Multiple Sclerosis Disease Report

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The *FasterCures* Philanthropy Advisory Service

*FasterCures / The Center for Accelerating Medical Solutions*  
*FasterCures / The Center for Accelerating Medical Solutions* is a nonprofit “action tank” whose mission is to identify and implement global solutions to accelerate the process of discovery and clinical development of new therapies for the treatment of deadly and debilitating diseases. *FasterCures*, as a center of the Milken Institute, is nonpartisan, nonprofit, and independent of interest groups.

Barriers to progress in accelerating cures exist all along the research continuum—from basic research to development, from medical education to medical practice, from investment capital to human capital. *FasterCures* is working to clear the path to faster progress, not just by analyzing barriers, but by overcoming them through action. A force to catalyze systemic change, *FasterCures*:

- Evaluates current systems of disease prevention, research, development, and treatment;
- Identifies barriers to efficiency, effectiveness, and expediency in those systems;
- Creates achievable action plans to improve those systems; and
- Provides seasoned leadership and expertise in implementing those action plans in concert with organizations searching for new medical solutions.

To guide its efforts, *FasterCures* developed a Blueprint for Change focused on the transformation needed in three areas of medical research: research leadership and innovation; research tools and resources; and the medical research environment. The *Philanthropy Advisory Service (PAS)* aims to promote progress in all three areas through more informed philanthropic investment.

**Helping Philanthropists Make Informed Investment Decisions**

The lack of independent, reliable data about nonprofit disease research opportunities is a major barrier to encouraging significant support for such research and to improving the efficiency and productivity of philanthropy. With grants from the Bill & Melinda Gates Foundation and the Pioneer Portfolio of the Robert Wood Johnson Foundation, *FasterCures* has developed the *PAS* to address this problem.

The objectives of PAS include:

- Helping philanthropists align their goals and expectations with the capabilities and approaches of research organizations;
- Identifying gaps in funding for areas crucial to the success of specific disease research efforts; and
- Promoting among potential donors a "continuum of cure" perspective that can help develop cures for deadly and debilitating diseases.

PAS creates an information marketplace to support informed philanthropic investment. It improves the efficiency and productivity of both philanthropists and the nonprofit disease research
organizations that depend on their support, especially in areas where there are demonstrated funding gaps in research and development.

**Philanthropy Advisory Service Analyst Reports**

**PAS** provides two types of reports—disease and organization reports.

- **Disease Reports** discuss the burden, progression, and existing treatments for a given disease; highlight priority research areas; and provide an overview of relevant activities in the commercial and nonprofit research sectors. These reports provide a broader understanding of the disease, its toll on the greater society, and any potential products in the pipeline, as well as describe promising research areas. This information establishes the contextual knowledge for readers to consider as they evaluate nonprofit organizations in a specific disease area, particularly with regard to whether an organization is addressing key research areas and challenges.

  **PAS** develops disease reports using desktop research. Each report is reviewed and validated by a Scientific Advisory Board, or SAB, composed of leading researchers and clinicians in that disease area.

- **Organization Reports** are developed describing the activities of nonprofit organizations involved in disease research. For diseases primarily affecting the developed world, organizations reviewed include those funding research, as well as those providing tools to support research efforts. For diseases primarily affecting the developing world, the organizations reviewed include product development partnerships as well as academic and private research organizations.

  These reports provide detailed information on strategy, research portfolio, management, and financials. They also include an assessment of the organization’s practices according to a set of metrics that *FasterCures* believes contribute to the acceleration of biomedical research. Readers can use this information together with the context outlined in the disease report as an aid to making philanthropic investment decisions.

  Organization Reports are developed based on information collected in the public domain, augmented by discussions with representatives of the organization, with input from the relevant **PAS** SAB.
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Summary

**Disease Definition**
Multiple sclerosis (MS) is a disease of the central nervous system (CNS) in which the body’s immune system attacks the myelin covering insulating the nerves, resulting in neural dysfunctions and disability. The disease is further categorized into four major sub-types based on the pattern of the attacks: relapsing-remitting, from which some patients move on to the secondary-progressive type; primary progressive; and progressive relapsing.

**Key MS Statistics for the United States**
While MS affects a relatively small number of patients and is not deadly in and of itself, its burden to the patients and the economy is sizeable due to its chronic and debilitating nature.

- There are 250,000-350,000 cases of MS in the United States;
- Every year, it is estimated that there are 10,400 new patients;
- In 2002, 3,200 deaths were attributed to MS, due to the associated complications and the malignant subtype (0.1 percent of total deaths in the United States), but the proportion of the disease burden is five times higher when the impact of disability is taken into consideration;
- MS is more common in females and strikes young adults, with onset occurring between 20 and 50 years of age in over 80 percent of cases; and
- While there are no accurate statistics on the cost of MS, the National Institute of Neurological Disorders and Stroke (NINDS) estimates the cost to amount to billions of dollars.

**Current Treatment**
Currently, there is no cure for MS. Several treatments are available to delay the progression of the disease for a limited period of time, including five drugs for the relapsing-remitting subtype and one for the progressive subtype, which is not widely used.

**Research Investment**
In 2007, the National Institutes of Health’s (NIH’s) investment in MS was $98 million, compared to $110 million in 2006 and $99 million in 2003. There are 234 clinical studies for MS, and NIH is involved in 12 percent of all active MS clinical trials, which is a lower participation rate than the 22 percent involvement it has for all conditions. However, industry sponsors 53 percent of all active MS trials, compared to 33 percent for all clinical trials across all conditions.

**Key Research Areas for Investment**
Research efforts to better understand MS and thus develop effective treatments are underway in the federal, academic, and commercial sectors. Further research especially is needed in the following areas:
Multiple Sclerosis Disease Report

- Better understanding of the disease and its subtypes, including the causes and drivers of progression, the interaction between the immune system and the brain, and differences in different types of lesions
- Tools to predict disease activities and courses, linked to patient categorization and treatment regimen
- Diversification of treatment strategies and investment in prerequisite basic research and research tools, including:
  - Continued investment in strategies focusing on inflammation
  - Emerging strategies focusing on neuroprotection, including better understanding of the mechanisms of neuronal damage and tools to measure disease progression and treatment effects
  - Emerging strategies focusing on neuronal repair, including research on the mechanisms of selective repair and tools to measure disease progression and treatment effects
- Development of symptomatic treatments to address the needs of existing patients.

Challenges

MS research faces critical challenges, including the following:

- Limited understanding of the causes and mechanisms of the disease
- Complex method of tracking disease progression and treatment effects
- Limited availability of biospecimens and quality data, as well as access to analytical tools
- Increasing costs and scale of clinical trials
- The dominant animal model reflects only one aspect of a complex disease
- Lack of multidisciplinary talent and limited drug development capability

Key Nonprofit Research Funders

There are four major nonprofit organizations that fund MS research, outlined below. In addition to these research-funding organizations, Accelerated Cure Project provides tools and resources for MS research.

<table>
<thead>
<tr>
<th>Name</th>
<th>Annual Research Funding</th>
<th>Research Funding / Expenses</th>
</tr>
</thead>
<tbody>
<tr>
<td>National MS Society</td>
<td>$44.2M</td>
<td>18%</td>
</tr>
<tr>
<td>Myelin Repair Foundation</td>
<td>$3.0M</td>
<td>70%</td>
</tr>
<tr>
<td>Nancy Davis Foundation for MS</td>
<td>$1.5M</td>
<td>65%</td>
</tr>
<tr>
<td>Montel Williams MS Foundation</td>
<td>$0.3M</td>
<td>51%</td>
</tr>
</tbody>
</table>
Key For-Profit Players

There are six MS treatments in the market, and there are 46 industry projects in clinical development.

**MS drugs in the market (companies)**
- Avonex (Biogen Idec)
- Copaxone (Teva)
- Rebif (EMD Serono, Pfizer)
- Betaseron (Bayer/Berlex Laboratories, Novartis/Chiron)
- Tysabri (Biogen Idec, Elan)
- Novantrone (EMD Serono)

**Companies with largest MS pipelines**
- Biogen Idec (6)
- Roche/Genentech (5)
- EMD Serono (4)
- Pfizer/Wyeth (3)
- Merck/Schering-Plough (3)
- Sanofi-Aventis (3)

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1 Sorted in the descending order of the drug's revenue in the United States, includes both drug developers and distributors, globally.
2 EMD Serono, known as Merck Serono outside of the United States, is part of Merck KGaA. Merck KGaA is based in Germany and is a different company from Merck & Co. This report will use the name EMD Serono rather than Merck Serono to minimize confusion.
3 Ranked by the size of pipeline. Number of compound trials applicable to MS in parentheses.
Disease burden

Overview

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) with an unpredictable course. The leading theory regarding characterization of MS is that it is an autoimmune disease in which the body’s immune system attacks the myelin covering responsible for insulating nerves. Without myelin, communication of the nerves is disrupted, which can affect movement, sensation, and cognitive functioning. Its name means “multiple scars or hardening,” and is derived from the observation of multiple areas of demyelination. The exact cause of MS is unknown, but it is believed that environmental factors, heredity, and potential viral infection may play a role in its onset. There is no cure for MS, but there are many treatment possibilities focused on alleviating the associated symptoms or trying to prevent relapses. As a more detailed understanding of the nervous system becomes available, new techniques are being developed to treat and cure MS.

Burden

MS is an autoimmune disease of the CNS, usually commencing in relatively young adulthood and affecting patients throughout their lives. It is the most common disabling neurological disease in young adults, with up to 60 percent of patients experiencing ambulatory issues within 20 years of onset. The disease can take many different courses—relapsing-remitting, primary progressive, secondary progressive, and progressive relapsing are the major categories.⁴ The National Institute of Neurological Disorders and Stroke (NINDS) estimates that the prevalence of MS in the United States as 250,000 to 350,000 based on diagnosed patients⁵ and incidence as 200 new cases diagnosed per week, which implies annual diagnosis of 10,400 new cases. Given that these numbers are based on cases diagnosed, the potential incidence and prevalence may be even higher, and recent estimates released by the World Health Organization (WHO) and the Multiple Sclerosis International Federation suggests a higher prevalence of 400,000 and an incidence of over 12,000 as of 2008. The numbers are higher in the United States than other parts of the world (Table 1).

Table 1: Statistics on MS

<table>
<thead>
<tr>
<th></th>
<th>United States</th>
<th>World⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence per 100,000</td>
<td>135</td>
<td>30</td>
</tr>
<tr>
<td>Incidence per 100,000</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Average age of onset</td>
<td>32.5</td>
<td>29.2</td>
</tr>
<tr>
<td>Male to female ratio</td>
<td>1:2.6</td>
<td>1:2</td>
</tr>
</tbody>
</table>

Source: Multiple Sclerosis International Federation, WHO.

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⁴ More details on disease subtypes are discussed in the Biology section of this report.
⁵ The National Multiple Sclerosis Society quotes prevalence of 400,000.
⁶ Prevalence and incidence data for the world are median.
Usually, patients experience the first symptoms of MS between the ages 20 and 50, with the mean age of onset in the United States being 32.5 years of age. However, disease onset at earlier or later ages is also possible, and the National MS Society estimates that there are about 8,000 to 10,000 pediatric MS patients. In terms of gender, twice as many women are diagnosed with MS as men, although gender disparity decreases as the age of diagnosis increases. In addition, MS is most common in the Caucasian population, especially for those with Northern European ancestry.

MS is rarely fatal, except in rare cases of malignant subtype, and usually does not lead to a drastic reduction in a patient’s life expectancy. However, disability caused by MS can lead to infectious complications, and the National MS Society estimates that the overall life expectancy of MS patients is 95 percent of the average population’s. According to WHO’s analysis of disease burden for the United States, MS was accountable for 3,200 deaths in 2002, or 0.1 percent of total deaths; in terms of DALYs (Disability-Adjusted Life Years), MS accounted for 0.5 percent of total DALYs or 105,000 DALYs in 2002.

The economic costs associated with MS are large, because it is a disease of young adults that affects patients throughout their lives. According to NINDS, annual costs of MS in the United States are in the magnitude of billions of dollars.8

**Risk Factors**

The risk factors for MS are not clearly identified. However, epidemiological studies are suggesting that both environmental and hereditary factors play a role in the disease onset.

Research indicates that there may be a strong environmental factor involved with the development of MS. The disease is five times more common in temperate climates than in tropical regions,9 and it is believed that moving to a new climate before the age of 15 results in adoption of the new region’s risk factors. After the age of 15, individuals are more likely to maintain the risk associated with where they grew up. Another phenomenon that highlights the possibility of environmental factors is the periodic detection of concentrations of MS patients in specific geographies. These cases have been studied thoroughly; however, no specific environmental factor has been found to date. These findings suggest two possibilities regarding an environmental factor: 1) around puberty, MS patients get an infection that remains latent until years later or 2) non-affected individuals come into contact with a protective substance that wards off the disease.

Exposure to specific types of common viruses also have been found to be associated with the risk of MS. Contracting common childhood infections later in life has long been hypothesized to be associated with the onset of the disease. Infection with the Epstein-Barr virus (EBV), one of the most common human viruses whose infection often goes unnoticed in childhood, can cause infectious mononucleosis if contracted later in life, which has been associated with MS. Other

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8 The Disability Adjusted Life Year or DALY is a health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of ‘healthy’ life lost by virtue of being in states of poor health or disability (1). The DALY combines in one measure the time lived with disability and the time lost due to premature mortality. One DALY can be thought of as one lost year of ‘healthy’ life and the burden of disease as a measurement of the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability.

9 More detailed figures not available.

9 However, recent research showed that the impact of latitude in prevalence is decreasing.
infectious agents such as human herpesvirus 6 and enteroviruses also have been associated with MS. Lifestyle factors, such as smoking and lack of sun exposure, also have been associated with higher risk of MS.

