STOPPING MS

Why the Immune System Goes Awry

The current therapies for MS emerged from our growing understanding of how the immune system works and how it can be manipulated to suppress or regulate immune attacks. We especially need to know more about the molecules that the immune system uses to attack the nervous system, because each of these serves as a potential therapeutic target for new therapies.

The National MS Society has current, multi-year commitments of about $32 million to support research projects focusing on stopping the immune system attack in MS.

Bonnie Dittel, PhD
Blood Center of Wisconsin
Milwaukee, WI
Area: Wisconsin/Midwest
Term/Amount: 10/1/10-9/30/13; $440,724
"Elucidating the role of cannabinoid receptor 2 in immune regulation during EAE"
Looking at how cannabis-related molecules interact with and affect the immune system and their potential for turning off immune attacks.

The class of drugs known as cannabinoids are perhaps best known for the effects of delta-9-tetrahydrocannabinol (THC), the active substance in marijuana. The effects of THC on the brain are mediated by molecules known as cannabinoid receptor 1 (CB1) on the surfaces of nerve cells, to which THC attaches. Immune system cells have a related cannabinoid receptor, CB2, which also binds THC along other cannabinoids.

In this research project, Bonnie Dittel, PhD, is looking at several cannabinoids that bind to CB2 and studying the effects they have on immune system cell activity. Dr. Dittel and colleagues have found that mice with the MS-like disease EAE, which were genetically modified to lack CB2 on some of their immune cells, developed very severe disease. Now Dr. Dittel's team is using natural and laboratory-manufactured cannabinoids to determine how they alter immune function and to find which ones suppress EAE most strongly, with an eye toward refining the use of cannabinoids to treat MS in people.

This research will produce better understanding of the role of CB2 in the immune system and could lead to a new class of treatments for MS.

Brian Evavold, PhD
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Term/Amount: 10/1/10-9/30/13; $442,898
"T cell affinity for myelin controls autoimmune disease severity and outcome" Using high-tech screening to study how the cells that control immune system activity respond to myelin, the nerve-protecting sheath targeted by MS immune attacks.

In MS, the immune system – the group of cells that normally protects the body from infectious agents such as viruses or bacteria – mistakenly attacks and damages myelin, the fatty substance that surrounds nerve fibers in the brain and spinal cord. Myelin and nerve fiber damage disrupts the signals in nerve fibers and leads to the varied symptoms of MS. Immune system cells called T cells coordinate immune system behavior: some increase the strength of an attack, while others limit or shut off attacks.

A vast body of evidence now supports a link between low levels of vitamin D and the development of MS

Brian Evavold, PhD, is looking at the affinity of T cells for myelin proteins – how tightly various T cells bind or stick to proteins from myelin – to see how this factor influences the course of disease. Using a newly developed high-tech method to measure T cell affinity, Dr. Evavold has found that in mice with EAE, a model of MS, T cells that respond to myelin proteins have a broad range of affinities for them. Now he is determining whether the different affinities influence the severity of disease. In addition, he is investigating whether human T cells have a similar range of affinities for myelin in MS.

This work could significantly increase our understanding of how the immune system attack on myelin is controlled and could lead to new avenues for developing treatments for MS.

Colleen Hayes, PhD
University of Wisconsin-Madison
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Area: Wisconsin/Midwest
Term/Amount: 10/1/10-9/30/13; $585,146
"Vitamin D and estrogen synergy in the control of EAE" Exploring how vitamin D and the sex hormone estrogen may interact to control MS-like immune attacks and its implications for MS.

In MS and EAE, an animal model of MS, myelin, the material that surrounds and protects nerve fibers, and the cells that produce myelin in the central nervous system are attacked by cells from the immune system. Colleen Hayes, PhD, and her colleagues suggested that the reason MS is more common in regions with less sunlight exposure is that the body makes vitamin D when the skin is exposed to ultraviolet (UV) light, and vitamin D is a natural inhibitor of MS. A vast body of evidence now supports this suggestion. Higher vitamin D levels have been strongly linked with less risk of developing MS and with fewer relapses and less disability in those with MS. Dr. Hayes and her colleagues have found vitamin D to be a potent inhibitor of EAE, and are investigating the details of this process to devise strategies for using vitamin D to inhibit MS.

Now Dr. Hayes and Dr. Halina Offner, M.D., are studying how vitamin D and estrogen, a female sex hormone, work together to decrease EAE in female mice. Their preliminary work has shown that estrogen is required for vitamin D to have its maximal protective effect on EAE. Now, using genetically modified mice, they are looking at the details of how vitamin D, estrogen, and their respective receptors interact, as a prelude to understanding these interactions in women

with MS.

This research could lead to a new understanding of the rapidly increasing female sex bias in MS, and to new ways to treat and possibly prevent MS in women.

Robyn Klein, MD, PhD
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Term/Amount: 10/1/10-9/30/13; $460,638
"Regulation of blood-brain barrier immune privilege during CNS autoimmunity" How to prevent breakdown of the barrier separating the brain and spinal cord from the bloodstream, for clues to stopping MS.

