Gothenburg, Sweden - October 12, 2010

MS Academia
Multiple Sclerosis Advanced Course
GENERAL INFORMATION

VENUE
The Course will take place at the:
Gothenburg Convention Centre, Sweden (GCC)
Mässans Gata 20, SE-402 26 Gothenburg, Sweden
www.gcc.se

LANGUAGE
The official language of this Course will be English.

TRAVEL INFORMATION
Gothenburg is the second largest city in Sweden. It is located on the Swedish west coast. Gothenburg is home to many students, as the city includes both the University of Gothenburg, one of the largest universities in the Nordic countries, and Chalmers University of Technology. The sea, trade and industrial history of the city is evident in its cultural life. Due to the Gothenburg’s advantageous location in the centre of Scandinavia, trade and shipping have always played a role in the city’s economic history, and they continue to do so. Gothenburg port has come to be the largest harbour in the whole of Scandinavia.
Gothenburg is a popular destination for tourists on the Swedish west-coast, and offers a number of cultural and architectural highlights. The first major architecturally interesting period is the 18th century when the East India Company made Gothenburg an important trade city. Imposing stone houses with a Classical look were erected around the canals. One example from this period is the East India House, which today houses Gothenburg’s City Museum. Other interesting buildings are the Gothenburg Museum of Art, the city’s theatre, the concert hall, the Gothenburg Opera house and the Museum of World Culture. One of Gothenburg’s most popular natural tourist attractions is the Southern Gothenburg Archipelago, which is a set of many picturesque islands that can be reached by ferry boat.
AIM OF THE COURSE
The goal of the Course is to disseminate a state-of-the-art knowledge in MS and to review outcomes of recent researches on management optimization. A focus on diagnostic criteria and prognostic markers will be provided. Clinical trials outcomes and potential benefits of drugs under development will be presented too.

LEARNING OBJECTIVES
This Course will offer to participants:

• Updates on etiological factors and pathogenetic mechanisms of MS.
• An overview of diagnostic criteria and other tools used to follow-up patients.
• A review of treatments of MS and its symptoms.
• Criteria to evaluate the efficacy/safety balance of each therapeutic approach.

TARGET AUDIENCE
This program is appropriate for clinicians and scientists involved in multiple sclerosis management.

ACCREDITATION
Serono Symposia International Foundation (www.seronosymposia.org) has submitted this program “MS ACADEMIA - Multiple Sclerosis Advanced Course” (Gothenburg, Sweden - October 12, 2010) for accreditation by the European Accreditation Council for Continuing Medical Education (EACCME).
SCIENTIFIC COMMITTEE

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University of Texas  
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TUESDAY - OCTOBER 12, 2010

8.00  Registration
8.45  Serono Symposia International Foundation Opening
      Giancarlo Comi, SSIF Scientific Committee President