There also may be a genetic factor, as research shows that the disease is more common in people of Northern European decent, while it is not observed in populations such as the Inuit, Yakutes, Hutterites, Hungarian Romani, Norwegian Lapps, Australian Aborigines, and New Zealand Maoris. Children of MS patients have a 5 percent chance of developing the disease themselves, whereas the general population has less than a .1 percent chance of developing MS. For identical twins, if one twin develops MS the other has a 30 percent chance of developing the disease. Since the correlation between identical twins is not 100 percent, this suggests that although there may be a genetic component, it is clearly not the only factor. Some scientists suggest that there are genetic predispositions to developing MS that are antagonized according to their environment.

Other studies indicate that multiple genes may affect the development of the disease. Genetic inheritance patterns have been suggested in individuals with MS, particularly regarding specific regions of the human leukocyte antigens (HLAs), which are involved in T cell activities. A group of alleles referred as HLA-DR2 shows a consistent association with the disease, possibly increasing the risk of MS by three times. Research on cases of familial MS and comparison of genetics in animal models and humans have identified multiple other genes potentially involved in the disease’s development; it is likely that MS is a complex disease triggered by the interaction of multiple genes and environmental factors.

Biology

Symptoms and Causes

MS is a chronic inflammatory illness. An MS “attack” refers to an episode of inflammation in the white matter\(^\text{10}\) of the brain and spinal cord, which destroys myelin and myelin-producing cells. Myelin is what gives the white matter its color, so demyelinated areas, usually referred to as “plaques,”\(^\text{11}\) can be distinguished. It is not known what triggers the immune system to attack one’s own myelin, or how immune cells, present in the blood vessels but usually absent in the CNS, overcome the blood-brain barrier and enter the brain.

\(^{10}\) Recent research suggests that gray matter is also affected by MS, though the target is still myelin.

\(^{11}\) Plaques are classified as active, chronic, or shadow-based on the status of inflammation and myelin repair.
Destruction of myelin disrupts neurological functions. Electric pulses travel by jumping from one node of Ranvier to another (parts of the axons not covered by myelin), but destruction of myelin disables this mode of communication. Also, MS attacks can damage the axons, and recent studies suggest that this may be more important to disease progression. The damage to myelin and axons leads to MS symptoms, depending on the function that the affected nerve conducts. Typical symptoms include:

- Impairment of vision, such as blurred vision, color distortion, temporary blindness (optic neuritis)
- Impairment in other senses, including pain, temperature, touch, and vertigo
- Cognitive decline
- Loss of control in physical functions, such as spasticity, tremor, ataxia, dysfunction in bladder or bowel
- Psychiatric symptoms such as depression or euphoria unrelated to the patient's actual feelings
- Disturbance in speech
- Fatigue, muscle weakness

**Progression**

The progression of MS can take different forms for each patient. MS usually is classified into six subtypes, depending on the degree of decline in neurological function and frequency of attacks (Figure 3):\(^\text{12}\)

- **Benign**: MS subtype that shows few relapse and little progression after the onset—over 15 years after initial attack. Patients remain neurologically fully functional.
- **Relapsing-remitting**: MS subtype that shows a series of attacks followed by remissions, during which functionality is restored. Each attack lasts about four to six weeks.

\(^\text{12}\) Note that different studies provide different estimates of the prevalence by subtype of MS. NINDS points out that benign MS accounts for 20 percent of cases. The National MS Society provides an approximate distribution among the subtypes of relapsing-remitting (85 percent), primary-progressive (10 percent), and progressive-relapsing (5 percent), and points out that epidemiologic data prior to the introduction of treatment options suggest that about half of the relapsing-remitting patients progresses to secondary-progressive MS. The graph was generated by combining these pieces of information.
Primary progressive: MS subtype that shows a progressive decline in functionality, without distinct remission periods.

Progressive relapsing: MS subtype that shows a progressive decline coupled with acute attacks.

Secondary progressive: MS subtype in which patients with originally relapsing-remitting disease develop a gradual decline. The decline period can be accompanied by attacks.

Malignant: Rare MS subtype in which symptoms develop rapidly to cause disability or death.

Patients with their first attacks are referred to as having clinically isolated syndrome (CIS), as the diagnosis of MS requires evidence of multiple attacks. Some CIS patients move on to develop definitive MS.

Although the subtypes of MS have been characterized by the clinical manifestation of attacks and degeneration, magnetic resonance imaging (MRI) results have shown that clinically unnoticed attacks are 5 to 10 times more frequent than those noticed, and MS is now thought to progress even without clinical manifestation.

The current hypothesis for the development of MS is that the combination of genetic susceptibility and environmental triggers (e.g., Epstein-Barr virus) results in the development of T cells reacting to myelin protein. An extended latency period is thought to follow, sometimes 10 years or more, during which inflammatory cells are accumulated. A systemic infection, unrelated to myelin itself, may trigger the first attack, if the blood-brain barrier, which usually prevents mass entry of white blood cells into the CNS, is compromised. Each attack creates damage to the myelin and the axon. With subsequent attacks, the ability of the CNS to repair and compensate for the damage may not be able to keep up with the damage, and the disease progresses to neurodegeneration. At the same time, scientists also hypothesize that the inflammatory attacks may be a reaction to the lesion formation or other changes in the CNS.

Damage of axons in MS is partially explained by demyelination as well as by the body’s effort to compensate for the loss in nerve conduction. As part of the attempt to restore conduction, the level of different ions such as sodium and calcium change and their channels redistribute, which is thought to contribute to axon degeneration through overactivation of some receptors and excitotoxicity.

**Interventions**

**Diagnostics**

There is no single test that can diagnose MS. Yet, the advent of MRI has made it possible to visually observe the plaques in the brain, especially when used with contrast agents, which was a significant advancement in diagnosis of MS.

In 2001, an international panel organized by the National MS Society developed a new set of criteria for the diagnosis of MS that incorporates the use of MRI, and the criteria was subsequently updated.
in 2005. In order to be diagnosed with MS, the disease should be proven to be present across multiple areas of the CNS (“dissemination in space”) and for an extended period of time (“dissemination in time”). The criteria combine multiple data points to gauge whether the patient has MS. The data and tools used include:

- Number of clinical presentations of attacks
- Number of clinical presentations of objective clinical lesions
- MRI image showing multiple plaques, in different locations and/or from different times
- Spinal tap to assess the presence/level of specific proteins and immune cell in the cerebrospinal fluid (CSF)
- Visually Evoked Potential test (VEP) for optic neuritis, a typical symptom of MS
- Blood tests to rule out other causes

**Treatments**

Currently, there is no known cure or prevention for MS, as the exact causes are still unknown. However, treatments are available to manage acute attacks, slow disease progression, and manage various symptoms. This section focuses on therapies that slow the progression and relapse of attacks; six different drugs are currently approved by the U.S. Food and Drug Administration (FDA) for such properties, out of which five are for the relapsing-remitting form and one is for the progressive form. In general, avenues of intervention against MS can be categorized into the following:

- **General immune therapies**: therapies that alter the body’s overall immune responses, not necessarily targeting specific antigen-antibody relations. These therapies often aim at overall boosting, suppression, or rebalancing of the immune system.
- **Targeted therapies focusing on myelin proteins or related immune response**: therapies that use specific antigens or proteins related to myelin and try to specifically modify the anti-myelin immune reaction.
- **Therapies addressing the blood-brain barrier**: therapies that seek to reduce MS attacks by preventing immune cells from entering the brain.
- **Neuroprotection and remyelination therapies**: therapies that seek to minimize the damage to neurons or restore their functions after attacks. Measures include preventing the death of neuron cells and preserving the axon, as well as stimulating the body’s ability to restore myelin (remyelination).

**Interferon beta** was the first drug to be approved for the treatment of relapsing-remitting MS, and affects both the general immune system and the brain-blood barrier. Antiviral interferons are proteins that help fight infection and regulate the immune system. Interferon beta affects the course of MS by 1) reducing the pro-inflammatory molecules and macrophage in the immune system, which attack the myelin sheath and absorb the destroyed myelin, and 2) reducing the molecules that enable T cells to penetrate the blood-brain barrier. Currently, three different brand-name products are on the market: Avonex, Betaseron, and Rebif. Yet, some patients may develop

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13 Called McDonald criteria, as the panel was chaired by Ian McDonald.
14 No FDA-approved treatments address this mechanism yet.
immune reactions to the drug,\textsuperscript{15} producing antibodies that neutralize the interferons, typically within two years of drug use. These patients need to use alternative therapies.

Another drug that affects the overall immune system is mitoxantrone, marketed under the brand name Novantrone. Novantrone is a chemotherapy agent that is used as an immunosuppressant in MS, inhibiting the production of immune cells. The drug is the only one approved for the progressive form of the disease, and has shown to temporarily, positively affect the course of MS. However, long-term impact is unclear and it has toxic side effects. Approximately 2 percent of patients develop cardiac complications, and the therapy can also result in leukemia.

\textbf{Glatiramer acetate}, marketed under the brand-name Copaxone, is a synthetic form of myelin basic protein. This drug has fewer side effects than most MS treatments, and has been shown to reduce the relapse rate by almost one third. The drug is thought to have the ability to stimulate anti-inflammatory properties of the general immune system. Glatiramer acetate binds to antigen-presenting cells, which in turn activate T cells’ anti-inflammatory properties; these T cells migrate to the brain and suppress the MS attacks.

\textbf{Natalizumab}, branded as Tysabri, prevents immune cells from crossing the brain-blood barrier. The drug is a monoclonal antibody against integrin alpha-4, which is instrumental in attaching different cells together and mediating cell-to-cell interactions. Trials of Tysabri were temporarily suspended in 2005 due to cases of brain disease (progressive multifocal leukoencephalopathy) as side effects. It was approved by the FDA after additional trials, but under a strict risk management policy. It is recommended that the drug is prescribed only to patients for whom other therapies do not work.

\textsuperscript{15} The share of patients developing immune reaction against interferon beta varies depending on the drug. For interferon beta-1b and interferon beta-1a administered subcutaneously, this occurs with approximately 25 percent of the patients, while for those receiving intramuscular injections of interferon beta-1a the ratio is 5 percent.
Research

Overview

MS is a disease for which research has been progressing in basic biology and treatment development, as well as in the search for markers for diagnosis and to measure disease progression. Traditionally, research has focused on immunology and treatments focused on the immunological aspects of the disease; however, new areas of research are turning to neuroprotection and regeneration, as it becomes apparent that MS is a complex disease that cannot be characterized just as an autoimmune disease. In addition, disease markers are a major focus of research, which is expected to accelerate the rate of progress in other research areas by enabling earlier diagnosis and serving as research tools.

In 2007, NIH invested $98 million in MS research. Funding in 2007 decreased compared to the previous year, when funding for MS amounted to $110 million. There were 234 active trials for MS as of February 2009. MS trials tend to be later-stage and therefore are more often supported by industry than is the case for other diseases.

Scientific Research

Summary

Table 2 summarizes the major areas of scientific research in MS and areas where more investment is required to overcome challenges and accelerate research. The areas of current research and challenges were identified and prioritized through consultation with FasterCures’ PAS Scientific Advisory Board for MS.

<table>
<thead>
<tr>
<th>Research continuum</th>
<th>Current research foci</th>
<th>Challenges or areas requiring investment</th>
</tr>
</thead>
</table>
| Disease understanding | • Genetic and environmental risk factors  
• Role of different immune cells and immunomodulators  
• Blood-brain barrier disruption  
• Mechanisms of destruction  
• Drivers of disease progression and gray matter pathology  
• Remyelination and regeneration | • Better understanding of MS’s causes, including the impact of genetic risk factors on different systems  
• Research on the drivers of disease progression, a prerequisite to treatment development  
• Differences in the underlying drivers of disease subtypes require development of tailored treatments  
• Underlying bases of selective lesion repair, which will contribute to treatment based on the mechanism |
| Prevention | • Epidemiology and risk factor research (see Disease Understanding) may be relevant once specific strategies are identified  
• Vitamin D’s influence on the expression of MS risk factor gene | • With increasing understanding on how vitamin D affects the expression of a MS risk factor gene, development of a preventive intervention based on the mechanism could be developed  
• Overall, better understanding of the disease and its risk factors will contribute to prevention |
| Disease markers | • Monitoring tools of disease activity | • Tools to predict disease activities and courses, tied |
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Research continuum | Current research foci | Challenges or areas requiring investment
--- | --- | ---
and prognosis | and treatment effectiveness • Predictors of disease severity • Prognosis for benign MS and CIS • Biomarkers for diagnosis | to prognosis-driven patient categorization and appropriate treatment strategies • Measurement of disease progression and treatment effects, not only in terms of inflammatory lesions but also neuroprotection and neuronal repair • Imaging of myelin to enable direct observation of demyelination and remyelination

Treatment | • Ongoing research on: – Systemic immune treatment – Modification of immune reaction against myelin – Prevention of immune cell entry to the brain – Treatment targeting the CNS’s role in inflammation • Emerging research on: – Neuroprotection – Remyelination and regeneration – Improved symptomatic treatment | • Diversification of treatment research across the three major avenues of disease-modifying treatments: – Treatments targeting inflammation, including those focusing on the CNS’s role in inflammation – Treatment targeting neuroprotection and prerequisite etiologic questions – Treatment focusing on repair and prerequisite etiologic questions • Development of symptomatic treatments to address the needs of existing patients

Delivery | • Access to specialists and treatment costs | • Access is limited for patients without insurance coverage • Need better collection of underlying delivery data

Source: FasterCures.

