

The Road Ahead: Nine Destinations

BY MARTHA KING

Illustration by J.W. Stewart

The Reverend Dr. Martin Luther King, Jr., once observed (in a different context), “We ain’t what we ought to be. We ain’t what we could be. We ain’t what we’re gonna be, but thank God we ain’t what we were!” The old civil rights analysis fits the MS movement very well. Anyone who was diagnosed before the 1990s can attest to what a different place the world of MS is today, even if some advances have come too late to be of personal use.

What needs to be done now?

In 2001, the Institute of Medicine (IOM, the independent nonprofit agency created by the federal government to advise on science and technology) issued a special study commissioned by the National MS Society. The Society asked IOM to

identify the most promising research directions in MS. In response, the IOM advisors created a “roadmap”—or more properly, according to Dr. John Richert, executive vice president for Research and Clinical Programs at the Society, “a list of essential destinations.”

“Our priorities are in accord with these destinations,” Dr. Richert said. “But priorities are not the same as a sequence. Completing number five doesn’t require completing one through four first. In fact, these destinations cannot be listed in order of importance, in part because no one knows all the things that could result from reaching any one of them. We do know that some emerging answers are likely to change or even eliminate other questions. One thing is certain: funding for research in all these areas is of compelling importance.”

The list of destinations starts (arbitrarily) with basic questions about human biology.

1 Unravel the genetic basis for susceptibility to MS

It is already established that MS is not a single-gene disorder. It involves multiple genes interacting with an environmental trigger or triggers. Research points toward infections rather than something toxic in air, water, or food as a triggering agent, though recent evidence hints that lack of sun exposure, leading to lower vitamin D levels, may play a role.

The search for genes involves scanning for patterns in the human genome and processing mind-numbing numbers of potential combinations. But the genetics of MS is likely to provide a key to accurate prognosis and a sound rationale for selecting treatments for an individual. Genetics will also identify biological molecules active in MS that will be attractive targets for new therapies. And finally, knowing which genes do what will help define and describe the disease itself.

“There could be more than 100 different genes with subtle roles in MS,” Dr. Richert cautioned. “There will be no one big bang. On the other hand, we can expect to learn volumes from each incremental finding.” The International MS Genet-

ics Consortium, a group of MS genetic experts, created with funding from the National MS Society, is collaborating in the search for the genes involved in susceptibility and in creating characteristics of the disease.

In San Francisco, Dr. Stephen Hauser has established a DNA “library” of genetic material from individuals with MS and people in families who have multiple members with MS. In compiling the library, Dr. Hauser’s team acquired a substantial collection of “trios”—a familial set, usually two unaffected parents and their offspring with MS.

Meanwhile, on the other coast, Dr. David Hafler (Harvard Medical School and Brigham and Women’s Hospital) is working with human genome expert Dr. Eric Lander at MIT to speed the search. One of their strategies is using “SNPs” from the trios. SNPs are single variations in genes, known scientifically as “single nucleotide

polymorphisms.” SNPs from trios offer a quick route to finding tell-tale patterns. Another of their approaches is called “haplotype mapping” and involves identifying and mapping blocks of genes on chromosomes that are inherited together in individuals.

This work is moving ahead with essential support from philanthropist Barbara Palmer, two Minnesota foundations, and others.



Dr. Stephen Goldman is focused on transplanting myelin precursor cells.

What the Society Has Contributed to Progress Against MS

The Society raises funds and awareness of MS problems in order to push research forward; it also serves as a catalyst for research around the world, stimulating collaboration among the best and most adventurous MS researchers anywhere. In 2007, the Society is investing \$45 million to support more than 380 new and ongoing research projects.

Here's a quick overview of Society contributions to advances that have helped get us where we are today—and will make moving ahead so possible.

In the last quarter century, the Society helped revolutionize MS treatment by funding:

- The first large-scale trial of an interferon in MS, resulting in development of three disease-modifying drugs. (Beta-seron, Avonex, Rebif)

- Early laboratory and clinical studies that led to a different disease-modifier. (Copaxone)

- Early laboratory work on the only disease-modifier approved for worsening MS. (Novantrone)

- Early clinical trials of the now standard treatment for MS spasticity. (Baclofen)

- Early studies of monoclonal antibody therapy. (Tysabri and others in the pipeline)

- Development of new imaging techniques to track effects of MS therapy. (MRI, MTR, MRS, DTI)

In the past quarter-century the Society upgraded the care available to people living with MS by:

- Developing new criteria for diagnosing MS more swiftly and consistently.

- Insisting that quality of life be a central outcome measure in trials of new treatments.

- Funding research to improve assessment and treatment of fatigue, depression, and cognitive symptoms.

- Funding the first research to show that exercise can effectively moderate MS fatigue.

- Funding early studies exploring complementary therapies including vitamin D, omega-3 fatty acids, cooling vests, and ginkgo biloba.

