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Tackling the mystery of MS progression

by Sara Bernstein

“We are a driving force of MS research and treatment to **stop disease progression**, restore function, and end MS forever.” With these words, the National MS Society has thrown down the gauntlet for all people affected by MS and taken up the challenge of figuring out perhaps the most mysterious aspect of this disease—why does MS progress or worsen over time? How can we stop it?

To begin to tackle these questions, the Society released a request for applications in

2010, inviting investigators to submit proposals for designing studies to identify risk factors that influence MS progression in large groups of people with MS. This initiative is supported by special funds provided by the Society's Greater Delaware Valley Chapter.

Two teams that were recommended for funding are testing strategies for tracking exposures to possible risk factors in large numbers of people with MS. One team is taking an international approach, and the other is

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taking advantage of a longstanding consortium of MS centers in one state. At the same time, a third study is searching for clues that determine whether a person with early symptoms will progress to developing definite MS.

Spanning the globe to stop MS progression

Howard L. Weiner, MD (Harvard Medical School) is a renowned champion of MS research and clinical care. In 2007, he received the National MS Society/American Academy of Neurology's John Dystel Prize for MS Research. Dr. Weiner's studies on the immunology of MS have helped form the

basis for the current understanding of immune mechanisms and therapy.

Now Dr. Weiner has established a consortium of champions to tackle the problem of MS progression—the SUMMIT Consortium. Joining him are Stephen Hauser, MD (University of California, San Francisco), MS genetics expert and also a Dystel prizewinner; Ludwig Kappos, MD (University Hospital, Basel) and Chris Polman, MD (VUMC, Amsterdam), all leaders in MS clinical research. Their respective centers focus on populations from different regions, but all have large MS patient

populations and have established the capacity to study them.

The groups are collecting data over two years on 1500 people with MS, data from clinical examinations, MRI scans, blood tests, and DNA samples. The groups are also collecting epidemiological data—searching for any factors that might unite people whose MS progresses, and differentiate them from those who do not progress. Suspected factors include family history, vaccination and infectious diseases history, tobacco smoking history, diet, sun exposure, gender hormones and pregnancy. The team will determine whether any of these factors are associated with disease progression during the two-year study period.

As a secondary goal, this team is combining genetic, MRI, and immunologic data compiled at each center, using the latest gene and protein chip technologies, to determine if any MRI findings or blood biomarkers (see p. 60) appear to be linked to MS progression.

The centers are putting all these data into a central repository for analysis. The project takes advantage of each center's already outstanding contributions to MS research. One example is the Comprehensive Longitudinal Investigation of MS at Boston's Brigham & Women's Hospital (CLIMB)—which already follows 1300 people and has resulted in more than 30 publi-

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cations; and the Medical Image Analysis Center at Basel, Switzerland that plays a leading role in evaluating MRIs in large MS trials.

Dr. Weiner and his colleagues in the SUMMIT Consortium are putting MS research's best feet forward with this collaborative effort, and the results are sure to point us toward ways for stopping MS progression in its tracks.

"A New York State of Mind"

The other team tackling the risk factors for MS progression has designed a project involving the New York State MS Consortium (NYSMSC). NYSMSC is composed of 15 MS treatment centers throughout New York State, and was established 15 years ago to develop a robust tool for following people with MS. The NYSMSC database now has data on more than 9,000 people with MS.

Bianca Weinstock-Guttman, MD, noted MS researcher and director of the Baird MS Center at the University of Buffalo, is studying a group of 500 people with MS. The team is using newly developed and sensitive neuropsychological, imaging, biomarker and patient-perceived measures along with the classic gold standard outcomes (such as the EDSS scale of MS disease activity). They are looking at the impact of a variety of factors, such as vitamin D levels, smoking history, and MS genetic risk.

In a unique aspect of this project, Dr. Weinstock-Guttman

and colleagues are including 20% African-American patients. African-Americans actually make up a much lower percentage of the general population but African-Americans with MS have been found to be at higher risk for a more rapidly progressive disease course. It is hoped that this kind of "oversampling" will help reveal whether the risk factors associated with disease progression in African-Americans are similar to or different from those of the general MS population.