SESSION I

ETIOLOGY AND PATHOGENESIS

Chairman: Hans-Peter Hartung, Germany

9.00  L1:  Genes
      Tomas Olsson, Sweden

9.30  L2:  Environment
      Paul O’Connor, Canada

10.00 L3:  Pathology
      Christine Stadelmann-Nessler, Germany

10.30 L4:  Immunopathogenesis
      Hans-Peter Hartung, Germany

11.00 Discussion
11.20  Coffee Break

SESSION II

DIAGNOSIS

Chairman: Fred D. Lublin, USA

11.40 L5:  MS: diagnosis and prognosis
         Xavier Montalban, Spain

12.10 L6:  Neurophysiology in diagnosis and monitoring of MS
         Letizia Leocani, Italy

12.40 L7:  MRI in diagnosis and monitoring of MS
         Frederik Barkhof, The Netherlands

13.10 Discussion
13.30  Working Lunch
SESSION III
TREATMENT

Chairman: Giancarlo Comi, Italy

15.00  L8: Clinical trials: methodology and analysis  
       Fred D. Lublin, USA

15.30  L9: Current disease modifying drugs: evaluating the evidence  
       Mark S. Freedman, Canada

16.00  L10: Safety issues  
       Gavin Giovannoni, UK

16.30  Coffee Break

16.50  L11: Treatment individualization and monitoring  
       Giancarlo Comi, Italy

17.20  L12: Future therapies  
       Jerry Wolinsky, USA

17.50  Discussion

18.00  End of the Course
DISCLOSURE OF FACULTY RELATIONSHIPS

Serono Symposia International Foundation adheres to guidelines of the European Accreditation Council for Continuing Medical Education (EACCME) and all other professional organizations, as applicable, which state that programs awarding continuing education credits must be balanced, independent, objective, and scientifically rigorous. Investigative and other uses for pharmaceutical agents, medical devices, and other products (other than those uses indicated in approved product labeling/package insert for the product) may be presented in the program (which may reflect clinical experience, the professional literature or other clinical sources known to the presenter). We ask all presenters to provide participants with information about relationships with pharmaceutical or medical equipment companies that may have relevance to their lectures. This policy is not intended to exclude faculty who have relationships with such companies; it is only intended to inform participants of any potential conflicts so participants may form their own judgments, based on full disclosure of the facts. Further, all opinions and recommendations presented during the program and all program-related materials neither imply an endorsement, nor a recommendation, on the part of Serono Symposia International Foundation. All presentations solely represent the independent views of the presenters/authors.

The following faculty provided information regarding significant commercial relationships and/or discussions of investigational or non-EMEA/FDA approved (off-label) uses of drugs:

Frederik Barkhof
- Declared receipt compensation for consultancy, committee membership or lecture fees from Bayer Schering, Merck-Serono, Sanofi-Aventis, Genzyme Corp, Novartis, Biogen-Idec, European Charcot Foundation, Lundbeck, Roche, UCB, Medicinova Inc., Jansen Alzheimer Immunotherapy, Novo Nordisk, GE Medical Systems.

Giancarlo Comi
- Declared receipt of grants and contracts from: Novartis, Teva Pharm. Ind. Ltd., Sanofi-Aventis, Merck Serono, Bayer Schering, Biogen-Dompe’.

Fred D. Lublin
- Declared sources funding for research from Acorda Therapeutics, Biogen Idec, Genentech, Novartis Pharmaceuticals Corp, Teva Neuroscience Inc, Genzyme, Sanofi Aventis, NIH, NMSS. Declared consulting agreements/advisory boards/DSMB from Bayer HealthCare Pharmaceuticals, Biogen Idec, BioMS Medical Corp, EMD Serono Inc, Genentech Inc, Novartis, Pfizer, Teva Neuroscience, Genmab, Medicinova, Actelion, Allozyne, Sanofi-Aventis, Questcor, Acorda, Avanir, Roche, Celgene, Abbott. Speakers’ Bureau/Honorarium Agreements: EMD Serono, Pfizer, Teva Neuroscience. Declared Financial Interests/Stock Ownership: Cognition Pharmaceuticals Inc. The author declared also that he may discuss unapproved agents that are in the MS developmental pipeline without any recommendation on their use.

Xavier Montalban
- Declared receipt of grants and contracts: Bayer Schering, Biogen Idec, Novartis, Merck Serono, Teva, Sanofi-Aventis, Almirall.

Paul O’Connor
- Declared receipt of grants and contracts from: Novartis, Biogen Idec, Sanofi-Aventis, Opexa. Declared receipt of honoraria or consultation fees from: EMD Serono, Sanofi-Aventis, Novartis, Biogen Idec, Opexa. Declared to be member of a company advisory board, board of directors or other similar group: Actelion, Roche, Novartis, Biogen Idec. Declared otherwise benefit from a relationship with a commercial enterprise: Data Monitoring Committee.

Tomas Olsson
- Declared receipt of grants and contracts from: Biogen Idec, Merck Serono, Sanofi-Aventis. Declared receipt of honoraria or consultation fees from: Biogen Idec, Merck Serono, Sanofi-Aventis.

Christine Stadelmann-Nessler
- Declared receipt of honoraria or consultation fees from: Merck Serono.