MS involves activity of immune system cells that damages the brain and spinal cord. The small blood vessels in the brain have a layer called the "blood-brain barrier" (BBB) that ordinarily limits the movement of immune system cells from the blood into the brain. In MS, and in an animal model of MS known as EAE, portions of the BBB break down, allowing destructive immune system cells to enter brain tissue and launch attacks.

For this project Robyn Klein, MD, PhD, is using EAE and brain tissue from people with and without MS to study the activity of several molecules involved in the movement of immune system cells through the BBB. Dr. Klein and colleagues hope to identify a substance that can be used to restore the BBB to normal function and block the entry of immune system cells into brain tissue.

This research will lead to new understanding of how the BBB fails in MS and could provide clues for treatments to restore function to the BBB and block immune system attacks in MS.

Vijay Kuchroo, PhD, DVM
Harvard Medical School
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Area: Greater New England/Northeast
Term/Amount: 10/1/10-9/30/13; $430,650
"Pathogenic and regulatory mechanisms in EAE" Finding ways to control the immune system attack on myelin, for clues to stopping nerve tissue damage in MS.

In MS, the immune system, which normally defends the body against foreign invaders, attacks and destroys myelin, and nerve fibers are destroyed as well. Myelin is the material that surrounds and protects nerve fibers in the brain and spinal cord. Immune system cells that are primarily responsible for coordinating and controlling the attack on myelin belong to a class known as "T cells". There are a number of different types of T cells, each with a specific role in activating or suppressing the immune system attack.

Vijay Kuchroo, DVM, PhD, and his colleagues are studying the behavior of a group of T cells known as "Th17" cells in mice with the MS-like disease EAE. They have found that Th17 cells are particularly aggressive in stimulating myelin damage. They have also found that other immune system cells can turn off the aggression of Th17 cells with signaling molecules known as cytokines. They are now looking at how Th17 cells and several other types of immune system cells interact to regulate EAE, and by implication, MS.

The results of this work could greatly increase our understanding of how the immune system damage to myelin can be controlled and may lead to new clues for stopping nervous tissue damage in MS.

National MS Society Research

The National MS Society is committed to freeing the world of MS. Our global support of MS research and treatment focuses on three key areas: stopping the progression of the disease, restoring function that's been lost, and ultimately ending the disease forever.

We do this by:

- Funding the most promising avenues
- Engaging the best and brightest minds
- Acting as a vital connector for people, resources and ideas
- Developing more and effective treatments faster
- Identifying and filling gaps in MS research

Research Objectives Outlined in Our Strategic Response 2011-2015

- We better understand the scientific mechanisms that lead to disease progression and we accelerate the development of new therapies.
- We pursue new avenues to discover how nerve cells are damaged and potentially repaired.
- We pursue new rehabilitation techniques and symptomatic treatments to restore neurological function and enhance quality of life.
- We identify risk and triggering factors that cause MS, and understand the biological interactions that lead to its development so that MS can be prevented.
- We expand and strengthen the quantity and quality of MS research worldwide to accelerate new discoveries and treatments for people with MS.

Society Research Spending:
$36 million in 2009 for 375 projects
Cumulative Investment:
$686 million (by end FY '09) since first 3 grants in 1947
Major Types of Society Research Support:
Grants: multiyear investigations by university-based scientists for basic and clinical research
High risk/high potential Pilot grants: one-year awards to test innovative, cutting-edge ideas
Industry Partnerships: milestone-driven drug development funding for private companies
Fellowships: to attract and train promising young investigators and doctors to focus on MS
Rehabilitation Research Fellowships: to meet the unmet need for specialists trained to conduct quality rehabilitation research
Health Care Delivery and Policy Contracts: to inform advocacy efforts and enhance quality of life for people with MS

Yasmina Laouar, PhD
University of Michigan
Ann Arbor, MI
Area: Michigan/Midwest
Term/Amount: 10/1/10-9/30/13; $435,049
"Role of TGFbeta in the control of autoimmune encephalomyelitis" Studying a signaling molecule that can inhibit immune attacks, and its implications for stopping MS.

In MS, myelin, the material that surrounds and protects nerve fibers, is attacked and destroyed in the brain and spinal cord by the immune system. The nerve fibers themselves are also damaged. The immune system consists of different types of cells that communicate and coordinate activity through a number of signaling molecules. Some of the molecules increase immune system attacks, while others tend to reduce or halt them.

Yasmina Laouar, PhD, is studying the role of the immune system signaling molecule known as TGF-beta, which often acts to suppress or limit immune system attacks. Dr. Laouar is using "transgenic" mice specifically engineered to lack docking sites to which TGF-beta attaches (called TGF-beta receptors). Dr. Laouar and colleagues found that these mice develop severe MS-like disease (EAE). Now they are trying to understand how the lack of TGF-beta receptors leads to spontaneous EAE, and how TGF-beta normally helps suppress EAE.

This work will provide new understanding of the role of TGF-beta in immune system control and may provide new avenues for research to treat MS.