**Disease Understanding**

**Key areas for further research:**
- Causes of the disease, including the systemic implications of genetic risk factors
- Drivers of disease progression
- Differences between disease subtypes
- Process of selective lesion repair

MS is a disease for which the cause is still unknown. Until recently, the immunologic characteristics of the disease guided much of the research agenda. However, recent research suggests that the disease is much more complex than previously thought, and scientists are questioning how central the role of the immune system is in the disease process. Many fundamental questions are yet to be answered.

**Causes of the disease**

Understanding the causes of MS is a fundamental research priority requiring more investment. Whether the disease starts in the peripheral immune system, with immune cells initiating the migration into the brain, or in the CNS, with changes in the brain actively drawing the immune cells to it, still needs to be clarified. However, no research has directly answered this question. Also, scientists do not yet know what factors (e.g., genetic, viral, environmental) are responsible for or associated with disease onset.

MS is a disease with multiple risk factors. In terms of genetic risk factors, the genes related to the antigen-presenting proteins in the immune system (HLA-DR2), more common in Northern Europe,
have long been associated with increased risk of MS. However, because the level of risk conferred by this gene explains only a small portion of the risks for MS, scientists have been searching for additional genetic risk factors. Recently, the International Multiple Sclerosis Genetics Consortium completed a major genome-wide association study, which identified two additional genetic risk factors, both involved in the regulation of the immune system, although the association was weaker than genetic risks associated with the HLA region. Other efforts to identify genes affecting MS include research on genetic risk factors that link MS with autoimmune diseases such as type 1 diabetes or Grave's disease.

As genes are identified as conferring risk for developing MS, the next step is to understand the role these genes play in disease progression and effects on different systems. Investment particularly is needed in research on the cumulative impact of multiple risk factor genes, as well as risks conferred by individual genes, in order to eventually identify a major target or targets that can alter disease process.

In addition to genetic risk factors, other factors are being investigated for their contribution to risk for developing MS such as infection, environmental factors, sex, and their interactions. Regarding infections, research continues on the role of the Epstein-Barr virus (EBV), the antibodies of which records show increases between late teens and late twenties in people who develop MS. Other infections and antibodies being studied include some forms of human herpesvirus 6, measles, mumps, rubella, influenza, and hepatitis B, as well as the presence of antibodies against myelin oligodendrocyte glycoprotein, although these are still in very early stages and strong associations have not yet been demonstrated.

Environmental factors such as nutrition or family composition is another area of risk factor research. Vitamin D, which has immunomodulatory properties and is closely linked to sun exposure, is an area that has been extensively studied and has been found to be linked with the disease in various patient types. In addition, the influences of younger siblings and hygiene have been studied, as these factors can influence the development of the immune system as a result of variance in frequency of infection.

The role of sex in MS is another area researched, as there are more female patients than male, and epidemiologic studies suggest that the female-to-male ratio is increasing. Some genetic risk factors are modified by sex—for example, the variants of interferon gamma gene seem to affect risk for MS in men but not in women. In addition, estrogen has been shown to modify the effect of a proinflammatory signaling molecule, and MS attacks seem to be less severe during pregnancy. Epidemiologic findings highlight another aspect of gender in MS, with studies showing that maternal “transmission” of MS (whether from the mother herself or through a maternal aunt or uncle) is much more significant than paternal transmission.

In addition, some researchers study the interaction of risk factors. For example, genetics seem to influence the impact of vitamin D in MS and vice versa, with a recent study showing that vitamin D affects expression of the major gene implicated in MS. Genotype for redheads is associated with MS, in a sex-dependent manner, and sun exposure in childhood was shown to reduce MS risk in non-redheads. Some risk factors also have been proven to be independent from each other, as was the case for the presence of EBV antibodies and a specific gene in HLA-DR complex.
Drivers of disease progression

Once the disease is triggered, understanding what drives the progress of the disease is another fundamental question that needs to be answered. While inflammation of myelin is a hallmark of the disease, questions that still need to be answered include whether it is a fundamental driver of disease progression or a reaction to another cause, whether the role of inflammation evolves over the course of the disease, and how it is related to neurodegeneration.

Much of the research on the initial stage of disease development has focused on the changes after the initial activation, including the role of different immune cells and immunomodulators, agents that modify the immune reactions. These have been traditional focus areas of MS research, but much more research is needed, especially on the roles of specific immunomodulators.

T cells have been a major focus of MS research. Scientists are researching the development of myelin-specific T cells, including how they develop and which specific part of the myelin basic protein (epitope) is linked to the immune reaction in MS. Scientists are also researching how T cells are activated in MS and how MS patients’ T cells are different from healthy individuals’ as well as whether there are any differences in regulatory T cells.

Although the focus of MS research has been on T cells, studies have suggested that B cells, another type of immune cell, also are activated in MS and produce auto-antibodies; research is ongoing to better understand what antigens they are reacting to. The antibodies produced by B cells and their effects on clinical outcome are other areas of research.

Research on the role of cytokines, a type of signaling molecules, is an important area of research. MS patients and EAE animal models show higher levels of certain pro-inflammatory molecules and lower levels of some anti-inflammatory molecules than normal subjects. Various signaling molecules involved in immune response are being studied for their involvement in MS. However, greater understanding of the immune system and the roles of its cells and molecules is essential to better understanding the disease.

Another actively researched topic in the early stage of the disease is the disruption in the blood-brain barrier. Researchers have identified specific adhesion molecules that must be in place to allow different types of white blood cells to move across blood vessels and enter the brain; their role in MS is being explored. Molecules with a potential role in the movement of immune cells across the blood-brain barrier include those secreted by immune cells as well as those present in MS lesions or secreted by the endothelial cells lining the blood vessels. However, it is unclear whether the immune cells initiate the trafficking across the blood-brain barrier or rather the brain recruits them—answering this question is critical to understanding the causes of the disease.

Scientists are also investigating the mechanism of destruction. Recent observations suggest that the majority of demyelination occurs through phagocytosis, the process through which solid particles are engulfed and destroyed by specific white blood cells. This process is mediated by both T cells and B cells, and the deposits are found in active lesions. Axonal loss is thought to follow demyelination, as research on animal models indicates that if remyelination is prevented, axonal degeneration is accelerated. In addition, the disease process is thought to result in ion imbalance, which also contributes to axonal loss.
At the same time, scientists think that demyelination and inflammation are not the only causes of axon degeneration. Studies of secondary progressive MS tissues and mice with chronic EAE have shown abnormalities in the tau protein, which stabilizes the microtubules, which in turn facilitate the transportation of nutrients and molecules in the axon. Scientists have observed abnormal tau phosphorylation and accumulation, which also leads to axon degeneration as observed in other neurodegenerative diseases such as Alzheimer’s disease. In addition, abnormality in mitochondria function and the death of oligodendrocytes may be also involved in this process—a possible common factor with other neurologic diseases.

**Differences between disease subtypes their drivers**

Another fundamental question pertaining to MS etiology is why are the MS subtypes different and what do they have in common? In addition to the differences in clinical course, subtypes differ in terms of patient demographics. For example, patients with primary progressive MS are in general 10 years older than those with relapsing remitting disease. Researchers also have recently started to study whether genetics affects the subtypes differently, focusing on the immune T cells. For example, population studies suggest that specific alleles in antigen-presenting protein genes may affect the disease subtype, severity of the disease, and disease outcome. Research on animal models is underway to understand how T cells are affected by these genes.

A major difference between the relapsing-remitting disease and the primary progressive disease is the extent of **gray matter pathology**. While MS’s hallmark is the lesions in white matter, research findings increasingly indicate that lesions in the cortex are widespread in MS. In addition, gray matter lesions occur in the early stage of the disease, and their extent is not correlated with lesions in the white matter. While gray matter lesions occur across all disease subtypes, they are especially noticeable in the progressive subtypes, which are characterized by the lack of inflammatory lesions. In addition, gray matter lesions are correlated with cognitive impairment and disabilities, symptoms that affect the patients’ quality of life but could not be explained by measures based on white matter lesions. How these lesions are formed is yet to be understood, but the process seems to differ from that of white matter lesions as the characteristics of the latter, such as significant inflammation and blood-brain barrier disturbance, are not observed. Scientists hypothesize that gray matter lesions could be a downstream result of white matter lesions, or could be due to an unrelated event, such as meningial inflammation or vulnerability of specific neurons.

Scientists are also studying the difference between the two progressive subtypes. For example, secondary-progressive MS patients have a thinner retinal nerve fiber layer and lower macular volume than primary-progressive MS patients.

**Process of selective lesion repair**

Another major question that needs to be answered in etiology is why some lesions repair themselves after an attack while others do not. Research is ongoing on what happens in the patients’ CNS between MS attacks and on the process of individual remyelination events, but the reason for selective remyelination is still unknown.

Scientists now understand that the absence of clinical attack in relapsing-remitting patients does not necessarily mean that the disease is inactive. Recent research showed that inflammation continues during remissions. Inflammations also were noticed in normal looking areas of brain,
Although the reaction was balanced by an anti-inflammatory mechanism. Scientists also observed changes in the composition of the lipid membrane, which is thought to disrupt the myelin sheath.

Evidence also is emerging that recovery from lesions does not necessarily involve remyelination. The brain does not simply recover from an MS attack but rather compensates for injuries by mobilizing other neurons. Small-scale observational studies have demonstrated that MS patients have more active neurons than the control group in conducting the same function, and imaging studies showed that functional connectivity in the brain is modified in MS patients.

As for the actual process of remyelination, scientists generally understand the overall process of remyelination, but have yet to clearly understand why remyelination fails to occur in MS. Myelination occurs when appropriate cell differentiation signals are in place, and oligodendrocyte precursor cells mature into myelin-producing oligodendrocytes to produce myelin to coat the axons. However, MS patients seem to have abnormalities in signals involved in this process, whether they are due to lack of positive signals or the presence of negative signals is under investigation.

**Other**

In addition to issues of disease etiology, scientists are seeking to better understand the factors affecting disease course and severity, including demographic risk factors and the characteristics of the first attack, including its location, severity, and outcome. In addition, pediatric MS is a distinct subgroup within MS where new research is conducted. Researchers are studying the pediatric disease’s distinct characteristics that are not shared with the adult disease, such as frequency of relapse, lesion pattern, or impact on cognitive function.

**Prevention**

Insufficient understanding of the causes of MS is a barrier to the development of preventive mechanisms. Advances in research on risk factors and epidemiology, summarized in the Disease Understanding section, will enable more research in this area. At the same time, however, specific potential approaches to prevention are emerging, notably through research on vitamin D. Recent research showed that vitamin D directly affects the expression of some genes in the HLA region, implying potential for preventive intervention.

**Disease Markers and Prognosis**

With the advent of MRI techniques that enable direct observation of MS lesions in the white matter, diagnosing MS, as defined as multiple lesions across time and location, has become easier. However, markers for other purposes still need to be developed, including predictive markers of disease activity as well as more accurate and sensitive measures of disease progression and treatment effectiveness.

Eventually, developing a disease categorization that provides clear direction in terms of treatment course will be critical. In addition, tools that can detect myelin itself, going beyond just myelin lesions, will be an important research advance.
**Predictors of disease activity**

Because MS is a disease with an unpredictable progression, especially in its early stages, identifying predictors of disease activity and its course is an important area of research. MRI imaging is an essential component of this effort; brain lesion volume, by itself or in combination with atrophy measures, has been shown to correlate with long-term disability and clinical progression. However, the ability of MRI to strongly predict clinical outcome is still an issue of debate. Other tools being investigated include the whole brain magnetization transfer histogram, and the Multiple Sclerosis Severity Score, a measure of disability. In addition, age is known to be a demographic predictor of disease course, and scientists have noted that prognosis after age 50, especially in terms of neurodegeneration, is more predictable than at an earlier age, during the progressive phase of the disease.

**Disease categorization and clinical treatment course**

Ultimately, research on prognostic markers will have to be linked to disease categorization and identification of effective treatment choices. Disease subcategories should be characterized by differences that have implications for treatment development and options, especially with regard to tailored approaches for disease subtypes. This implies that more needs to be done within the categorization scheme, and scientists suspect that current categorization schemes are combining patient subgroups that are fundamentally different. While personalized medicine is yet to be a topic in MS research, scientists are trying to understand what causes the differences in treatment results. For example, research suggests that differences in interferon beta treatment outcomes may be associated with genetic variances. However, development in this area is challenged by limitations in computational tools and analytical talent, lack of a large pool of standardized data, and a limited attempt to analyze clinical trial data by patient characteristics.

**Measurement of disease progression and treatment effectiveness**

The importance of biomarkers does not stop with diagnosing the disease and providing prognosis. Another important aspect of biomarkers is the sensitivity to disease stage, to provide a measurement of disease progression and treatment effectiveness. Currently, major tools used for such purposes are the Expanded Disability Status Scale (EDSS), a clinical measure of disability; and imaging using gadolinium, which identifies MS lesions. However, new imaging agents, such as Gadofluorine M and ultra small superparamagnetic particles of iron oxide, are thought to have higher sensitivity and capability for capturing information previously available only through postmortem biopsy. New imaging technologies to capture inflammation are also being developed, including new forms of MRI that shows better contrast and shorter acquisition time and techniques that detect smaller and earlier inflammation.