Jerry Wolinsky
- Declared receipt of honoraria or consultation fees from: Acorda Therapeutics, Bayer HealthCare, Consortium of MS Clinics, Eli Lilly, EMD Serono, facet Biotech, Hoffman La Roche, Medscape CME, Novartis, Peptimmune, Sanofi-Aventis, Serono Symposia International Foundation, Teva and Teva Neurosciences, CMSC, the NMSS, Johns Hopkins University, Northwestern University, the University at Buffalo, the University of Utah, the University of South Florida Professionals Conferencing. Declared receipt of grants and contracts from: National Institutes of Health, National Multiple Sclerosis Society, Sanofi-Aventis, Clayton Foundation for Research.
The following faculty have provided no information regarding significant relationship with commercial supporters and/or discussion of investigational or non-EMEA/FDA approved (off-label) uses of drugs as of September 24, 2009.

Mark S. Freedman
Gavin Giovannoni
Hans-Peter Hartung
Letizia Leocani
ABSTRACTS
(L1 – L12)
GENES

Tomas Olsson
Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

There is solid evidence for variants of genes influencing the risk for multiple sclerosis (MS). The reason for positioning them is to allow further research to understand their function in the immune cascade leading to MS with the long term goal to develop more precise therapy and prevention. Progress in this area has until now been slow, but now with new technologies, and new theoretical insights, there is an explosive development.

The genetics of MS can be discussed in terms of genes within or outside the human leukocyte antigen (HLA) complex, designated MHC in other species. As to non-MHC genes, gene mappings in MS experimental models suggest that these are many, in the order of 50-100. In a few instances these have been positioned, orthologous associated to human MS and function uncovered. Variants of Vav1 in the rat regulate proinflammatory cytokine production/regulatory T cells, disease incidence and is associated to human MS (Jagodic M. et al. Sci Transl. Med, 2009). It is therefore an interesting target. Also in human MS non-HLA genes are many, at this moment at least 12 has been unequivocally associated to MS, many more to be expected after publication of the most recent human whole genome scan. The odds ratios (ORs) of these are in the order of 1.1 to 1.2. Such small ORs are regarded too small to be of interest by some scientists. However, crucial pathways are indicated important for further research on MS pathogenesis. Interestingly, nearly all genes uncovered are related to immune function giving further evidence for MS being an immune mediated disease rather than primarily neurodegenerative.

Genes of the HLA complex may exert much stronger effects. Collective overwhelming evidence demonstrate the class II HLA DRB1*15:01 as the MS predisposing allele with an OR of ~3. Despite this knowledge there is still little consensus on the reason for this association, and little is done to understand the biology behind. However, in my opinion, experience from animal models strongly suggests that it is preferences in the class II molecule binding and presentation to CD4+ T cells that are critical. It will be vital to reappraise this hypothesis ahead, with a goal to develop more precise therapies in MS. Association to the class I genes, providing molecules presenting peptides to CD8+ T cells, has been more controversial. However, several association studies have replicated a protective influence of HLA-A2 (OR~0.5). Experimentally, such alleles can induce CD8+ T cells producing TGFβ that are associated with suppression of disease. Understanding the human A2 effect will be important.

Just a fraction of the heritability of MS can be explained if adding the different known risk genes. Likely explanations are epigenetic factors, gene-gene and gene -lifestyle/environment interactions.

We have studied the interaction between smoking and MS risk genes. The overall MS risk for current smokers gives an OR of 1.7 compared to never smokers. Current smokers with two MS immune response risk genes compared to never smokers without these genes have on OR of 20, that is, a 2000 % increased risk for disease (Hedström A. et al., submitted). Hypothetically, inflammatory irritation in the lung in context with MS risk genes may trigger MS. These immune reactions will be important to study. Furthermore, upcoming studies of MS genetics should take lifestyle/environmental factors into account.
ENVIROMENT

Paul O’Connor
Department of Neurology, St. Michael’s Hospital, University of Toronto, Toronto, Canada

The exact cause of MS remains unknown, but the disease is widely believed to result from the interaction of environmental and genetic/epigenetic factors.

The environmental factors that appear to contribute to the disease include Vitamin D deficiency, Epstein-Barr virus infection and smoking. Stress per se does not appear to cause MS, although relapses often occur at times of patient stress.

The case for Vitamin D deficiency as a risk factor rests on several independent strands of evidence. MS is more prevalent in countries with less sunshine and less skin synthesis of Vitamin D. The level of childhood sun exposure is inversely related to MS risk. Military recruits with higher levels of Vitamin D are less prone to subsequently develop MS. Supplementation with Vitamins including D lowers the risk. The month of birth effect suggests that infants born after the winter are at a higher risk. A vitamin D responsive area (VDRE) exists next to the MHC immune response gene complex. Vitamin D has been shown to suppress EAE in mice. There is some evidence that higher Vitamin D levels are associated with a lower risk of MS relapses. The effect of Vitamin D could occur at various times in life, including prenatally.