Dr. Weinstock-Guttman and colleagues are uniquely poised for the MRI aspects of these studies, as the Buffalo Neuroimaging Analysis Center is a leading facility in MS imaging research. This team has already gathered substantial preliminary data for this effort, showing distinct MRI findings in African-Americans, associations between Epstein-Barr virus and MRI outcomes, and a link between smoking and brain tissue volume loss.

This innovative approach to risk assessment provides exciting opportunities to demonstrate how MS is related to the most compelling risk factors and to identify their role in predicting disease progression.

Examining early progression

Society-funded investigations dealing with the problem of MS progression include a new, large-scale study by Alberto Ascherio, MD, DrPH (Harvard School of Public Health and professor of

Medicine at Harvard Medical School), who is an internationally recognized expert in the epidemiology of neurodegenerative diseases.

Dr. Ascherio's team previously found that higher vitamin D intake and high blood levels of vitamin D are associated with a significantly lower risk of developing MS, and that smoking, and elevated levels of antibodies to Epstein-Barr virus (EBV, a herpes virus known to cause infectious mononucleosis), are associated with an increased risk of MS.

Now this expert group is attempting to determine whether these factors play a role in the progression from clinically isolated syndrome (CIS, a first demyelinating event indicating high risk for developing MS) to definite MS, and in the early progression or worsening of definite MS. With co-funding from the National Institutes of Health, Dr. Ascherio's group is conducting this study by evaluating blood samples and data from more than 1600 individuals with CIS who were followed for progression to MS with clinical and MRI exams.

This study presents a unique opportunity to examine links among vitamin D levels, EBV infection, and cigarette smoking and their possible impact on early MS progression.

Stopping MS progression is a dream of all people affected by MS. These teams are uniquely poised to make important strides in that direction.

Researchers search for footprints— or “biomarkers”—to help track the course of MS

When someone is diagnosed with MS, the future is far from clear. What symptoms will they experience? Will the disease worsen rapidly, slowly, or barely at all? What would be the best choice of treatment?

Imagine if there were a “footprint,” in the form of a pattern of molecules, visible in a blood test or spinal fluid test—that would tell clinicians exactly what to expect and how to best treat that individual.

Molecular footprints exist. They are called “biomarkers.” In 2005, researchers at the Mayo Clinic in Rochester, Minn., identified one such biomarker that has been a game changer in the world of MS. An antibody called “aquaporin-4” was identified in the blood of individuals with a relatively rare disorder called neuromyelitis optica (NMO). This antibody clearly distinguished this disorder from MS for the first time. The NMO biomarker created an explosion of research and new hopes for better treatments for those with this disorder. Now researchers funded by the National MS Society and others are engaged in a heated search for biomarkers that would similarly help propel MS research and treatment.

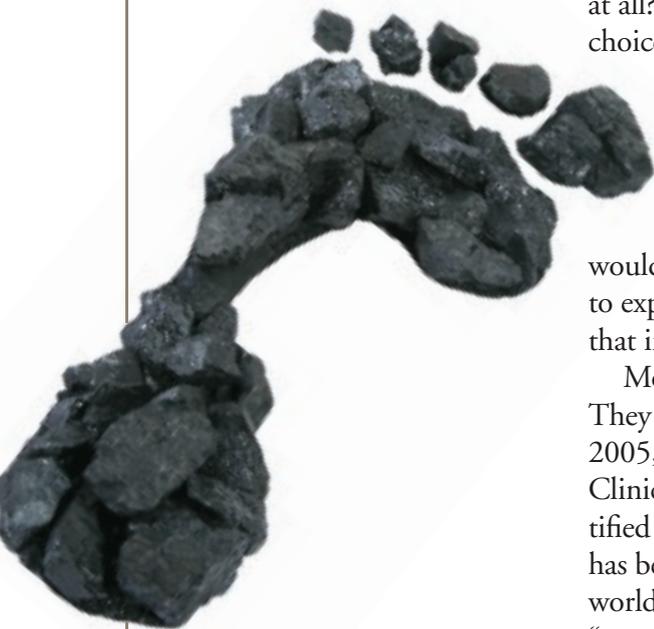
The latest news

In October 2010, several groups reported exciting findings on MS biomarkers at ECTRIMS (European Committee for Research & Treatment in MS), a meeting where nearly 1,000 presentations focused solely on MS research.