Scientists also are exploring alternative measures of disease progression beyond inflammatory lesions. For example, measures of neuron degeneration are getting more interest and growing in importance. Optical coherence tomography (OCT), which measures the thickness of the retinal nerve fiber layer and is used in the diagnosis of glaucoma, is being explored as a tool to track axonal degeneration in MS. Research suggests that the results of this method are reproducible across different clinical practices, which adds more promise. Yet, some scientists question the reliability of using retinal pathology to measure the overall disease, as that tissue seems to undergo more inflammation and injury than other parts of the brain. The extent of spinal cord atrophy is another measure considered to measure disease progression.
In addition, scientists are exploring measures to augment existing tools. For example, the level of a specific proinflammatory signaling protein is being studied for its potential link to MS attack onset and disease severity, and the Multiple Sclerosis Functional Composite and other clinical metrics such as time required to walk 25 feet are being studied to supplement the information obtained through EDSS for primary progressive patients. In addition, low-contrast letter acuity score, a type of eye exam, has been suggested as a proxy measure of brain lesion burden when screening for clinical trials.

**Imaging tools to detect myelin**

Imaging tools that can directly detect myelin are believed to have great potential to accelerate research. Current imaging tools focus on detecting myelin lesions in white matter, rather than myelin itself. Imaging techniques that can directly identify myelin will enable scientists to directly observe not only demyelination as a result of inflammation but also remyelination, whether as a spontaneous process or as a potential treatment. In addition, such a tool would enable imaging of gray matter lesions as well.

**Other**

In addition to these research areas, scientists are seeking to improve the method for diagnosing MS. With the trend toward early treatment, scientists are looking for tools that can diagnose MS earlier and more accurately, including through the use of blood and CSF markers.

Scientists also are searching for potential markers for specific symptoms of MS, either predictive markers or measurement tools to measure the degree of symptoms, such as cognitive impairment and functional deterioration, especially in ambulatory patients.

**TREATMENTS**

**Key areas for further research:**

- Diverse treatment strategies based on:
  - Inflammation
  - Neuroprotection
  - Repair
- Symptom management

So far, much of the effort in treatment development has focused on reducing inflammation. All of the currently approved treatments focus on inflammation, although the specific mechanism through which each treatment functions varies.

However, as scientists learn more about the immune system and the complexity of MS, the development of treatments that address other mechanisms are becoming more important. Uncertainty about whether immune-system-driven inflammation is the fundamental cause of the disease or a reaction that leads to repair requires a more diverse approach to treatment development, including focusing on the CNS aspects of the disease. Treatment research is being diversified to include strategies protecting neurons from degeneration or promoting the neuronal repair process. In addition, these emerging treatment options also have the potential to address the progressive disease subtype, for which treatment options have been limited so far.

It should also be noted that these emerging areas are where collaboration with other fields within neurology is important, as many pathways are shared, and the MS field can make a contribution.
because other neurodegenerative diseases usually are diagnosed after neurons start to die whereas MS often is diagnosed prior to degeneration.

Overall, multiple treatments are entering late-stage trials, and new treatment approaches are being explored. In addition, researchers are trying to develop treatments that can be taken orally rather than injected as well as developing new formulations of existing drugs, to improve patient convenience as well as regimen compliance, and to reduce side effects. In addition, researchers are trying to better understand the mechanism of drugs already on the market and to treat patients at an earlier stage of the disease.

**Treatment research targeting inflammation**

Strategies that can stop MS inflammation are the most active areas of treatment research in MS, despite recent debate about the role of inflammation in the disease process. Treatment strategies targeting inflammation can be further classified as the following:

- Systemic immune treatment
- Modification of immune reaction against myelin
- Prevention of immune cell trafficking across the blood-brain barrier

**Systemic immune treatment:** With interferon beta as an established therapy for MS, scientists are seeking to leverage other agents with immunomodulatory properties to help restore normal immune reaction in MS patients. Various immunomodulatory agents are under investigation, including cytokines that regulate the immune reaction and white blood cell differentiation. Many of the agents being studied can be taken orally to reduce patient burden. Multiple agents are currently in Phases 2 and 3 trials, and others are being explored in the laboratory or in small clinical trials.

As the immune system is believed to be the main culprit of MS attacks, suppression of the immune system has been a long-term strategy in MS research, as evidenced by the approval of mitoxantrone for secondary progressive MS. Scientists are developing treatments that target specific types of immune cells, such as B cells and T cells, as well as the microglia and macrophage.

Suppression of B cells is a relatively new treatment strategy, as scientists came to recognize their importance in the disease process. Scientists are researching the effect of existing MS treatments on B cells, and some existing treatments actually may increase B-cell activities. Various agents reducing the number of B cells are in Phase 2 or 3 clinical trials, many of them used in cancer chemotherapy. In addition, researchers are trying to understand whether the timing of B-cell treatment matters, as an animal study showed that B-cell depletion is effective after disease onset but not as a preventive measure.

T cells have long been the target of immune suppression in MS. Multiple agents, many of them derived from cancer treatment or treatment for organ transplantation, are being studied for their effectiveness in treating MS. Multiple agents are under investigation, ranging from early-stage trials to Phase 3 trials. In addition, scientists are researching whether inhibition of a subset of T cells inhibiting specific signaling can benefit patients.
Other types of immune cells against which therapies are developed are microglial cells and macrophages. Microglial cells are the first trigger of immune response in the brain and present antigens to T cells in the CNS; macrophages absorb entities perceived as foreign, either before or after T-cell action. Multiple compounds focusing on these cells are being studied, although they are still in early stages of investigation.

**Modification of immune reaction against myelin:** Scientists are exploring strategies to modify the immune reaction against myelin, rather than destroying immune cells entirely. Scientists are studying therapeutic strategies to **attack T cells reacting to myelin**. While general immune therapies affect the body’s whole immune system, the approaches reviewed here target only the specific immune response against myelin, leaving general immune function intact.

One strategy is to induce an immune response against the T cells reacting against myelin, vaccinating the patients against those T cells. This approach has shown some short-term effect for relapsing-remitting patients, and such a T-cell vaccine has just completed a Phase 2 trial. A similar approach is developing a vaccine against the peptide characteristic of the myelin-destroying T cells, rather than using the whole T cell.

Other approaches focus on **altering the T cell response to myelin**, rather than destroying the myelin-reacting T cells altogether. Such strategies include protein antigen feeding, which is drawn from the observation that taking an antigen orally can help reduce immune response against that specific antigen. In mice fed with myelin protein antigen, scientists have observed fewer relapses; clinical trials are being conducted to determine effectiveness. In addition, DNA vaccines, which inject the DNA encoding the myelin basic protein, are another strategy to modify the immune system to tolerate myelin. The approach was shown to have the potential to reduce immune reaction to myelin and brain lesions, although the results need to be validated in larger trials.

**Prevention of immune cell entry to the brain:** Multiple strategies to prevent T cells from crossing the blood-brain barrier to reach myelin are being studied. The commercialization of natalizumab is one outcome of such efforts, although its availability is limited due to serious side effects.

Several surface molecules that mediate immune cell entry into CNS, either on the white blood cells or the blood vessels, are being studied for their value as targets for this treatment strategy, along with enzymes that mediate crossing the barrier. One compound that addresses this mechanism by disturbing the function of a molecule needed in cell adhesion resulted in reduction of new lesions in a Phase 2 trial. In addition to agents that can disturb cell adhesion, scientists are researching antibodies against adhesion molecules.

**Treatment strategies targeting neuroprotection**

In addition to therapies that target immune cells, additional therapies to protect the neuron from damage and reduce clinical symptoms are being developed to address the needs of MS patients.

Various efforts are being explored to protect the neurons from the attacks and reduce the lesions. Substances being studied include agents with antioxidant properties, anti-excitotoxic agents, and agents that can suppress inflammation. Another area of research aims at improved protection of the neurons from ion imbalance, and clinical trials are under way for potassium and sodium...
channel blockers. Researchers also are studying whether modification of some of these agents can reduce neurodegeneration.

Other areas of research deserving focus include understanding the impact of the myelin sheath on axons as well as the impact of multiple lesions on an axon. In addition, developing tools to monitor treatment effects is another area that needs research, as there is no adequate imaging technique to measure treatment effects in terms of preventing or slowing neuron death. Developing techniques to measure changes in nerve conduction will be important to pursuing therapeutic strategies in this area.

**Treatment strategies targeting repair**

After an MS attack, the body has been observed to produce more oligodendrocytes to naturally **remyelinate the axons**, and this process is thought to be linked to the remission phases. Scientists are researching substances that can stimulate this process. In mice, a specific type of human antibody was shown to be able to trigger remyelination, though the mechanism and applicability to humans is yet to be confirmed.

Other research that falls into this category includes exploring various protein growth factors, local environment for MS lesions, or small molecules to stimulate myelin and axon repair. Molecules that guide oligodendrocyte precursor cells are being explored for their potential to induce remyelination.

**Stem cells** are another area of interest for repair. Treatment using mesenchymal stromal cells—stem cells that have the potential to develop into various types of cells—reduced axonal damage, modified the immune activities, and showed potential for remyelination and neuron regeneration. An early stage trial of limited participants reported some improvement in disability with limited side effects.

Oligodendrocyte precursor cells, which can develop into oligodendrocytes that produce myelin, as well as astrocytes and neurons, are another type of stem cell being studied. Understanding what induces these cells to develop into one type of cell rather than another is an important area of research for the success of stem cell therapy across diseases, and research suggests that inflammation affects these cells’ path of development.

However, further progress in this area requires deeper understanding of the process of cell differentiation, especially at the molecular level. For remyelination, it is crucial to understand the timeframe in which remyelination needs to happen and the reason why spontaneous repair is not universal. Also, developing imaging techniques that allow direct observation of myelin will contribute to research acceleration in this area by enabling measurement of treatment effects.

**Rehabilitation and symptomatic treatment**

Rehabilitation is an important aspect of treatment in MS, as the disease affects the patient for an extended period of time, and reducing disability can make a significant impact on quality of life. Various rehabilitation therapies to help reduce symptoms are in place in addition to pharmacologic treatment to address specific symptoms.
Neurorehabilitation through exercise, physical therapy, and hydrotherapy are examples of areas where research is ongoing. Research is also ongoing for management of specific symptoms such as pain, fatigue, depression, and cognitive symptoms, through both non-pharmacological therapy and symptomatic drugs. Cognitive dysfunction is an area of special interest, as this is a symptom that has an especially negative impact on quality of life.

Other areas of treatment research

In addition to research that focuses on developing new therapeutics, researchers are also striving to better understand the mechanisms of existing drugs, how they affect various aspects of the disease, and what causes the variance in efficacy. Long-term benefits and side effects are also areas of research. In addition, researchers are studying whether patients with CIS can benefit from early treatment.

Care Delivery

Because MS is a lifelong disease, access to treatments and disease management resources is an issue for patients. Because most MS drugs are biologics—which require stricter quality control and have no generic equivalents available in many countries—the high cost of treatment associated with brand-name drugs and quality control in generic versions, where available, are major areas of concerns. Insurance coverage, financial burden, and quality of life issues are major areas of concern.

Research efforts in this area are focusing on access to neurologists by patient demographics and disease pattern, as well as quality of life studies. The National MS Society’s Sonya Slifka Longitudinal MS Study is an effort to collect data that can be used to better understand delivery issues, and worldwide data is compiled by WHO and the Multiple Sclerosis International Federation, published as Atlas: Multiple Sclerosis Resources in the World 2008. Scientists point out that delivery research should leverage clinical trials as add-on studies. In order for such an approach to succeed, appropriate funding and organizational arrangements will be required.

Research Infrastructure

Summary

Table 3: Major Research Tools and Resources for MS and Challenges

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<tr>
<th>Tool category</th>
<th>Existing tools and efforts</th>
<th>Challenges or areas requiring investment</th>
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| Biospecimens    | • Multiple biospecimen repositories have been developed, with some efforts to standardize collection protocols  
|                 | • Data from major studies that collect samples, such as genome-wide association studies or longitudinal studies | • Area with very limited investment  
|                 |                                                                                           | • Limited sample sizes, due to limited autopsy practice  
|                 |                                                                                           | • Lack of linkage of specimens with longitudinal clinical and imaging data  
|                 |                                                                                           | • Data pooling not possible due to outstanding differences in protocols  
|                 |                                                                                           | • Data collected in treatment trials not fully exploited |

16 The underlying data can be found at the Atlas of MS Database site, www.atlasofms.org.
<table>
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<tr>
<th>Tool category</th>
<th>Existing tools and efforts</th>
<th>Challenges or areas requiring investment</th>
</tr>
</thead>
</table>
| Clinical trials      | • Patient registry and clinical trial network in place, but not widely used due to incompatibility with healthcare system and research practice | • Low patient enrollment  
• Difficulties in conducting placebo-controlled trials  
• Leveraging clinical trials as an opportunity to increase disease understanding |
| Animal models        | • EAE as the widely accepted MS model, but limited to the inflammatory aspect of MS  
• Other models include virus-induced models, toxin-based models, and transgenic or mutant mouse models. | • Development and acceptance of alternative models representing other aspects of the disease  
• Search for a spontaneous MS model  
• Effective management of existing models |
| Drug development capability | • Most expertise and infrastructure reside in industry  
• NIH and some academic research centers with some infrastructure for drug development  
• Emerging efforts to increase industry-academia partnerships | • Limited understanding of the drug development process and statistical expertise for clinical trial design outside of industry  
• Difficulties in securing funding in translational research for treatment development  
• Need to further increase collaboration between academic researchers and industry |
| Research training    | • Traditional recruiting based on young investigator interest, limited success in attracting new talent, both in basic and clinical research | • Need for multidisciplinary talent, with expertise in clinical, radiology, or bioinformatics research for mass analysis of genetics and proteomics data  
• Strategy to increase interest from young clinicians to focus on neurology research, including industry partnership |
| Analytical tools     | • Limited number of research centers with analytical infrastructure | • Access to computational tools  
• Lack of standardization in analytical methodology |

Source: FasterCures.

Table 3 summarizes the major tools available for MS research and areas where more investment is required to overcome challenges and accelerate research. Major tools and associated challenges were identified and prioritized through consultation with FasterCures’ PAS Scientific Advisory Board for MS.