Viruses have been long thought to play a role in causing MS. The fact that CSF oligoclonal banding is seen in CNS infections and in MS has lent support to this idea. However, it has not been possible to consistently recover viral DNA from MS plaques and viral models of MS do not replicate the pathology of the disease. MS patients are more likely to report a history of symptomatic infectious mononucleosis due to Epstein-Barr virus (EBV) infection. A study of US military personnel indicated that before developing MS all of the EBV- antibody negative personnel became EBV antibody positive.

Smoking tobacco appears to be a risk factor both for developing MS and for a worsened course of the disease.

The identification of environmental factors involved in causing MS is of great importance as this would provide a potential means of preventing or ameliorating the disease. Although genes are also important, the maximal concordance rate in identical twins is about 30% underlining the major role of environmental factors (and the epigenetic changes that they might produce) in MS pathogenesis.
Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system. Pathologically, MS lesions are characterized by demyelination, inflammation, a variable extent of axonal damage, and gliosis. In most patients, an early relapsing-remitting disease phase responding well to immunomodulatory treatments is followed by a progressive phase, where the disease is characterized by few, if any, Gd-enhancing lesions and an unresponsiveness to anti-inflammatory drugs. There, neurodegenerative mechanisms have been proposed to replace inflammation as the main driver of tissue damage. To assess whether neuronal loss might be a component of the progressive disease phase, we examined spinal cord tissue from a cohort of MS patients. A moderate amount of neuronal loss was found to occur early in the disease but did not overtly progress with disease duration. However, changes in neurofilament phosphorylation in the neuronal cell body and a loss of axons in demyelinated lesions of the white matter correlated with disability scores and disease duration. Our data show that chronic demyelination of axons in MS leads to altered neurofilament phosphorylation not only in the axon, but also the neuronal cell body. These metabolic changes correlated with disease severity and disease duration, and may thus represent a pathological substrate of progression. This presentation will address aspects of disease progression in MS from a neuropathological point of view.
IMMUNOPATHOGENESIS

Hans-Peter Hartung
Department of Neurology, Heinrich-Heine University, Düsseldorf, Germany

Abstract not in hand at the time of going to press.
MS: DIAGNOSIS AND PROGNOSIS

Xavier Montalban
Unit of Clinical Neuroimmunology, Hospital Vall d’Hebron, Barcelona, Spain

Abstract not in hand at the time of going to press.
The availability of new disease-modifying treatments for multiple sclerosis (MS) has raised the interest on paraclinical measures to monitor the disease evolution and to assess therapeutic response. Evoked potentials (EPs) reflect function of central sensorimotor pathways which are affected by MS. EPs abnormalities may reveal subclinical lesions, objectivate the involvement of sensory and motor pathways in the presence of vague disturbances, provide indication on the demyelinating nature of the disease process. Their value in the diagnosis of definite MS is much lower than that of MRI, more sensitive to brain and cervical spinal cord lesions. More promising is the application of EPs in the assessment of disease severity and in monitoring the evolution of nervous damage. Cross-sectional and longitudinal studies have demonstrated a good correlation between disability and evoked potential abnormalities. As a consequence, they can be utilised to monitor the progression of demyelination and axonal damage. Therefore, they are potentially useful as paraclinical end-point in phase III clinical trials to evaluate the efficacy of new therapies which can modify the natural course of the disease, while they are of limited value in phase II clinical trials because of their low sensitivity to disease activity. Moreover, evoked responses can be useful in testing the effects of drugs potentially modifying central conduction. Finally, recent evidence indicates that EPs performed early in the disease may help predicting a worse future progression in the long term. If confirmed, these data suggest a possible usefulness of EPs in the early identification of patients who are more likely develop future disability, thus requiring a more frequent monitoring or being potential candidates for more aggressive disease-modifying treatments.
MRI IN DIAGNOSIS AND MONITORING OF MS

Frederik Barkhof
Image Analysis Center (IAC), VU University Medical Center, Amsterdam, The Netherlands

Neuroimaging, and especially magnetic resonance imaging (MRI), is often being used to demonstrate dissemination of lesions in the CNS in patients with multiple sclerosis (MS). In the recently adopted diagnostic criteria for MS, as proposed by an international panel [McDonald et al.], strong emphasis is placed on the use of information derived from MRI. In this setting, where one relies more heavily on MRI than previously, a high specificity is warranted. To demonstrate dissemination in space (DIS), the international panel has chosen to rely on the criteria by a European study group [Barkhof et al.], which have been shown to be more specific (and accurate) than previous criteria.