Virtually every new molecule uncovered in the immune attack in MS has potential as a target for new therapies to stop the disease process

Jason Lees, PhD
University of Maryland at Baltimore
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Term/Amount: 10/1/10-9/30/13; $268,236
"Molecular mechanisms of secondary T-cell recruitment to established CNS lesions" Determining how the population of immune system attack cells changes from early to later stages of MS-like disease for clues to new treatment approaches.

The symptoms of MS result from an immune system attack against myelin, the material that surrounds and protects nerve fibers, in the central nervous system (CNS: brain, spinal cord and optic nerves). The nerve fibers are also damaged. Immune system cells known as T cells are important in MS and in an experimental model of MS known as EAE. In MS and EAE, T cells enter the tissue of the CNS from the blood in small numbers at the start of the disease and in larger numbers, a behavior known as secondary recruitment, as the symptoms develop.

In this research project, Jason Lees, PhD, is studying T cells throughout the course of EAE, looking for evidence that the mechanisms that allow T cells to be recruited to already established areas of myelin damage differ from the mechanisms that allow early T cells to initiate the damage. Dr. Lees and his colleagues are also attempting to discover how the T cells that are recruited to an existing area of myelin damage may then go on to cause damage in a new region of the CNS.

This research will provide a better understanding of how the population of T cells change during the progress of EAE, and could yield new approaches for therapies effective in specific stages of MS.

Michael Racke, MD
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Term/Amount: 10/1/10-9/30/13; $468,954
"Regulation of oxidative stress in autoimmune demyelination" Investigating a molecule in clinical trials to understand its influence on immune factors and how it may provide protection to the nervous system in MS.

While there are now several treatments for MS, all of those approved by the FDA are given by injection or intravenous infusion. An experimental drug that is given orally that recently showed promising results in a clinical trial in MS patients is called BG00012 (Biogen Idec) or dimethyl fumarate.

Dr. Racke's team is trying to find out how BG00012 works in MS. They believe that it may alter signaling molecules or cytokines made by immune cells in such a way that they no longer have the same disease-causing potential. The team is investigating its influence on immune factors, and also looking at changes in the nervous system that may make it more likely to withstand the immune attacks that occur in MS, a process called neuroprotection.

These studies should give us added insight into how BG00012 works in MS and may also provide new ideas about how the brain gets damaged by the immune system in the first place.

John Russell, PhD
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Term/Amount: 10/1/10-9/30/13; $489,697
"Cytokine and chemokine regulation of regional CNS inflammation and pathogenesis" Analyzing interactions between immune messengers in directing the location of immune attacks for clues to causes of MS severity and symptoms.

Cells of the immune system normally protect the body from infectious agents including viruses and bacteria. In MS, however, the immune system attacks myelin, the substance that surrounds and protects nerve fibers in the central nervous system (CNS: brain, spinal cord and optic nerves). In their normal function, and in MS, immune system cells use a number of "signaling molecules" known as cytokines and chemokines to organize and coordinate their activity. MS is known for its variability among different individuals and at different times in the same individual. Differences in the location and the type of active signaling molecules may explain much of the variability of MS.

John Russell, PhD, and colleagues are studying how the distribution of cytokines and chemokines affects the movement of immune system cells in different regions of

the CNS in mice with EAE, a model of MS. They are also looking at how specific gene alterations that cause the loss of particular signaling molecules affect the course of the disease.

This research could provide new insights about why MS is so variable, and lead to new ideas for treating specific stages of MS.

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Term/Amount: 10/1/10-9/30/13; $523,971
Paid by the National MS Society South Central Region

"Inhibition of FLT3 signal trasduction in APCs as an approach to MS therapy."
Evaluating a way to stop MS attacks by blocking specialized cells that make nervous system tissues a target.

In the central nervous system (CNS) of people with MS, the material that surrounds and protects nerve fibers, myelin, is destroyed by immune system cells. Without their protective myelin, nerve fibers do not conduct signals correctly, and they become vulnerable to destruction, resulting in the symptoms of MS. The immune system cells known as T cells are main players in the attack that destroys myelin, but T cells get clues about what to attack from cells known as antigen presenting cells (APCs).

Katharine Whartenby, PhD, is studying drugs that interfere with a process that allows APCs to give clues about what to attack. She is focusing on mice with EAE, an MS-like disease. Dr. Whartenby and colleagues have found that some of these drugs can reduce the number of APCs in the CNS, and that this makes EAE less severe. Now they are looking at details of how the drugs alter the interaction between APCs and T cells, and determining which ones enter the CNS easily. Potential advantages of these drugs are that they are given orally and are already in trials for other diseases, such as myeloid leukemia.

This research will shed light on whether a new treatment approach may hold potential for MS.

To convince insurers that rehabilitation really does help MS, there needs to be evidence that can only come from carefully designed and conducted studies

RESTORING FUNCTION

Rehabilitation

Rehabilitation regimens that can help people with MS achieve maximal physical, psychological, social and vocational potential have gained increasing acceptance in recent years. But to convince doctors and insurers that rehabilitation really does help, there needs to be scientific evidence that can only come from carefully designed and conducted studies.

The National MS Society has current, multi-year commitments of about $6 million to support investigations focusing on rehabilitation in MS.