**Biospecimens**

Access to biospecimens is important in disease research across many diseases, but it is especially so in MS because it is an area where better understanding of the causes of the disease and its progression is crucial. For example, understanding the role of genetic risk factors and their impact on bodily systems, discussed in the previous section, requires access to large genetic and tissue data repositories. To maximize their value, biospecimens need to be linked to clinical and imaging data for better understanding of the disease course.

**Existing Resources**

Several biospecimen repositories collect tissue and CSF samples that can be used for MS research. The Human Brain and Spinal Fluid Resource Center at the University of California, Los Angeles, established in 1961, runs the MS Human Neurospecimen Bank, which collects brain, spinal cord, and CSF samples. The Rocky Mountain MS Center Brain & Tissue Bank in Colorado is another tissue bank, established in 1976. The Center has pledges from 1,100 MS patients to donate their
brain tissue and has distributed samples to 180 investigators to date. In 2008, the University of Illinois at Chicago MS Tissue Repository, which focuses on brain samples, was established. Many of these sites received support from NIH or other government entities as well as the National MS Society, and these three repositories follow the same protocol in specimen collection.17

Another effort to increase the availability of MS biospecimens includes the creation of a network of multiple sample collection sites sharing the same protocol and a single resource access interface. The Accelerated Cure Project collects biospecimens at six repositories across the country—Johns Hopkins School of Medicine, Multiple Sclerosis Clinical Center University of Texas Southwestern Medical Center at Dallas, Multiple Sclerosis Research Center of New York, Shepherd Center, Inc. in Atlanta, University of Massachusetts Medical School, and Barrow Neurological Institute in Phoenix—and makes the samples available to researchers. The initial collection, which started in 2004, focuses on blood samples and clinical data, but plans are in place to expand the collection to CSF and tissue samples.18

Other sources of MS biospecimens include samples collected as part of major studies. The University of California, San Francisco Multiple Sclerosis Genetics Group collects DNA data from MS patients and their family members not affected by MS as part of a multi-center study to understand genetic susceptibility of MS.

Biospecimens from Veterans’ Affairs Medical Centers also are often used in research. In addition, specimen collections based in continental Europe or in the United Kingdom maintain high quality samples.

**Challenges**

Biospecimens and data for MS are resources that especially require additional investment. Despite multiple efforts to collect biospecimens, current efforts have limitations in terms of sample size, compatibility across different initiatives, linkage with clinical data, and insufficient longitudinal approach. Complexities of the patient consent forms are also pointed out to be a barrier to expanding tissue banks. In addition, brain donation from MS patients is especially limited because patients often die outside of hospitals of causes unrelated to MS, and autopsies are not routinely performed and are even decreasing in the United States. The development of a national brain bank that uses a single protocol and linked to MRI and microarray data would benefit not only MS research but all neurologic research.

Another potential source of biospecimens is patient data and samples collected during clinical trials, usually owned by pharmaceutical companies. These data are very well-characterized with links to clinical data. However, their proprietary nature restricts access to data, and there is no system in place to facilitate sharing. Clinical trial data also have their own limitations, including the short duration of data collection, typically two or three years. Additional follow-up and innovative IP arrangements are needed to fully exploit these data. Some NIH-sponsored trials collect data for five years, which may be able to provide longer-term perspectives.

17 More information on National MS Society’s involvement in research resource development can be found in the PAS organizational report on the Society.

18 For more details, see the summary for Accelerated Cure Project in the Nonprofit Landscape section of this report or the PAS organizational report on Accelerated Cure Project.
Clinical Trials

Existing Resources

Clinical trials are a crucial step in treatment development, as well as an important opportunity to understand the disease itself. However, a shortage of patient enrollment is a major issue in MS trials. The North American Research Committee On Multiple Sclerosis (NARCOMS) Project, initiated in 1993, is a patient registry with over 32,000 MS patients enrolled. It is an effort to increase patient accessibility. The registry is maintained by the Consortium of MS Centers, a professional organization with about 200 MS healthcare provider organizations as members. The registry collects patient data such as demographics, medical history, and treatment received, and it is also used to recruit patients to enroll to clinical trials.

Another clinical trials resource is the Multiple Sclerosis Cooperative Research Group (MS-CORE), established in 2003 with initial funding from the National MS Society. MS-CORE is a clinical trial cooperative with 80 trial sites across North America. While it has not been widely used for MS trials, its infrastructure provides the potential to accelerate the roll-out of trials.

Challenges

While patient registries collect patient data and facilitate trial enrollment, researchers point out that they do not completely solve the problem of patient access. Challenges include the difficulties in updating registries and their incompatibility with the U.S. healthcare system.

Problems in trial enrollment are posed by not only the relatively small number of MS patients overall, but also by trial design issues. Trials using placebos are encountering more obstacles to enrollment as well as raising ethical concerns given the existence of treatments. Some trials seek to solve such a problem by expanding trial sites to international locations such as Eastern Europe.

In addition, etiologic research could better leverage industry-led clinical trials as an opportunity to increase disease understanding by tapping into their access to patients. Most industry-led clinical trials focus on evaluating the efficacy of a potential treatment, but etiology studies can be added through collaboration between the industry and academia. However, such add-on studies have to take ethical issues into consideration, and more funding is needed for such studies.

Disease Models

Existing Resources

The disease model for MS, EAE, was first induced in 1933. Mice are the most widely used animals, though some primates are also used. The models are created by injecting myelin basic protein and an adjuvant to the animal, which causes CNS inflammation and demyelination of the neurons.

In addition to EAE, other disease models used in research include virus-induced models, toxin-based models, and transgenic or mutant mouse models. Virus-induced models are based on the observation that some infections affect the risk of developing MS, and some infections in mice actually lead to CNS autoimmunity and demyelination. Mouse models based on Theiler’s virus is
one of the most common examples of virus-induced models, and models using Semliki Forest virus are also used.

Toxin-based models use chemicals to induce demyelination by damaging the oligodendrocytes or the myelin. While these models are not based on a potential disease mechanism, scientists can create lesions to specific locations, which can be an advantage to research on remyelination.

Genetic mutations or manipulations also generate disease models on which studies are conducted. Some transgenic mouse models are created by incorporating the human MS risk genes into mice, while others are created by manipulating gene expression of the immune system in the CNS. In addition, mice with natural genetic mutations that affect myelin formation are used.

**Challenges**

Among these models, the EAE model is the most established and widely accepted. However, although the EAE model may be a good proxy of MS for the inflammation aspect of the disease, it does not mimic the degenerative aspects of the disease. As a result, it is not an adequate research tool for research, especially focusing on neurodegeneration. Yet, the field accepts EAE as the standard model for MS research, and alternative models are not well accepted. This makes progress more challenging.

In the long run, better understanding of the causes of the disease and the role of genetic risk factors will enable the development of better animal models of MS. In the short run, screening collections of existing models, such as those available through the Jackson Laboratories, to find a spontaneous MS model with symptoms closer to MS, may be a strategy in the search for better animal models.

The research community also needs investments to better manage and maintain the existing models used in MS research. NIH has some efforts in place to collect various models used in research.

**Drug Development Capability**

The pharmaceutical industry is leading the drug development process in MS. Most of the required infrastructure and expertise, such as statistical expertise to design clinical trials as well as understanding of the drug development process and regulatory requirements resides in industry. While there is some drug development infrastructure available at NIH as well as at some research centers such as the Max Planck–Innovation’s Drug Discovery Center and Harvard NeuroDiscovery Center, the capacity is limited. In addition, translational research for treatment development is an area for which securing funding is challenging.

Increased collaboration between academia and the industry would contribute to accelerated translation of basic research into potential clinical applications. Efforts to create avenues for such collaborations are emerging, including the Biomarkers Consortium led by the Foundation for the National Institutes of Health, and Fast Forward, led by the National MS Society. In addition, some governments in other countries provide incentives for such collaboration.
**Research Training**

Researchers with appropriate expertise and skills are definitely a resource needed in MS research. Scientists point out that multidisciplinary talent is especially needed, with expertise in areas such as biostatistics, epidemiology, and radiology.

However, attracting research talent to MS is a difficult task, because of increasing student preference for private practice in the United States, decreasing interest in academic and clinical research careers, and the relatively limited number of patients in the United States. While this is a problem across clinical research, MS is facing additional challenges as it is an area where attracting clinicians is also difficult. Field-specific efforts, such as rotation programs with industry, may help encourage choice of a career in MS research, and various ways of providing additional incentives should be explored.

**Analytical Tools**

In addition to human resources, access to computational tools is an area where more resources are needed. Many of the major research questions described in earlier sections rely on genetic and pharmacogenetic analyses to find an answer. While some academic research centers have analytical infrastructure in place, such tools are not widely available and access is often limited, which makes the effort more challenging. Proteomic analysis, also needed to answer etiologic questions, is even more challenging, due to lack of standardized methodology and inconsistent data. This calls for a standardized, central technological platform.
Clinical Trials

As of February 2009, there were 234 ongoing clinical trials in MS (Figure 5).\(^9\)

Trials in MS have a higher share of Phase 3 trials than other diseases, at the expense of earlier stage studies. This is probably because many drugs in trials for MS have been previously developed for other indications, such as chemotherapy agents for different types of cancers.

In terms of trial sponsors, MS is a disease area where industry presence is pronounced, with more than half of the trials sponsored by industry, compared to 33 percent for all diseases combined during the same time period. NIH support of MS research was 10 percent lower than for other diseases. On the other hand, involvement of U.S. government and foreign government entities are on par with other diseases. Compared to the strong role of industry, the share of other players such as universities and nonprofit organizations is smaller than in other diseases.

As for the content of trials, 47 trials were observational studies focused on understanding the disease process, while the rest were interventional trials that focus on modifying the disease outcome. About two-thirds of all MS trials involved a drug or a biologic, compared to 54 percent for all trials. All other types of interventions had slightly lower or similar representation in MS than in other diseases.

\(^9\) Excluding studies that are completed, terminated, suspended, or withdrawn from 287 MS-related trials listed on ClinicalTrials.gov.
The share of interventions using drugs and biologics was especially high in industry-sponsored trials, accounting for 98 percent of trials. The importance of drugs and biologics also strong in trials sponsored by non-industry organizations, accounting for more than 70 percent of all such trials.

**Funding**

In 2007, NIH’s investment in MS research was approximately $98 million. This was a decrease of 10 percent compared to $110 million in the previous fiscal year and going back to the 2003 level (Figure 6). In addition, NIH funding for MS is projected to be flat through 2009. Given that the prevalence of MS in the United States is about 300,000, the current level of NIH’s investment translates into $327 of research investment per existing patient.

During the same period, the overall NIH budget grew at a 1.8 percent compound annual growth rate during 2003-2007, unadjusted for inflation. As a result, the share of MS investment out of the total NIH budget has slightly decreased over time, and now stands at 0.3 percent of total. This is lower than the share of MS out of total disease burden measured in DALY’s, which is estimated to account for 0.5 percent of total disease burden in the United States.  

20 In January 2009, NIH updated the methodology through which it calculates its investment in each disease. Based on this new methodology, the investment in MS amounted to $149 million in 2007 and $169 million in 2008. However, in order to show the trend over an extended period of time, this report shows the data based on the historical methodology.
Market Analysis

Overview

This section provides an overview of the commercial landscape of MS treatment. Six drugs are available in the United States for the treatment of MS, mostly biologics. The global market for relapsing-remitting MS drugs has been growing at 20 percent compound annual growth rate during the recent years, and the approximate market size is $7 billion.

As of 2008, the R&D pipeline has 46 compounds in clinical trials, of which 10 are in Phase 3 trials. Major players include Biogen Idec, EMD Serono, Teva, Bayer Healthcare, and Sanofi-Aventis. Several companies without an MS drug on the market also invest in MS research, many of them with a compound in Phase 3 trials.

Products

Currently, there are six treatment options available for MS in the United States; five of them are for the relapsing-remitting form of MS and one is for the chronic, progressive type (Table 2).

Table 2: Pharmaceutical Companies with MS Drugs Launched in the United States

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active ingredient</th>
<th>Manufacturer</th>
<th>Distributor co-marketer</th>
<th>Patent expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex</td>
<td>Interferon beta</td>
<td>Biogen Idec</td>
<td>N/A</td>
<td>2008-2013</td>
</tr>
<tr>
<td>Betaseron</td>
<td>Interferon beta</td>
<td>Bayer</td>
<td>N/A</td>
<td>2007-2008</td>
</tr>
<tr>
<td>Copaxone</td>
<td>Glatiramer acetate</td>
<td>Teva</td>
<td>Sanofi-Aventis</td>
<td>2014</td>
</tr>
<tr>
<td>Novantrone</td>
<td>Mitoxantrone</td>
<td>EMD Serono</td>
<td>N/A</td>
<td>2006</td>
</tr>
<tr>
<td>Rebif</td>
<td>Interferon beta</td>
<td>EMD Serono</td>
<td>Pfizer</td>
<td>2009-2015</td>
</tr>
<tr>
<td>Tysabri</td>
<td>Natalizumab</td>
<td>Biogen Idec</td>
<td>Elan</td>
<td>2014-2020</td>
</tr>
</tbody>
</table>

Note that Tysabri was approved with a risk management program in place, called TOUCH (Tysabri Outreach: Unified Commitment to Health) Prescribing program. Tysabri can be distributed only through registered prescribers, infusion centers, and pharmacies associated with the infusion centers.

Most MS drugs are developed by biotechnology companies or specialized drug companies that focus on MS, with additional companies involved in the distribution through partnerships or acquisitions. For example, Bayer acquired Schering in 2006, the original producer of Betaseron; Pfizer
distributes Rebif in the United States through a co-marketing agreement. Similarly, Sanofi-Aventis collaborates in the marketing of Copaxone, and Elan has exclusive distribution rights of Tysabri in the United States.