In the past quarter century, the Society laid groundwork for a better future by:

- Developing “gold standard” outcome measures for designing clinical trials.

- Ensuring reliable clinical trial results through special training for doctors.

- Funding new MRI techniques to better track effects of new therapies.

- Recognizing that gender and ethnic disparities in MS must be taken into account in research and clinical settings.

- Exploring the economic impact of MS.

2 Define the basis for MS “heterogeneity”

“Heterogeneity” means that MS is not uniform—something people familiar with MS have long suspected. Now, thanks to the Society-funded MS Lesion Project, there is evidence from studies under the microscope that there are as many as four different patterns of tissue injury in MS. They do **not** correlate with the four familiar clinical types of MS—relapsing-remitting, progressive-relapsing, primary progressive, or secondary progressive.

“The MS Lesion Project is helping to shed light on whether the target of injury is different in different types of MS,” explained Dr. Patricia O’Looney, vice president of Biomedical Research at the Society. “If MS has different causes, then this would help to tailor therapies towards specific types of MS,” she said.

Dr. Claudia Lucchinetti at the Mayo Clinic and her international colleagues in the Lesion Project have reported that people with one type of tissue injury responded to a dramatic rescue treatment called plasmapheresis. Other fundamental differences are suspected. If further work confirms these findings, a big question looms. What drives these differences?

The MS Lesion Project has received substantial support from the Thaler Howell Foundation, Florida.

3 Identify factors called “biomarkers”

The ideal “biomarker” is an easily measurable change in something in the body that provides information. A biomarker might indicate the presence of MS,

identify the type of MS, predict an individual’s course, or indicate the likelihood of response to a treatment. The characteristics uncovered by the Lesion Project are in fact biomarkers, but at present they require samples of brain tissue, making them too invasive for common use.

At Brigham and Women’s Hospital in Boston, Dr. Howard Weiner, this year’s John Dystel Prize recipient, is employing a technology called “antigen arrays” to identify and quantify molecules found in blood and associated with the clinical courses of MS. Will these molecules prove to be prognostic biomarkers?

Dr. Weiner’s team is just one of many groups seeking markers, and hope is high that useable markers will soon be identified.

4 Understand the immunology of MS

It’s called a biological cascade—a rushing waterfall. The name well describes the rapid chain of events in the human immune system as MS drives it to destroy myelin and injure axons.

Around the world, scientists are laboring to reduce this downpour to an understandable sequence of causes and effects. Dr. Lawrence Steinman, who received the Dystel Prize in 2004, is among them. One of his many current projects is an investigation of the role of “osteopontin,” a protein that appears to help immune cells continue attacking a target instead of self-destructing as would be normal in a fight against infection. As an indication of just how complex the immunology of MS may be—this same protein plays an essential part in maintaining healthy bones.

Dr. Steinman’s work is going forward

with important support from the Society and Dr. and Mrs. Michael Morykwas.

5 Understand the process that destroys tissue in MS

Three kinds of brain cells are directly involved in MS: Neurons or nerve cells (with their long fibrous axons), oligodendrocytes (the mother of myelin), and astrocytes (they form a supporting scaffold for brain tissues—and also the scar material called “sclerosis”).

Some of what happens in MS is the result of “conversations” among these cells and among immune cells that travel into the central nervous system. Many Society funded investigators are chipping away at the central puzzle of how myelin and axonal tissues are destroyed.

At the University of Alabama, Dr. Ety (Tika) Benveniste is working on an aspect of cell-to-cell conversations, hoping to learn if abnormal interactions between brain cells and immune cells lead to damage in MS. If her team can identify links, the findings might also point the way to better therapies.

From here, the list begins to concentrate on outcomes: new approaches based on the biology of MS.

6 Develop cures for three aspects of MS

Stop MS by blocking the inflammation. An inflammatory immune attack destroys myelin and dam-

ages axons. All the disease-modifying drugs block some inflammation and *partly* stop MS, but even Tysabri, the most potent of the FDA-approved drugs, falls short of stopping MS cold.

Work on this aspect of MS therapy is in high gear, as can be seen in “Happening Now” on page 16. Today, many investigators are looking beyond inflammation as they seek additional ways to block the destructive MS process.

Repair MS damage. Armed with new knowledge about how MS behaves on a cellular level, including the revelation that quite a bit of myelin repair can occur naturally, research groups are in hot pursuit of the factors that drive repair. They hope natural repair mechanisms can be boosted to do a more thorough job.

Axons stripped of their myelin may break. Nerve cells die if too many of their axons break. When nerve cells die, long-term disability results. Can scientists induce stem cells to furnish the brain with

cells capable of developing into new nerve cells or into new myelin-producing oligodendrocytes? Or could stem cells, or a formula of natural growth factors, help the nervous system’s own resident repair cells do a more efficient job? Scientists in the Nervous System Repair and Protection Initiative, funded by the Promise: 2010 campaign, think so.