MRI in the McDonald criteria
The DIS criteria include at least 1 juxtacortical lesion, at least 1 enhancing lesion, at least 1 infratentorial lesion, and at least 3 periventricular lesions. The Barkhof criteria provide a cumulative chance model, based on 4 dichotomized criteria. The international panel has chosen to implement these criteria as modified by Tintore et al. In this modification, an optimal cut-off of 3 positive criteria has been proposed, and a substitution of a gadolinium-enhanced lesion by at least 9 T2 lesions, to demonstrate DIS. For the demonstration of dissemination in time (DIT), a gadolinium-enhanced lesion at 3 months or later suffices, or a new T2 lesion (originally defined as being apparent on a further follow-up scan, but probably also at month 3). Recent studies have shown that the implementation of these criteria have good predictive value for the development of CDMs according to the older (mostly clinical) Poser criteria [Barkhof et al., Dalton et al.]. In the 2005 revision of the McDonald criteria [Polman et al.], slight modifications have been introduced, e.g. replacement of missing infratentorial lesions or 9T2 lesions with spinal cord lesions.

Spinal cord MRI is often useful
In cases where there is doubt about the applicability of the brain MRI criteria (older patients, cerebrovascular risk-factors), the performance a spinal cord scan can be extremely helpful, since incidental cord lesions are extremely uncommon in ageing and cerebrovascular disease, and very frequent in MS (even in patients without cord symptoms or signs). Other indications for a spinal cord scan include: primary progressive MS, cord presentation, and rarely, a negative brain scan with strong clinical suspicion of MS. The use of MRI in the spinal cord has recently been reviewed by the MAGNIMS group [Lycklama].

Monitoring treatment using MRI
Serial MRI shows a vast amount of disease activity that goes undetected clinically. To a large extent, the significance of such subclinical activity remains undetermined. The number of active (gadolinium-enhancing) lesions is closely linked to (concurrent) relapse-activity, but its predictive value wears off over time [Kappos], and the predictive value for evolution of disability is limited (as is the case for relapses). Measures of cerebral atrophy form (serial MRI) may prove more effective in this regard. While MRI plays a major role in evaluating the effect of new therapies in randomized clinical trials, its importance in monitoring individual patients remains uncertain. If any, the usefulness of MRI may be to rule out subclinical relapses in patients, when there is doubt about the institution or modification of anti-inflammatory treatment.

References:
CLINICAL TRIALS: METHODOLOGY AND ANALYSIS

Fred D. Lublin
Department of Neurology, Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai School of Medicine, New York, NY, USA

Trial design in multiple sclerosis has advanced considerably over the past two decades, successively building and improving on previous successes in the implementation and analysis of new clinical trials. Most of these trials have been successful and this has led to the regulatory approval and commercial availability of seven agents as disease modifying therapies for multiple sclerosis. During this period, outcome measures have been validated to determine the efficacy and safety of such agents, notably those useful in reducing the inflammatory aspects of disease. These include measurements of relapse reduction (annualised relapse rate, time to first relapse, proportion of subjects relapse free), disability (change in EDSS score, change in MSFC score) and MRI metrics (measurements of gadolinium-enhancing lesions, T1 and T2 lesion load). Recent trial design has shown that one can answer some clinical questions after one year on study and that these results may be predictive of more robust two-year trial data. The other important recent lesson involves emergence of rare complications of immunomodulatory therapy. As therapies become more successful in reducing inflammation in MS, new metrics will be needed, such as the measure of disease activity-free state. Other important challenges include use of placebo and active controls, the hazards of open label studies, the apparent reduction in disease activity seen in both treated and untreated patients.

