



Research Now is a quarterly feature of **Momentum**, produced by the Society's Research and Clinical Programs Department.

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INSIDE:

64 The bold world of genetics research

66 Physician-scientists

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The discovery of MS genes is not the end, but rather the beginning.

Dystel Prize winner Dr. David Hafler on the genetic roadmap to ending MS

by Sara Bernstein

Breaking new ground on the immune attack in multiple sclerosis was just the start for David Hafler, MD (Yale University, New Haven, Conn.). Now, this noted physician-scientist has joined with MS geneticists around the globe to plot out the roadmap that can end MS forever. For these and other feats, Dr. Hafler was awarded the 2010 John Dystel Prize for MS Research, joining a pantheon of researchers who've made outstanding contributions toward

COURTESY OF YALE

understanding, treating, or preventing MS (see box, p. 63).

Taking on the T cell

Dr. Hafler wasted no time in making major contributions to MS research. His background was well suited to the disease, since he was interested in immunology even in high school, and learned the ropes of neuroscience from a series of "wonderful mentors" such as the late Dale McFarlin, MD, then head of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health.

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MS occurs when the immune system attacks the nervous system, and T cells are major players in this attack. Dr. Hafler was the first to provide evidence that circulating T cells migrate into the brain and spinal cord. **The New England Journal of Medicine** 1985;312:1405 His laboratory consistently developed novel methods of studying T cells, and was among the first to apply the techniques of T cell cloning, by which researchers can amplify and study these cells more closely. **The Journal of Experimental Medicine** 1988;167:1625

Dr. Hafler also was among the first to demonstrate a defect in the function of regulatory T cells in people with MS. These are T cells that can actually suppress the immune attack. **The Journal of Experimental Medicine** 2004;199:971

“Funding from the National MS Society was absolutely critical to me during these early years, especially during the tenuous stage from being a postdoctoral

fellow to becoming a faculty member,” he said. Dr. Hafler earned the Society’s prestigious Harry Weaver Neuroscience Scholar Award, which provides five years of salary and grant support to promising researchers who have concluded their training and are just beginning academic careers as independent investigators in MS research.

As his career progressed and the field of immunology grew more complex, Dr. Hafler began to look for guidance. “When I started studying immunology, there were—for example—two known interleukins [immune messenger proteins],” he said. “Now there too many to count! We needed to go after the bigger picture in MS research, to figure out what to study.”

The bigger picture meant genetics, since genes provide the “instructions” that drive the entire body, including the immune system and the nervous system. The field of genetics exploded in 2003 with the completion of The

Human Genome Project, the map of all genetic material in humans. “This is perhaps the greatest library that humankind ever created,” said Dr. Hafler.

The follow-up to the Human Genome Project, the International HapMap Project, added even more power to the field of genetics by mapping common genetic variations found in the human population. Comparing these variations in people with and without specific disease can help to pinpoint disease genes. These projects, and the development of gene “chip” technology that could analyze hundreds of thousands of variations at once, are the tools that Dr. Hafler and others called on to help demystify MS.

Competitors become collaborators

Dr. Hafler realized early on that the strength of genetics findings would lie in numbers, and would require many geneticists around the globe working together. In 2003, he put together a team with Drs. Stephen Hauser (University of California, San Francisco) Alastair Compston (University of Cambridge) and Eric Lander (Broad Institute of MIT and Harvard), to successfully compete for what became the Palmer Collaborative MS Research Center Award: MS Targeted Haplotype Project (see box, this page).

“It was difficult at first,” notes Dr. Hafler. “We weren’t used to working together. We realized, though, that this would be our



Barbara Palmer

The Palmer Collaborative MS Research Center Award: MS Targeted Haplotype Project is named in honor of Barbara Palmer, who funded the project through a \$1 million gift to the National MS Society. Ms. Palmer’s connection to the Society’s Central New England Chapter goes back 30 years to the time when her daughter, Jan, was diagnosed with MS. Her grandson Jacob is carrying on this tradition in the chapter’s Bike MS. Ms. Palmer has made a number of gifts to the chapter, including \$100,000 to the Hilton Research Challenge.

About the John Dystel Prize

Oscar Dystel, now Honorary Life Director of the Society's National Board, and his late wife, Marion, established the John Dystel Multiple Sclerosis Research Fund to honor their late son, John, a lawyer whose promising career was cut short by progressive MS. The fund provides for the **John Dystel Prize for Multiple Sclerosis Research**, which is given annually to a scientist who has made significant contributions to the understanding, treatment, or prevention of MS.

A legend in the publishing world, Oscar Dystel also established the John Dystel Fellowship Fund, which trains registered nurses specifically in MS care. John's sister Jane—a literary agent and active volunteer for the National MS Society—is continuing the family's tradition by joining her father in promoting research for a cure and efforts to improve care for people living with severe MS. A third generation has also begun participating. Jane's son, Zachary, contributed gifts he received for his bar mitzvah to the Society. The \$15,000 John Dystel Prize for MS Research, given jointly by the National MS Society and the American Academy of Neurology, has been awarded every year since 1995. To learn more, visit nationalmssociety.org/dystelprizewinners.