“We need to clarify the ideal source of cells for transplantation and the



Dr. Ety Benveniste looks at how brain cells and immune cells talk to each other.

most appropriate route of administration. We have already shown that human oligodendrocyte precursors will mature and form new myelin very effectively when transplanted into the brains of mice," said team member Dr. Steven Goldman of the University of Rochester. "This suggests that these cells may be suitable for the large amount of repair needed in brain damaged by MS."

Dr. Goldman's work is going forward with vital support from the Alan Buegeleisen Fund and the Barancik Foundation.

Protect tissues from MS damage. Many experts also suspect that the nervous system's susceptibility to MS injury could be reduced or prevented. In 2005, researchers in Italy published results showing that immature precursor cells injected into the bloodstream will migrate to a damaged area deep within the brain and protect the tissue there from injury. Dr. Gianvito Martino and his colleagues accomplished this in mice, with support from the Society.

Building on this work, Dr. Goldman reported in 2006: "We identified five signaling pathways present in immature myelin-making cells residing in the adult human brain. These pathways may regulate the ability of the immature precursors to become mature oligodendrocytes and make myelin. We also found a factor that inhibits one of these pathways, and that factor may become our first 'target' for a nerve-protection therapy."

"I can see a future where a patient may take immune-modulating therapy to turn off the immune system, a remyelinating therapy to help make new myelin, and an axon-protecting therapy to prevent any further damage. Combinations may be our best chance for making people better," said Dr. Peter Calabresi of Johns Hopkins who heads another of the four Repair and Protection "Dream Teams" supported by Promise: 2010.

Merry and Richard Slone of New York and Bill and Roxanne Davis of Washington are among those who are generously supporting Promise: 2010 Dream Teams with leadership gifts.



Dr. Katia Noyes seeks the best method to assess cost-effectiveness of MS drugs.

7 Devise more inclusive clinical trials

When a new therapy is tested, the number of relapses or measurable disease worsening have long served as the clearest indicators that the new agent is working. People with progressive MS are excluded from clinical trials that use outcome measures that don't apply to them. Then, when a therapy is initially approved, they are excluded again, since nothing is known about the effectiveness—or the safety—of the new treatment in their type of MS. This is of deep concern to MS researchers.

New outcome measures could make clinical trials shorter, and more accurate, efficient, and cost-effective. Most importantly, the results might apply immediately to progressive forms of MS.

One new measure may be coming into its own through work by Drs. Elliot Frohman, Laura Balcer, and their colleagues at the University of Texas Southwestern Medical Center at Dallas MS Clinic and the University of Pennsylvania. "Optical coherence tomography," or OCT, is the scientific name for imaging the optic nerve. This painless procedure, which can measure nerve fiber loss, can be conducted in a doctor's office. Can OCT serve as an outcome measure for clinical trials in MS? Research is underway.



Dr. Elliot Frohman is exploring optic nerve imaging as a benchmark for clinical trials.

8 Gain the ability to test treatments before clinical trials

Both biomarkers and genomic markers—or patterns in DNA—can be used to screen candidate drugs, eliminating those that are worthless before spending time and money on clinical trials. Thanks to advances in robotics, high-speed computer technology, and information from the Human Genome Project, MS researchers are now using "high-throughput screening" or HTS to effect a short-cut. The technique is capable of processing up to 100,000 compounds a day.

Dr. Bruce D. Trapp (Dystel Prize, 2003) and his colleagues at Cleveland Clinic Foundation are using HTS to identify the molecules that trigger immature precursor cells to become mature myelin-making cells. This work is funded by a special Society "Collaborative MS Research Center Award," which has allowed Dr.

Trapp to work with a world-renowned expert who has identified targets for cancer treatment. The cross-disciplinary team is screening a library of 200,000 small molecules, and have begun to test some "hits" in cell cultures and animal models to determine how much triggering they can accomplish.

Dolly and Merwyn Dan of Illinois are among those who have supported Dr. Trapp's work.

9 Pioneer new therapies for the MS symptoms that disable people

"While the search for cures and the work to improve clinical trials forges ahead, people with MS continue to struggle with daily symptoms," Dr. Richert said. "The problems range from the chronically irritating to catastrophically disabling. Fatigue, pain, other sensory disturbances (such as tingling or vertigo), loss of walking ability, and cognitive problems affect people with progressive and relapsing MS alike. The need for effective therapies for MS symptoms will disappear when we have cures—but they are urgent research priorities now.

"Please read the stories on rehabilitation research on pages 46–50. As the IOM review confirmed, enabling people to move ahead with their lives despite MS is an essential destination on our roadmap," Dr. Richert summed up. ■

Martha King is editor of this magazine.