The active ingredients available for the relapsing-remitting type can be characterized as the following based on their mechanisms of intervention:

- Interferon beta: General immune therapy and strengthening of blood-brain barrier
- Glatiramer acetate: General immune therapy
- Natalizumab: Preventing entry of immune cells to the CNS

**Market Share**

The overall market for relapsing-remitting MS has been growing at 20 percent per year over the last five years. The growth has been driven by Rebif and Copaxone. By drug category, interferon beta has been growing at 16 percent per year, while glatiramer acetate and natalizumab have been growing much more rapidly. Tysabri, which was initially introduced to the market in 2004 and withdrawn due to side effects, was reintroduced in 2006 with a safety plan in place, and accounted for 5 percent of total market in 2007 (Figure 7).

The only FDA-approved drug for a more chronic progressive form of MS is mitoxantrone, an immunosuppressant used for the treatment of MS and various cancers, marketed as Novantrone by EMD Serono. However, as generic mitoxantrone became available in 2006-2007, the product has ceased to be a major brand product for which companies track sales numbers. Generic producers of mitoxantrone include Teva, Abraxis, Bedford, and Hospira.
Out of the six major treatment options, exclusivity already has expired for four, subjecting them to potential competition. However, of Avonex, Betaseron, Copaxone, and Novantrone, Novantrone is the only therapeutic for which a generic therapeutic equivalent has been introduced, which is undermining the brand name drug’s profitability. For other drugs, introduction of generic versions is more complex, as these are biologics, for which the generic introduction process, governed by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments), does not apply. This is due to the complexities involved in biologics production, such as the risk of contamination or use of different original cells. Competitors still can introduce the same biologics once the FDA exclusivity expires, so competition may increase in terms of choice of producers. Momenta Pharmaceuticals announced that it is developing a generic version of Copaxone in collaboration with Novartis.

**Pipeline**

As of March 2008, there are 46 drugs under clinical development for MS. Figure 8 shows the distribution of the development efforts across stages of development. The majority are in Phase 2 trials, and the compound listed as having completed trials is actually a new formulation of Rebif.

Out of the 46 drug candidates, 13 are joint efforts between two companies, while the remaining are stand-alone efforts. Multiple companies have two or more drug candidates in the pipeline, and many of them are companies already with an MS drug on the market, such as Biogen Idec and EMD Serono.

The companies with three or more MS drugs in the pipeline are listed on Table 3, along with the phase of development.

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22 Three compounds had trials in multiple stages, in which case each trial was counted as a separate trial in the graph. One compound was in clinical trials but without phase information—which is counted in the total but not represented in the graph.
Multiple Sclerosis

Disease Report

<table>
<thead>
<tr>
<th>Company</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Post-Trial23</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biogen Idec</td>
<td></td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Roche/Genentech</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>EMD Serono</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Pfizer/Wyeth</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Merck/Schering-Plough</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td></td>
<td>2</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Source: PhRMA.

In addition to the companies outlined in Table 2, seven companies have a Phase 3 compound in development, which include the following:

- Bayer HealthCare and Genzyme: Campath (alemtuzumab)
- Acorda Therapeutics: Fampridine
- Novartis: Fingolimod
- Talecris Biotherapeutics: intravenous immunoglobulin
- Teva Pharmaceuticals: Laquinimod
- BioMS Medical and Eli Lilly: MBP-8298

23 PhRMA lists the new formulation of Rebif, which has completed trials, as a joint effort between EMD Serono and Pfizer. However, it should be noted that Pfizer focuses on the distribution of Rebif and EMD Serono leads the research and development process.
Commercial Players

Overview

This section provides a brief summary of selected companies that are active in MS disease R&D. Existing and potential MS drugs, sales, and R&D focus on MS are briefly described for each company.

This overview surveys companies with an approved MS drug on the U.S. market, and companies with three or more MS drug candidates in their R&D pipeline. Recent mergers and acquisitions have created several entities with larger MS pipelines, as the R&D portfolios are merged. However, in those cases, which compounds will eventually be pursued by the combined entities remains to be seen.

Key Companies

**Biogen Idec**

Biogen Idec, headquartered in Cambridge, MA derived $2.8 billion in revenue from MS drugs in 2008. Its MS revenue is the largest of all players active in MS. Revenue from the MS portfolio, Avonex and Tysabri, accounts for 68 percent of its total revenue. Other drugs by Biogen Idec include Rituxan, a chemotherapy agent, and Fumaderm, used for psoriasis.

Biogen Idec’s R&D budget amounted to $1.1 billion in 2008, and focuses on four areas, oncology, immunology, neurology, and cardiopulmonary diseases. Biogen has six ongoing clinical trials for MS with five products, four Phase 2 trials and two Phase 3 trials. Its Phase 3 trials include BG-12, an immunomodulator, for relapsing-remitting MS; and Rituxan, depleting B cells, for primary progressive MS. Some of its MS drugs are developed in collaboration with other companies such as Genentech or PDL BioPharma

**Elan Corporation**

Elan is a biotech company based in Dublin, Ireland, focusing on neuroscience, especially in neurology, autoimmune diseases, and acute pain. Elan derived revenue of $557 million from the distribution of Tysabri in 2008, which accounted for 56 percent of its revenue.

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24 One drug is going through two trials, one for relapsing-remitting MS and the other for primary progressive MS.

25 Now part of Roche.
Elan spent $323 million on R&D in 2008, which was equivalent to 32 percent of its revenue that year. Its R&D pipeline is dominated by neurodegenerative diseases including Alzheimer's disease and Parkinson's disease and autoimmune diseases such as Crohn's disease and multiple myeloma. It does not have any new compounds in investigation for MS.

**EMD Serono**

EMD Serono is a division of Merck KGaA, based in Frankfurt, Germany. Its business includes pharmaceuticals, accounting for 72 percent of 2008 revenue, and chemicals, accounting for the remaining 28 percent. The prescription pharmaceutical division is known as EMD Serono in North America and Merck Serono elsewhere. Merck KGaA originally was the parent company of the U.S.-based Merck & Co., which became an independent company in the early 1900s. EMD Serono focuses on biologics and small molecules, and was formed following Merck's acquisition of Serono in January 2007, merging its existing medical division, Merck Ethicals, with Serono. In 2008, Rebif generated revenue of $2 billion, which accounted for 27 percent of EMD Serono's total revenue. EMD Serono's other major products include Erbitux for tumor, Gonal-f for fertility treatment, Concor for cardiovascular diseases, and Glucophage for diabetes. In addition, Novantrone, prescribed to patients with progressive MS, is part of EMD Serono's portfolio as Serono purchased the commercialization rights for Novantrone from Amgen in 2002. However, income from Novantrone is not significant at this point due to the availability of generics.

In 2008, EMD Serono spent $1.6 billion in R&D, which amounts to 22 percent of the revenue. Neurology is seen as one of the major therapeutic areas for EMD Serono, along with oncology, autoimmune and inflammatory diseases, fertility, and endocrinology. It has a portfolio of four compounds, including a new formulation of Rebif in registration and marketing. EMD Serono also is developing oral cladribine, which completed its Phase 3 trial for MS. Cladribine is a compound already on the market to treat hairy cell leukemia, and oral cladribine for MS was designated as a Fast Track product by FDA.

**Teva Pharmaceuticals**

Teva is an Israeli pharmaceutical company that defines itself as “a global pharmaceutical company that develops, produces and markets generic drugs covering all major treatment.” Copaxone is one of its two proprietary drugs, and was in-licensed from the Weizmann Institute of Science in Israel. Teva recorded revenue of $2.3 billion from Copaxone in 2008, which amounts to 20 percent of its total revenue. Azilect, prescribed for Parkinson's disease, is its other major brand-name drug.

Teva's R&D expenses in 2008 amounted to $786 million, or 7 percent of its revenue in 2008, and its efforts focus on neurological disorders, autoimmune diseases, and oncology. Its pipeline includes laquinimod in Phase 3 trials, which has been designated as a Fast Track product by the FDA. Teva also is entitled to royalty payments from EMD Serono if the latter commercializes the oral

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26 Numbers may differ according to the exchange rate used. We have used the average exchange rate for the year.
27 A FDA designation that facilitates the development and expedites the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs.
formulation of cladribine for MS (currently in Phase 3 trials), as Teva has acquired IVAX, originally a co-developer of the drug.

**Bayer HealthCare**
Bayer, based in Germany, is a company with operations in healthcare, crops and seeds, and material. Bayer’s healthcare division derives $1.7 billion in revenue from the MS drug Betaseron, which accounts for 11 percent of the revenue from the division; in terms of Bayer’s overall revenue, it accounts for 3 percent of the total revenue. Betaseron was licensed by FDA in 1993, becoming the first drug ever to be approved for MS. It originally was developed by Berlex Laboratories, a subsidiary of Schering, which was acquired by Bayer in 2006.

Bayer’s healthcare division spent $2.6 billion in R&D in 2008. Its internal research focuses on oncology, cardiology, women’s healthcare, and diagnostic imaging. It has two compounds under development for MS, including alemtuzumab in Phase 3 trials in collaboration with Genzyme. Alemtuzumab currently is marketed under the brand name Campath as a treatment for B cell chronic lymphocytic leukemia.

**Sanofi-Aventis**
Sanofi-Aventis, based in Paris, France, recorded $974 million in revenue from sales of Copaxone in 2008, which accounted for 2 percent of its total revenue. Sanofi-Aventis in-licensed Copaxone and has an alliance agreement with Teva, which allows it to market the drug in multiple countries.28

Sanofi-Aventis spent approximately $6.7 billion in R&D in 2008, equivalent to 17 percent of its revenue. It has seven major therapeutic areas, one of which is the CNS. It has two compounds under development for MS. Teriflunomide, an oral immunomodulator, is in Phase 2 trials as an adjunct therapy and in Phase 3 as a monotherapy; the other compound is nerispirdine in Phase 2 trials for symptomatic treatment of MS.

**Pfizer/Wyeth**
Pfizer, based in New York, NY, is a pharmaceutical company with revenue of $48 billion and R&D expenses of $8 billion as of 2008. It co-markets Rebif with EMD Serono in the United States since 2002. Pfizer shares all R&D and marketing costs in the United States with EMD Serono, in addition to an initial fee of $200 million. In return, Pfizer receives payments based on the drug’s sales.

Pfizer is a co-developer of a new formation of Rebif with EMD Serono, for which application has been submitted to FDA. With the acquisition of Wyeth, the combined entity now has MS compounds in Phase 1 and 2 trials. In addition, Pfizer has a collaborative arrangement with Millennium Pharmaceuticals in developing anti-inflammation agents.

**Roche/Genentech**
Roche, based in Switzerland, is a pharmaceutical company with revenue of $42 billion and R&D expenses of $8.2 billion as of 2008. With the recent merger with Genentech, the combined entity has four compounds in five clinical trials for MS, including Genentech’s collaboration with Biogen

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28 In North America, Teva became the sole distributor of Copaxone in 2008.
Idec, such as Rituxan in Phase 2 and 3 trials; and ocrelizumab, antibodies against B cells, in Phase 2 trials.

**Merck/Schering-Plough**

Merck, based in New Jersey, is a pharmaceutical company with revenue of $24 billion and R&D expenses of $4.8 billion as of 2008. With the recent announcement of merger with Schering-Plough, the combined entity has three compounds in development for MS, including interferon-alpha in Phase 2 trials.
Nonprofit Players

Overview
This section provides a brief overview of the nonprofit organizations involved in MS research. Their involvement can include directly funding or supporting research, for example, by charting the research roadmap, collecting tissue samples, or enhancing communication among researchers. This section focused only on organizations with some research component; organizations that are involved solely in patient support are not included.

This profile includes four research-funding organizations as well as one organization that provides tools and resources for research (Figure 10). Among research funding organizations profiled here, the National MS Society stands out in terms of its research-grant budget, which is larger than the combined research budgets of all other organizations identified. Still, two other organizations have research grant budgets of more than one million dollars. The organization that provides tools and resources is the Accelerated Cure Project, which focuses on drafting a research map and developing tissue repositories.

Key Organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>USD Thousands, most recent fiscal year</th>
</tr>
</thead>
<tbody>
<tr>
<td>National MS Society*</td>
<td>44,220</td>
</tr>
<tr>
<td>Myelin Repair Foundation</td>
<td>2,972</td>
</tr>
<tr>
<td>Nancy Davis Foundation for MS</td>
<td>1,516</td>
</tr>
<tr>
<td>Montel Williams MS Foundation</td>
<td>267</td>
</tr>
<tr>
<td>Accelerated Cure Project</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Bar not to scale

Figure 10: Overview of research grant budget of organizations that fund research in MS.
Source: IRS form 990.

National Multiple Sclerosis Society
Established in 1946, the National Multiple Sclerosis Society is engaged not only in funding research but also in advocacy efforts and supporting MS patients. Its ultimate goal is “a world without
multiple sclerosis.” It has a national office and a network of over 50 local chapters across the country. Its research program relies on a peer-reviewed grant process and funds a wide array of research ranging from basic science to policy and delivery, including some large-scale research initiatives identified as under funded. It also funds the development of research infrastructure, such as biospecimen repositories and clinical trial networks. It currently funds more than 380 projects, and its research grant expenses in 2007 amounted to $44 million, which was equivalent to 18 percent of its total expenses. In addition, the Society recently launched Fast Forward, a wholly-owned subsidiary that seeks to accelerate treatment development by providing small pharmaceutical or biotechnology companies funding for early-stage clinical trials.