Another critical area of development will be tools for assessing potential effects on progressive disease, the treatment of which is the major unmet therapeutic need in MS today. Here the mainstay of response would be change in disability metrics. Also to be evaluated, as we consider potential strategies for repair and recovery, will be metrics for gauging improvement. In addition to enhancing our clinical analyses, we need to better implement advanced MRI metrics such as magnetization transfer imaging, diffusion tensor imaging, high field imaging and spectroscopy into multi-center therapeutic trials.
CURRENT DISEASE MODIFYING DRUGS: EVALUATING THE EVIDENCE

Mark S. Freedman
Multiple Sclerosis Research Unit, The Ottawa Hospital, Ottawa, Ontario, Canada

As new therapies enter the marketplace, we must evaluate the evidence supporting their efficacy in order to compare their relative value for our patients. Patient populations, diagnostic definitions, and especially the response of placebo groups have changed over the years, making it nearly impossible to simply compare efficacy outcomes from various trials. A perfect example is to compare the same medication and the effect it achieved over a decade of various trials evolving to date; contemporary studies yield greater efficacy, yet medications have not really changed. Evidence based approaches help to iron out these differences and concentrate on “absolute” efficacy, which can be reduced to a more conservative comparator, the “number needed to treat” or NNT. These NNT values are not perfect comparators either, since they may underestimate true treatment effects, especially when rates of the outcome measure become very small such that overall differences between treatment and placebo groups is also reduced. Though statistically the effects are proven, the magnitudes become even more difficult to compare. Future trials focusing on outcome measures such as relapse rates will no doubt require many more patients to show what studies a decade or more ago did with a fraction of the patients. Still one should have an approach to compare agents based on known, validated outcome measures. We must also be careful to weigh primary outcomes on their individual merits without some of the more exploratory outcomes, no matter how compelling they may be. For example, an agent that may show only modest effects on relapses, but markedly affects brain volume (atrophy) can be construed as powerful if one puts a lot of emphasis on the MRI outcome even though it is not the primary. If brain atrophy was more important than relapse reduction, it needs to be made the primary and randomization would then be based on it. It cannot simply be assumed that randomization to insure the groups are equal in terms of their overall risk of having a relapse, need not be also equally distributing patients based on their risk of losing brain volume. To do so would be to first select the groups based on known and perceived “risks of atrophy”, then randomizing them accordingly. It is also not enough to consider just the perceived benefits of an agent, without taking into account any risk of “harm” that might be taken in order to gain the benefit; a similar conservative measure of this is the “number needed to harm” or NNH. It is the true “benefit to risk” ratio that will undoubtedly take over as the mainstay for comparing contemporary and future treatments. One method could be to compare the “likelihood of help vs. harm” by simply calculating the NNT vs the NNH. However, as new agents with different properties loom for the treatment of MS, we are discovering that although the “benefits”, based on validated outcome measures, can be comparable, the “harm” however is not and each new agent seems to bear its own new type of “harm.”
L10

SAFETY ISSUES

Gavin Giovannoni
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Abstract not in hand at the time of going to press.
Abstract not in hand at the time of going to press.
FUTURE THERAPIES

Jerry Wolinsky
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The early to mid-1990s saw the introduction of the first evidence-based, disease modifying therapies for multiple sclerosis. Subsequently, our therapeutic armamentarium has grown, but as elegantly reviewed in earlier presentations, substantial unmet needs remain. Nevertheless, our experiences with current registered therapies provide an important benchmark with which to evaluate newer drugs in active clinical development. Fortunately, the pipeline of new therapeutic agents to control inflammatory aspects of the disease is quite rich, as approaches that might limit progressive phase aspects of the disease or stimulate repair are being sought. In this session, we will consider where these newer agents reside in the therapeutic pipeline and review in some detail those drugs with the shortest potential time lines to the clinic. Both cladribine and fingolimod have already been submitted for regulatory review; with fingolimod soon to be released as an approved drug for relapsing MS in the USA. The development programs for teriflunomide, alemtuzumab, laquinimod and fumarate are not far behind. As time allows, we will consider the different mechanisms of the actions of these drugs, current knowledge of their likely safety and efficacy, and how they may fit into our therapeutic armamentarium over the next five years - assuming that they are able to make it through the registration process unscathed.