■ Richard Rudick, MD, Richard Ransohoff, MD, and colleagues (Cleveland Clinic and Foundation) carefully examined blood samples from 85 people with MS just starting treatment with interferon beta-1a, using gene-chip technology that measured the responses of 166 genes regulated by this therapy.

They found that a proportion of participants developed three or more new areas of tissue damage (lesions) while on the drug. The authors concluded that MS in this subgroup may be driven by a different kind of immune response. Gauging negative responses early in treatment may help identify a therapy better suited to this unique immune response. (Abstract #125)

■ Katherine Riester, MPH (Biogen Idec) and colleagues measured the levels of specific immune cells—CD56bright NK cells—among participants in the CHOICE trial, now completed, which compared the experimental therapy daclizumab to



interferon beta-1a.

Looking back, people who were taking daclizumab and had increased levels of these cells at an early point in the study turned out to be free of new disease activity on MRI scans later on. The findings suggest that such cell counts may turn out to be a biomarker for predicting benefit before it is clinically apparent. Daclizumab is now in phase 3 studies. (Abstract #P557)

■ Suhayl Dhib-Jalbut, MD (UMDNJ, New Brunswick, NJ) and colleagues measured immune messenger proteins in people undergoing treatment with Copaxone for two years. Increases in the proteins IL-4 and IL-10 and decreases in IL-18, caspase-1 and TNF-alpha at six months predicted treatment benefit at two years.

If confirmed, these findings hold hope that early tests might make it unnecessary to prolong treatment that isn't working. (Abstract #P554)

■ Hollie Schmidt and colleagues reported on work in progress by the Accelerated Cure Project MS Repository, which has collected blood samples from more than 2000 people at 10 MS centers nationwide. Data have been provided to 34 research teams worldwide who are using these to search for biomarkers and MS risk factors.

Project investigators are establishing two patient groups—one comprising people with early MS

to identify biomarkers, and one comprising people with progressive MS to identify risk factors for progression. (Abstract #P963)

Learning from Lyme disease

The Society is funding one new investigation searching for MS biomarkers sparked by findings in Lyme disease. Immunology specialist Steven Schutzer, MD (UMDNJ-New Jersey Medical School) reported in 1999 that early after infection, the human body can produce a specific antibody that binds to parts of the Lyme disease agent. This discovery led to a test that could diagnose Lyme disease at a much earlier point than previously possible. In 2010, Dr. Schutzer and colleagues determined the complete genetic blueprints for 13 different strains of the bacterium that cause Lyme disease, which should lead to a better understanding of how genetic variations among strains may result in different courses of illness experienced by people with Lyme disease.

Now Dr. Schutzer is turning his considerable expertise to help people with MS. “Our goal is to find biomarkers that can help diagnosis multiple sclerosis when it is suspected,” said Dr. Schutzer. “Because the spinal fluid is the closest relevant source to the brain—a ‘liquid window’—it is the most logical source to begin our examinations.”

Dr. Schutzer's team created a comprehensive database comprising CSF proteins from more than 200 people without MS to support this proposal. “To show how useful this resource is, we analyzed a group of people with headaches whose CSF lab values were reported as normal. We actually found major differences in 50 proteins between these people with headaches and others in our database!”

Now the team is studying samples of CSF from people with clinically isolated syndrome, a first demyelinating event indicating high risk for developing MS, using a variety of cutting-edge “proteomics” techniques that can identify numerous proteins in the fluid simultaneously.