**Myelin Repair Foundation**

Established in 2002, the Myelin Repair Foundation focuses on funding research to develop treatments focused on the mechanism of myelin repair. Its mission is “to accelerate the discovery of myelin repair treatments to improve the lives of people suffering from multiple sclerosis (MS), and to establish the Accelerated Research Collaboration™ (ARC™) model as a new paradigm for medical research.” The Foundation has a consortium of five laboratories, which drafts the research plan and collaborates to execute the plan. The Foundation has identified multiple drug targets, and it is further validating them. Collaboration with industry is a core component of the organization’s strategy to ensure commercialization of its research outcomes. The Foundation's grant expenses stands at $3 million, which amounts to 70 percent of its total expenses.

**The Nancy Davis Foundation for Multiple Sclerosis**

Established in 1993, The Nancy Davis Foundation for Multiple Sclerosis is dedicated to “the treatment and ultimately a cure for MS.” Funding research is the core activity of the Foundation, and all funds raised through its Race to Erase MS annual gala are used to support The Nancy Davis Center Without Walls (CWOW) program. The CWOW is a network of seven MS research centers in the United States, and they work collectively to rapidly roll out trials of promising MS treatments. The Foundation invested $1.5 million in research grants in 2007, which represents 65 percent of its total expenses.

**The Montel Williams Multiple Sclerosis Foundation**

The Montel Williams Multiple Sclerosis Foundation was established in 2000 by celebrity Montel Williams, who has been diagnosed with MS. The Foundation is "dedicated to furthering the scientific study of multiple sclerosis,” and its main goals are “to provide financial assistance to select organizations and institutions conducting the most current research, to increase allocations for research from the federal government and to raise national awareness about MS.” The foci of its research grant program are 1) detecting and preventing multiple sclerosis, 2) restoring the myelin sheath, and 3) developing new treatment protocols. During the fiscal year ending in June 2007, the Foundation invested $267,305 in grants, representing 51 percent of its total expenses of $526,051.

**Accelerated Cure Project**

Accelerated Cure Project was incorporated in 2001, and its mission is “curing MS by determining the causes of MS.” Its budget in 2007 was $1.8 million. The major activity of Accelerated Cure Project is developing the MS Repository, which collects blood samples as well as clinical and epidemiological data. Currently, the program enrolls participants at nine sites, and plans are in
place to conduct longitudinal follow-up. The samples and data collected, as well as additional material derived from them, are made available to researchers. As of February 2009, about 1,500 samples were collected. Its goal is to enroll over 5,200 subjects by 2012.
Glossary

4-aminopyridine: A potassium channel blocker. It is used primarily as a research tool and is helpful in characterizing subtypes of potassium channels. It has been used clinically in Lambert-Eaton syndrome and multiple sclerosis because by blocking potassium channels it prolongs action potentials thereby increasing transmitter release at the neuromuscular junction.

ABS-75: A fullerene derivative. Fullerene molecule consists of 60 carbon atoms and is researched for its neuroprotective properties, attributed to its antioxidant potential.

Activated Leukocyte Cell Adhesion Molecule: A receptor expressed on T cells which is involved in the adhesion of cells. Also referred as ALCAM or CD166.

Alemtuzumab (Campath): Used to treat B-chronic lymphocytic leukemia (a slowly developing cancer in which too many of a certain type of white blood cell accumulate in the body). Alemtuzumab is in a class of medications called monoclonal antibodies. It works by activating the immune system to destroy cancer cells.

Antibody: Any of a large number of proteins of high molecular weight that are produced normally by specialized B cells after stimulation by an antigen and act specifically against the antigen in an immune response, that are produced abnormally by some cancer cells, and that typically consist of four subunits including two heavy chains and two light chains. Also called immunoglobulin.

Antigen: Any substance (as an immunogen or a hapten) foreign to the body that evokes an immune response either alone or after forming a complex with a larger molecule (as a protein) and that is capable of binding with a product (as an antibody or T cell) of the immune response.

ApoE4: Apolipoprotein E (ApoE) is a naturally occurring protein that helps transport cholesterol through the bloodstream. ApoE4 is a specific form of this protein, and people with this type of ApoE protein have higher risk of developing Alzheimer’s disease.

Astrocyte: Star-shaped cell; especially any comparatively large much-branched glial cell, which forms the supporting tissue that is intermingled with the essential elements of nervous tissue especially in the brain, spinal cord, and ganglia, is of ectodermal origin, and is composed of a network of fine fibrils and of flattened stellate cells with numerous radiating fibrillar processes.

Atacicept: An experimental immune-modifying drug delivered in injections under the skin

Ataxia: An inability to coordinate voluntary muscular movements that is symptomatic of some nervous disorders.

ATL11021: An experimental antisense drug in clinical trials. The drug inhibits the production of VLA-4 (Very Late Antigen-4; also known as Integrin alpha4beta1). VLA-4 is involved in both cell-cell and cell-extracellular matrix adhesion and is implicated in multiple bodily functions including inflammation and immune cell function.
Axon: A usually long and single nerve-cell process that usually conducts impulses away from the cell body.

Azathioprine: A purine antimetabolite $C_9H_7N_7O_2S$ that is used especially as an immunosuppressant.

B cell: Any of the lymphocytes that have antigen-binding antibody molecules on the surface, that comprise the antibody-secreting plasma cells when mature, and that in mammals differentiate in the bone marrow. Also called B lymphocyte.

Blood-brain barrier: A naturally occurring barrier created by the modification of brain capillaries (as by reduction in fenestration and formation of tight cell-to-cell contacts) that prevents many substances from leaving the blood and crossing the capillary walls into the brain tissues. Abbreviated as BBB.

CD11: A group of three different alpha chains (CD11a, CD11b, CD11c) that are associated with an invariant CD18 beta chain (antigens, CD18). The three resulting leukocyte-adhesion molecules (receptors, leukocyte adhesion) are lymphocyte function-associated antigen-1, macrophage-1 antigen, and antigen, p150,95.

CD18: Cell-surface glycoprotein beta-chains that are non-covalently linked to specific alpha-chains of the CD11 family of leukocyte-adhesion molecules (receptors, leukocyte-adhesion). A defect in the gene encoding CD18 causes leukocyte-adhesion deficiency syndrome.

CD4: A large glycoprotein that is found on the surface especially of helper T cells, that is the receptor for HIV, and that usually functions to facilitate recognition of antigens by helper T cells.

CD8: a glycoprotein found especially on the surface of cytotoxic T cells that usually functions to facilitate recognition by cytotoxic T cell receptors of antigens complexed with molecules of a class that are found on the surface of most nucleated cells and are the product of genes of the major histocompatibility complex.

Central nervous system: The part of the nervous system which in vertebrates consists of the brain and spinal cord, to which sensory impulses are transmitted and from which motor impulses pass out, and which supervises and coordinates the activity of the entire nervous system.

Cerebrospinal fluid: Liquid that is comparable to serum but contains less dissolved material, that is secreted from the blood into the lateral ventricles of the brain by the choroid plexus, circulates through the ventricles to the spaces between the meninges about the brain and spinal cord, and is reabsorbed into the blood through the subarachnoid sinuses, and that serves chiefly to maintain uniform pressure within the brain and spinal cord. Also called spinal fluid.

Cladribine: An antineoplastic agent used in the treatment of lymphoproliferative diseases including hairy-cell leukemia.

Clinically isolated syndrome (CIS): The initial neurologic episode caused by inflammation and demyelination in the central nervous system. Some patients with CIS develop multiple sclerosis.
**CTLA4 immunoglobulin immunoglobulin:** Also called abatacept, the Cytotoxic T-lymphocyte-associated protein 4. immunoglobulin is used to treat adults with moderate to severe rheumatoid arthritis, and it interferes with costimulation of T cells.

**CXCL12:** Also called stromal cell-derived factor 1 or pre-B cell growth-stimulating factor, CXCL12 is part of a group of cytokines that activate the immune cells. CXCL12 is often researched in the context of research on HIV/AIDS or cancer metastasis.

**Cyclophosphamide:** An alkylating agent and important immunosuppressant. Acts by alkylating SH and NH2 groups especially the N7 of guanine.

**Cyclosporine:** A cyclic undecapeptide from an extract of soil fungi. It is a powerful immunosuppressant with a specific action on T lymphocytes. It is used for the prophylaxis of graft rejection in organ and tissue transplantation.

**Cytokine:** Any of a class of immunoregulatory proteins (as interleukin, tumor necrosis factor, and interferon) that are secreted by cells especially of the immune system.

**Doxycycline:** Antibiotic used to treat infections such as pneumonia and other respiratory tract infections, Lyme disease, acne, infections of skin, genital, and urinary systems, and anthrax (after inhalational exposure). It is also used to prevent malaria. Doxycycline is in a class of medications called tetracycline antibiotics. It works by preventing the growth and spread of bacteria.

**E-selectin:** This protein is found in cytokine-stimulated endothelial cells and is thought to be responsible for the accumulation of blood leukocytes at sites of inflammation by mediating the adhesion of cells to the vascular lining.

**Endothelium:** An epithelium of mesoblastic origin composed of a single layer of thin flattened cells that lines internal body cavities.

**Enterovirus:** A genus of single-stranded RNA viruses of the family Picornaviridae that multiply especially in the gastrointestinal tracts of humans and swine but may infect other tissues (as nerve and muscle), that may produce clinically evident conjunctivitis, encephalitis, meningitis, myelitis, or myocarditis, and that include the poliovirus and several species including numerous serotypes named as coxsackieviruses and echoviruses.

**Epstein-Barr virus:** A herpesvirus (species Human herpesvirus 4 of the genus Lymphocryptovirus) that causes infectious mononucleosis and is associated with Burkitt’s lymphoma and nasopharyngeal carcinoma.

**Ethonafide:** An anthracene-based cancer drug similar to mitoxantrone.

**Excitotoxicity:** The action of an agent that binds to a nerve cell receptor, stimulates the cell, and damages it or causes its death.
**Expanded Disability Status Scale (EDSS):** The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis. It assesses the disability status of eight functional systems, each rated from no disability to death due to MS.

**Experimental autoimmune encephalomyelitis (EAE):** An inflammatory autoimmune disease that has been induced in laboratory animals and especially mice by injecting them with diseased tissue from affected animals or with myelin basic protein and that because of the similarity of its pathology to multiple sclerosis in humans is used as an animal model in studying this condition.

**Fampridine:** See 4-aminopyridine.

**Flupirtine:** A drug used as a pain killer, with neuroprotective properties.

**Glia:** Supporting tissue that is intermingled with the essential elements of nervous tissue especially in the brain, spinal cord, and ganglia, is of ectodermal origin, and is composed of a network of fine fibrils and of flattened stellate cells with numerous radiating fibrillar processes.

**Glucocorticoids:** Any of a group of corticosteroids (as cortisol or dexamethasone) that are involved especially in carbohydrate, protein, and fat metabolism, that tend to increase liver glycogen and blood sugar by increasing gluconeogenesis, that are anti-inflammatory and immunosuppressive, and that are used widely in medicine.

**Granulocyte-macrophage colony-stimulating factor:** Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine/growth factor that causes the bone marrow to make more of certain types of immune system cells and blood cells. A man-made version (also known as sargramostim or Leukine) is often used to boost white blood cell counts after chemotherapy.

**Graves' disease:** A common form of hyperthyroidism characterized by goiter and often a slight protrusion of the eyeballs. Also called Basedow's disease, exophthalmic goiter.

**Gray matter:** Neural tissue especially of the brain and spinal cord that contains cell bodies as well as nerve fibers, has a brownish gray color, and forms most of the cortex and nuclei of the brain, the columns of the spinal cord, and the bodies of ganglia.

**Herpesvirus:** Any of a family Herpesviridae of double-stranded DNA viruses.

**HLA-DRA:** HLA-DRA is one of the HLA class II alpha chain paralogues. This class II molecule is a heterodimer consisting of an alpha and a beta chain, both anchored in the membrane. It plays a central role in the immune system by presenting peptides derived from extracellular proteins. Class II molecules are expressed in antigen presenting cells (APC: B lymphocytes, dendritic cells, macrophages).

**Human herpesvirus 6:** A recently discovered human herpesvirus that was found in certain lymphoproliferative disorders, replicates in a number of different types of leukocytes, and is associated with the childhood disease rosella (exanthema subitum).
**Human leukocyte antigen complex:** The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders (such as viruses and bacteria). Also called major histocompatibility complex.

**IL2RA:** The interleukin 2 (IL2) receptor alpha (IL2RA) and beta (IL2RB) chains, together with the common gamma chain (IL2RG), constitute the high-affinity IL2 receptor. Homodimeric alpha chains (IL2RA) result in low-affinity receptor, while homodimeric beta (IL2RB) chains produce a medium-affinity receptor. Normally an integral-membrane protein, soluble IL2RA has been isolated and determined to result from extracellular proteolysis. Alternately-spliced IL2RA mRNAs have been isolated, but the significance of each is presently unknown.

**IL7RA:** Interleukin 7 receptor alpha. The protein encoded by this gene is a receptor for interleukine 7 (IL7). The function of this receptor requires the interleukin 2 receptor, gamma chain (IL2RG), which is a common gamma chain shared by the receptors of various cytokines, including interleukine 2, 4, 7, 9, and 15. This protein has been shown to play a critical role in the V(D)J recombination during lymphocyte development. This protein is also found to control the accessibility of the TCR gamma locus by STAT5 and histone acetylation. Knockout studies in mice suggested that blocking apoptosis is an essential function of this protein during differentiation and activation of T lymphocytes. The functional defects in this protein may be associated with the pathogenesis of the severe combined immunodeficiency (SCID).