Jane Dystel and Oscar Dystel

only way to achieve our true passion—figuring out the disease process in MS.”

The Palmer Center award allowed the investigators to form the International MS Genetics Consortium, a collaborating powerhouse of investigators, many of whom were formerly competitors, to pool expertise in genetics, database design/construction, and clinical assessment and immunology of MS.

In 2007, the IMSGC completed the largest replicated whole genome scan specific to MS conducted to date. They identified and confirmed several genes that may contribute to MS susceptibility, presenting possible new targets for better therapies. **The New England Journal of Medicine** 2007; 357:851

The ultimate map of MS

In 2008, the IMSGC won a large research grant from the Wellcome Trust to undertake a whole genome scan involving approximately 10,000 individuals with MS to identify MS-related genes. Led by IMSGC co-founders Alastair Compston and Stephen Sawcer, the project identified 20 or so regions that are clearly associated with MS risk. “We are now completing another large study of 10,000 people to confirm these findings,” reports Dr. Hafler. “These studies should tell us all of the allelic variants [alterations in the normal sequences of genes] that are associated with MS.” The validation study is being funded by a major research grant from the National MS Society, with

support from donors. The team expects to confirm the association of 100 or so genes to MS.

Although it's tremendously exciting to be this close to finding MS-related genes, Dr. Hafler cautions that that this is hardly the end of the search. “The discovery of MS genes is not the end, but rather the beginning of a biologic roadmap for ending the disease.”

“Right now, we are surrounded by reams of data in MS research—numerous immune system cells and proteins that show involvement in the disease. These genetic variants will allow us to figure out the pathways of immune system activity. They will point us in the direction of what to study.” This information should lead to the actual cause of MS, point to

new and better therapies, and ultimately reveal a way to end MS forever.

Funding the future

Figuring it out will take time and effort. “We need careful analysis of these genes to find out what each of their functions are and how they affect the course of MS. Why do some people recover, and others go on to develop progressive MS?”

Bringing more minds and hands to the job should speed up this effort. Dr. Hafler believes that attracting and training young scientists should be a top priority for the Society and other funding sources—particularly physician-scientists, who serve as a bridge between the clinic and the laboratory (see page 66). “By far, the biggest obstacle facing young investigators is the lack of funding.” National MS Society leaders are developing new strategies to address this issue.

Dr. Hafler hopes that the sheer excitement of the IMSGC’s work will attract young minds to MS research. “The brightest and the best migrate to a field where they can have an impact,” he said. “The IMSGC whole genome scan has produced the most important data set ever generated in MS research. We are constructing a roadmap that scientists can use to solve the major questions facing people with MS.”

The bold world of genetics research: What does it mean for people with MS?

We are closer than ever to finding the genes that make people susceptible to developing multiple sclerosis. In this issue of **Research Now**, Dr. David Hafler describes the imminent discovery of all of the common gene variants that lead to the risk of developing MS (see page 61). What does this mean for people with MS? MS is not directly inherited, and other factors determine whether a person will actually end up with MS, so the answer is a little complicated, but very hopeful.

Making complex genetics simple

Finding an association between a gene and MS should help to predict if you or your kids will develop the disease, right? It’s probably not that simple, say the experts. The International MS Genetics Consortium (IMSGC), which was established with support from the National MS Society, took a fresh look at data from two previous genome-wide scans for MS-related gene variations. They found that many variations, working together, had a highly significant association to MS susceptibility, but there is no one mastermind. “It is becoming increasingly clear that single genes explaining a large proportion of heritability do not exist,” they wrote this

year, concluding that MS risk is governed by a cumulative effect of variants throughout the genome that, on their own, have only very small connections to MS. **The American Journal of Human Genetics** 2010;86:1–5

A key effort is underway to organize this information. The Web site www.msgene.org is a collection of published genome-wide MS studies, launched by IMSGC collaborators and hosted by the Alzheimer Research Forum Web site. At this writing, there are 622 MS genetics studies listed on the site, which examined 669 genes for associations to MS. Sound overwhelming? Site developers have ranked the strength of these associations, providing a valuable resource to MS geneticists.

Genes and the environment

Studies that report on one gene or one trigger seem to swing between “yes, they are linked” and “no, they’re not.” Perhaps the final answer depends on a combination of a specific gene and a specific trigger working together. Researchers are working to understand how MS gene variations may interact with environmental triggers.

