). **Conclusions:** The severity of overall symptoms was more strongly associated with physical activity than any of the individual symptoms in this sample of people with MS. The management of global symptoms could be an important aspect of encouraging adoption and maintenance of physical activity in MS, and researchers should consider quantifying physical activity as an outcome of symptom management programs.

**Disclosures:** EM Snook has nothing to disclose.

**Funding:** No funding reported

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## **ACTRIMS-ECTRIMS-LACTRIMS 2008**

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and Research in Multiple Sclerosis