“We will begin with a ‘wide-net capture’ which may yield hundreds of proteins, and

Timothy Coetzee, PhD, was named Chief Research Officer of the National MS Society in January. Dr. Coetzee has been engaged in the MS movement his entire career, beginning with a Society-funded postdoctoral fellowship in myelin research. He joined the Society in 2000 as Director of Research Training Programs, and most recently served as president of Fast Forward, the Society's drug development subsidiary.



gradually drill this number down to a shorter list of promising biomarker candidates ready for validation testing,” he said. Dr. Schutzer is working on this exciting project with leading scientists at Pacific Northwest National Laboratory who developed these proteomic techniques, as well as MS expert Patricia K. Coyle, MD (Stony Brook University, NY). This project is named the Admiral Thor Hanson Biomarkers in MS Project, in memory of a former CEO of the Society.

Biomarkers in kids with MS

Lauren Krupp, MD (SUNY-Stony Brook, NY) is renowned internationally for her work

with children and adolescents who have MS, and heads one of the six Pediatric Network Centers of Excellence established with funding from the Society’s Promise:2010 campaign. Now she is conducting an extensive society-funded search for biomarkers in blood plasma in this population.

“A simple blood test that provides a rapid diagnosis would be a major advance in managing MS in children, especially if it made lumbar puncture unnecessary, because this often requires anesthesia in children,” said Dr. Krupp. Her team also is using novel proteomics techniques to examine blood samples from 40 children with MS, 30 children

with other neurologic diseases, and 30 healthy controls.

“Our study is the first proteomic analysis in pediatric MS to include both control groups,” said Dr. Krupp. “We chose to study children rather than adults with MS because disease triggers might be more readily identified due to the narrow window between underlying tissue damage and clinical symptoms.” Findings might shorten the diagnostic process for everyone.

These teams are bringing top expertise to bear on the search for MS biomarkers. The results could lead to discoveries with implications for many different aspects of this complex disease.

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MS Research: The Society's commitment

The mission of the National MS Society is to mobilize people and resources to drive research for a cure and to address the challenges of everyone affected by MS.

In 2010 we spent \$36 million to support 325 research initiatives. Cumulatively, the Society has invested in excess of \$721 million (through 2010) to support research. Our funding has been critical in:

- ❖ Creating tools and processes to quickly and accurately diagnose MS
- ❖ Developing most of the approved MS disease-modifying drugs
- ❖ Identifying genes that contribute to MS susceptibility
- ❖ Demonstrating a link between vitamin D and MS risk
- ❖ Recruiting, training, and retaining the MS researchers who are making breakthroughs today

- ❖ Discovery of the potential for neural repair
- ❖ Getting more potential MS therapies into the pipeline than at any other time in history

To achieve our mission we must do more: more funds for MS research, more research in progressive MS, more researchers and scientists focusing on MS. Our global support focuses on three key areas:

- Stopping** the progression of the disease
- Restoring** function that's been lost
- Ending** the disease forever

We will achieve these goals by pursuing all promising avenues; engaging the best and brightest minds; connecting people, resources and ideas; speeding development of treatments; and identifying and filling gaps.

Our research focus through 2015 reflects the Society's Strategic Response priorities, moving us closer to

- ❖ Better understanding the scientific mechanisms that lead to disease **progression**.
- ❖ Accelerating the development of **new therapies** (see cover story, page 21).
- ❖ Pursuing new avenues to discover how nerve cells are damaged and potentially **repaired**.
- ❖ Developing new rehabilitation techniques and symptomatic treatments to restore neurological function and enhance **quality of life**.
- ❖ Identifying risk and **triggering factors that cause MS**, and understanding the biological interactions that lead to its development so that MS can be prevented.
- ❖ Expanding and strengthening the quantity and quality of MS research worldwide to **accelerate new discoveries** and treatments for people with MS.

Our research focus will move us closer to reaching our vision—**A World Free of MS.** ❖