**Immunoglobulin:** Antibody.

**Integrin:** Any of various glycoproteins that are found on cell surfaces (as of white blood cells or platelets), that are composed of two dissimilar polypeptide chains, that are receptors for various proteins which typically bind to the tripeptide ligand consisting of arginine, glycine, and aspartic acid, that promote adhesion of cells (as T cells) to other cells (as endothelial cells) or to extracellular material (as fibronectin or laminin), and that mediate various biological processes (as phagocytosis, wound healing, and embryogenesis).

**Interferon alpha:** An interferon produced by various white blood cells that inhibits viral replication, suppresses cell proliferation, and regulates immune response and that is used in a form obtained from recombinant DNA to treat hairy cell leukemia, AIDS-related Kaposi's sarcoma, condylomata acuminata, and certain chronic hepatitides.

**Interferon beta:** An interferon that is produced especially by fibroblasts, possesses antiviral activity, and is used in a form obtained from recombinant DNA especially in the treatment of multiple sclerosis marked by recurrent attacks alternating with periods of remission.

**Interferon gamma:** An interferon produced by T cells that regulates the immune response (as by the activation of macrophages and natural killer cells) and is used in a form obtained from recombinant DNA in the control of infections associated with chronic granulomatous disease and sometimes in the treatment of other conditions (as basal-cell carcinoma, Bowenoid papulosis, leukemia, or rheumatoid arthritis).

**Interleukin 10:** A cytokine produced primarily by monocytes and to a lesser extent by lymphocytes. This cytokine has pleiotropic effects in immunoregulation and inflammation. It down-
regulates the expression of Th1 cytokines, MHC class II Ags, and costimulatory molecules on macrophages. It also enhances B cell survival, proliferation, and antibody production. This cytokine can block NF-kappa B activity, and is involved in the regulation of the JAK-STAT signaling pathway. Knockout studies in mice suggested the function of this cytokine as an essential immunoregulator in the intestinal tract.

**Interleukin 13:** An immunoregulatory cytokine produced primarily by activated Th2 cells. This cytokine is involved in several stages of B-cell maturation and differentiation. It up-regulates CD23 and MHC class II expression, and promotes IgE isotype switching of B cells. This cytokine down-regulates macrophage activity, thereby inhibits the production of pro-inflammatory cytokines and chemokines.

**Interleukin 17:** Secreted by active T cells, this molecule is a proinflammatory cytokine.

**Interleukin 2:** An interleukin produced by antigen-stimulated helper T cells in the presence of interleukin 1 that induces proliferation of immune cells (as T cells and B cells) and has been used experimentally especially in treating certain cancers.

**Interleukin 4:** One of a group of related proteins made by leukocytes (white blood cells) and other cells in the body. Interleukin-4 is made by a type of T lymphocyte. It causes B lymphocytes to increase and to make antibodies and also increases the production of T lymphocyte. Interleukin 4 made in the laboratory is used as a biological response modifier to boost the immune system in cancer therapy. Interleukin 4 is a type of cytokine. Also called IL-4.

**Interleukin:** Any of various compounds of low molecular weight that are produced by lymphocytes, macrophages, and monocytes and that function especially in regulation of the immune system and especially cell-mediated immunity.

**Low-contrast letter acuity score:** Visual acuity measured using charts with letters in gray rather than in black. Research have shown that the visual scores using the low-contrast charts are more sensitive to MS patients’ visual capacity than the scores using high-contrast charts.

**Macrophage:** A phagocytic tissue cell of the immune system that may be fixed or freely motile, is derived from a monocyte, functions in the destruction of foreign antigens (as bacteria and viruses), and serves as an antigen-presenting cell.

**Magnetic Resonance Imaging:** A noninvasive diagnostic technique that produces computerized images of internal body tissues and is based on nuclear magnetic resonance of atoms within the body induced by the application of radio waves. Abbreviated as MRI.

**Magnetization transfer imaging:** An imaging technique able to detect white matter abnormalities before lesions can be seen on standard MRI scans by calculating the amount of "free" water in tissues. Demyelinated tissues and damaged nerves show increased levels of free” (versus "bound") water particles.
Melanoma Cell Adhesion Molecule: A cell adhesion molecule present in the lining of the blood vessels and other cells including some T cells. Its expression also increases in cancerous melanocytes as their metastatic potential increases, while it is not expressed in normal melanocytes.

Mesenchymal stromal cells: A specific type of stem cells that can develop into a variety of cells.

Methotrexate: A toxic drug C_{20}H_{22}N_{8}O_{5} that is an analog of folic acid and is used to treat certain cancers, severe psoriasis, and rheumatoid arthritis. Also called amethopterin.

Microglia: Glia consisting of small cells with few processes that are scattered throughout the central nervous system, have a phagocytic function as part of the reticuloendothelial system, and are now usually considered to be of mesodermal origin.

Mitoxantrone: An antineoplastic drug that is used in the form of its dihydrochloride C_{22}H_{28}N_{4}O_{6}·2HCl either alone or in combination in the treatment of some leukemias and carcinomas.

Mononucleosis: an abnormal increase of mononuclear white blood cells in the blood. Infectious mononucleosis is an acute infectious disease associated with Epstein-Barr virus and characterized by fever, swelling of lymph nodes, and lymphocytosis, also called glandular fever, kissing disease, or mono.

Multiple Sclerosis Functional Composite: A multidimensional clinical outcome measure that includes quantitative tests of leg function/ambulation (Timed 25-Foot Walk), arm function (9-Hole Peg Test), and cognitive function (Paced Auditory Serial Addition Test).

Multiple Sclerosis Severity Score: Derived from data from longitudinal studies, the Multiple Sclerosis Severity Score relates scores on the Expanded Disability Status Scale (EDSS) to the distribution of disability in patients with comparable disease durations.

Myelin: A soft white somewhat fatty material that forms a thick myelin sheath about the protoplasmic core of a myelinated nerve fiber.

Naltrexone hydrochloride: The hydrochloride salt of naltrexone, a noroxymorphone derivative with competitive opioid antagonistic activity. Naltrexone and its metabolite 6-beta-naltrexol reverse the effects of opioids by binding to various opioid receptors in the central nervous system (CNS), including the mu-, kappa- and gamma-opioid receptors; opioid effects of analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia, and physical dependence are inhibited. Naltrexone is longer-acting and more potent compared to naloxone.

Neurofilaments: Filaments that act as a structural framework that helps to define the shape and size of the neurons.

NMDA receptor: A class of ionotropic glutamate receptors characterized by affinity for N-methyl-D-aspartate. NMDA receptors have an allosteric binding site for glycine which must be occupied for the channel to open efficiently and a site within the channel itself to which magnesium ions bind in a voltage-dependent manner. The positive voltage dependence of channel conductance and the high
permeability of the conducting channel to calcium ions (as well as to monovalent cations) are important in excitotoxicity and neuronal plasticity.

**Node of Ranvier:** A small gap in the myelin sheath of a myelinated nerve fiber

**Notch1:** Notch signaling is a cell signaling mechanism that participates in a variety of cellular processes: cell fate specification, differentiation, proliferation, apoptosis, adhesion, epithelial-mesenchymal transition, migration, and angiogenesis. It has four subtypes ranging from Notch1 to 4.

**Ocrelizumab:** A humanized monoclonal antibody against CD20, which is under development for inflammatory diseases and B cell-related cancers.

**Ofatumumab:** A fully human, high-affinity IgG1 monoclonal antibody directed against the B cell CD20 cell surface antigen with potential antineoplastic activity. Ofatumumab binds specifically to CD20 on the surfaces of B cells, triggering complement-dependent cell lysis (CDCL) and antibody-dependent cell-mediated cytotoxicity (ADCC) B cells overexpressing CD20. The CD20 antigen, found on over 90 percent of B cells of B cell lymphomas and other B cells of lymphoid tumors of B cell origin, is a non-glycosylated cell surface phosphoprotein that acts a calcium ion channel; it is exclusively expressed on B cells during most stages of B cell development.

**Oligoclonal bands:** CSF oligoclonal banding is a test to look for inflammation-related substances in the CSF, the clear fluid that flows in the space surrounding the spinal cord and brain. Oligoclonal bands are substances called immunoglobulins, which suggest inflammation of the central nervous system. The presence of oligoclonal bands may be a sign of multiple sclerosis.

**Oligodendrocyte:** A glial cell resembling an astrocyte but smaller with few and slender processes having few branches.

**Optic neuritis:** Inflammation of the optic nerve.

**Optical coherence tomography (OCT):** Non-invasive imaging technique, similar to ultrasound, which, that promises to have a broad range of applications for the diagnosis and management of a variety of ocular diseases.

**Osteopontin:** A protein with multiple roles, including immune system modulation, inflammation, cancer metastasis, and cell survival.

**Paramagnetic Myeloperoxidase sensor:** An enzyme present in leukocytes. It is believed to be linked to inflammation and cardiovascular problems.

**Peptide:** Any of various amides that are derived from two or more amino acids by combination of the amino group of one acid with the carboxyl group of another and are usually obtained by partial hydrolysis of proteins.
**Phagocytosis**: The engulfing and usually the destruction of particulate matter by phagocytes that serves as an important bodily defense mechanism against infection by microorganisms and against occlusion of mucous surfaces or tissues by foreign particles and tissue debris.

**PPAR gamma**: Peroxisome Proliferator-Activated Receptor-Gamma. This receptor is part of the family of receptors that regulate gene expression. There are three different types of PPAR gamma, and PPAR gamma 3 is expressed in various cells including the macrophage.

**Progressive multifocal leukoencephalopathy**: A progressive and fatal demyelinating disease of the central nervous system that typically occurs in immunosuppressed individuals due to loss of childhood immunity to a double-stranded DNA virus of the genus Polyomavirus (species JC polyomavirus) ubiquitous in human populations and that is characterized by hemianopia, hemiplegia, alterations in mental state, and eventually coma. Abbreviated as PML.

**P-selectin**: This protein is stored in the alpha-granules of platelets and Weibel-Palade bodies of endothelial cells. This protein redistributes to the plasma membrane during platelet activation and degranulation and mediates the interaction of activated endothelial cells or platelets with leukocytes.

**Retinoid**: Any of various synthetic or naturally occurring analogs of vitamin A

**rHlgM22**: A recombinant human monoclonal antibody that binds to myelin and oligodendrocytes.

**Rituximab**: A recombinant chimeric murine/human antibody directed against the CD20 antigen, a hydrophobic transmembrane protein located on normal pre-B and mature B lymphocytes. Following binding, rituximab triggers a host cytotoxic immune response against CD20-positive cells.

**Semaphorins**: A group of signaling proteins that play an important role in guiding the development of axons. Humans have about 20 different types of semaphorins. Research also suggests that some semaphorins are involved in the activation of the immune system.

**T cell**: Any of several lymphocytes (as a helper T cell) that differentiate in the thymus, possess highly specific cell-surface antigen receptors, and include some that control the initiation or suppression of cell-mediated and humoral immunity (as by the regulation of T and B cell maturation and proliferation) and others that lyse antigen-bearing cells. Also called T lymphocyte.

**Tau**: A protein that binds to and regulates the assembly and stability of neuronal microtubules and that is found in an abnormal form as the major component of neurofibrillary tangles.

**Tetrathiomolybdate**: An ammonium salt with potential antiangiogenic and antitumor activities. Tetrathiomolybdate has been found to deplete systemic copper reserves through an unknown mechanism. This agent has been shown to inhibit the activities of cuproenzymes, including superoxide dismutase 1 (SOD1) and cytochrome c oxidase (COX), which may contribute to its antiangiogenic and antitumor effects.

**Tissue plasminogen activator**: A clot-dissolving enzyme that has an affinity for fibrin, that catalyzes the conversion of plasminogen to plasmin, that is produced naturally in blood vessel
linings, and that is used in a genetically engineered form to prevent damage to heart muscle following a heart attack and to reduce neurological damage following ischemic stroke.

**Transforming growth factor beta**: A protective cytokine that inhibits or regulates the activity of certain immune cells.

**Tumor necrosis factor**: A protein made by white blood cells in response to an antigen (substance that causes the immune system to make a specific immune response) or infection. TNF can also be made in the laboratory. It may boost a person’s immune response, and also may cause necrosis (cell death) of some types of tumor cells. TNF is being studied in the treatment of some types of cancer. It is a type of cytokine.

**Visually Evoked Potential test (VEP)**: A test in which the brain’s electrical activity in response to visual stimuli (e.g., a flashing checkerboard) is recorded by an electroencephalograph and analyzed by computer.

**Von Willebrand factor**: A protein secreted especially by endothelial cells that circulates in blood plasma as a large variable aggregation consisting usually of repeating dimers, that mediates platelet adhesion to collagen in subendothelial tissue at injury sites, that is often found complexed to factor VIII in plasma where it serves to protect it from degradation, and that is deficient or defective in individuals affected with von Willebrand's disease.

**White matter**: Neural tissue especially of the brain and spinal cord that consists largely of myelinated nerve fibers bundled into tracts, has a whitish color, and typically underlies the gray matter.
Acronyms

CIS: clinically isolated syndromes
CNS: central nervous system
CSF: cerebrospinal fluid
DALY: Disability-Adjusted Life Years
DNA: Deoxyribonucleic acid
EAE: experimental autoimmune encephalomyelitis
EBV: Epstein-Barr virus
EDSS: Expanded Disability Status Scale
FDA: U.S. Food and Drug Administration
MRI: magnetic resonance imaging
MS: multiple sclerosis
NARCOMS: North American Research Committee On Multiple Sclerosis
NIH: National Institutes of Health
NINDS: National Institute of Neurological Disorders and Stroke
OCT: optical coherence tomography
RNA: Ribonucleic acid
VEP: visually evoked potential test
WHO: World Health Organization
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