In a recent study of gene-environment interactions, Philip De Jager, MD, Alberto Ascherio, MD, DrPH (Harvard Univer-

sity) and colleagues analyzed data and blood samples from 148 women with MS and 296 women without MS enrolled in the ongoing Nurses' Health Studies. The data show that having the HLA DR15 gene (which helps to control how the immune system is activated) increased a person's risk of MS from two to nearly three times that of those without the gene. Those with high levels of Epstein-Barr virus antibodies (studies suggest that MS risk is increased in people who have been exposed to the virus, and thus have circulating antibodies) had up to twice the risk of developing MS. Those with both HLA DR15 **and** high levels of Epstein Barr virus antibodies were **nine** times as likely to develop MS. **Neurology** 2008;70:1113–18 Further research is required to confirm the findings, but the results point to the potential of studying genes and environmental triggers together to better understand the cause of MS.

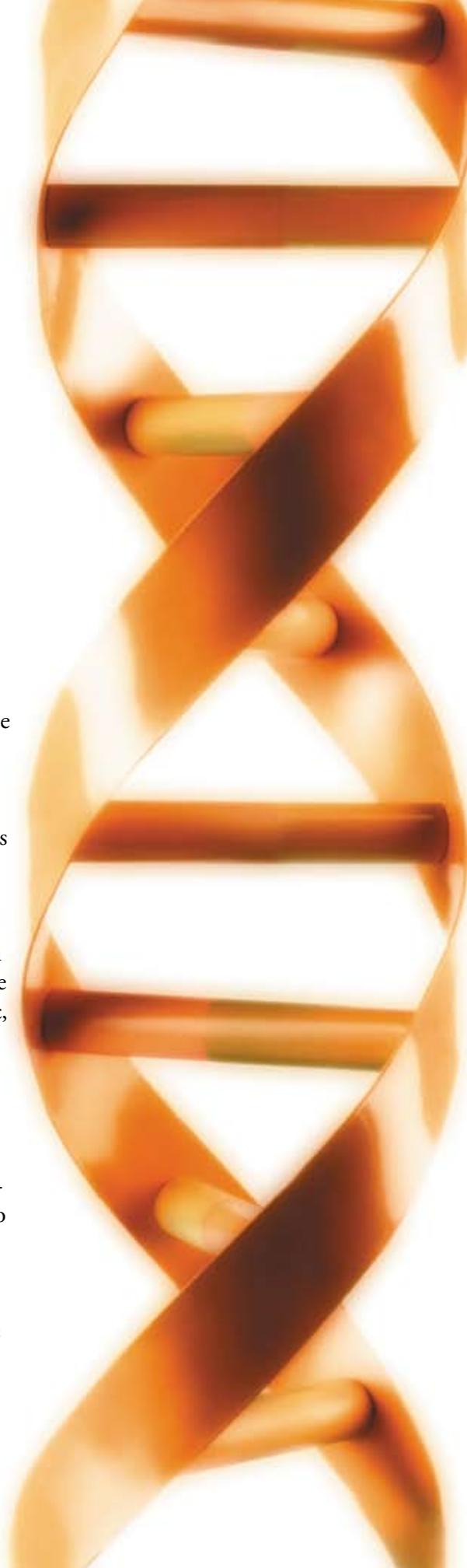
Figuring out "pharmacogenomics"

Although a single gene may not confer susceptibility to MS, it may yield an important clue, such as how the person will respond to a treatment. "Pharmacogenomics" is the study of how genes influence the response to therapies. Currently approved MS therapies don't work for everyone. Since earlier treatment has been linked to better out-

comes, having a way to predict whether a person's MS would respond to a specific therapy could save months or even years of guesswork and potentially improve outcomes.

Jorge R. Oksenberg, PhD (University of California, San Francisco) and colleagues conducted the first genome-wide pharmacogenomic study in MS, screening the genetic material of more than 200 people with relapsing-remitting MS and following them for two years while on interferon beta therapy. The results showed significant differences between those who responded to therapy versus those who did not. Many genes that differed between the two groups were associated with ion channels (tiny pores along nerve fibers that help with nerve impulse conduction) and cell signaling pathways. **Archives of Neurology** 2008;65:337–344 Although more work is needed before these findings can be used in the clinic, this is the beginning of an era that could lead to personalized medicine for people with MS.

So, the answers that we are deriving from genetics are not simple. But this bold field is providing the information needed to develop more targeted therapies to stop MS in its tracks. And when more is understood about how MS genes, other risk factors and triggers work together, we may have what we need to end MS forever.



Why we need more physician-scientists in MS and what stands in the way

by Richard Rudick, MD

We call it “translational” research—turning basic laboratory findings into treatments that will help people. With an explosion of data coming from biomedical research labs, who are best able to apply new knowledge to MS? Physician-scientists. These MDs, and I count myself among them, have one foot in the lab and one in the clinic.

The problem

At this critical juncture—at what many consider the most exciting time in the history of MS research—fewer and fewer neurologists are choosing a training path that will equip them to conduct translational research. Here are some aspects of this problem.

Many challenges await young investigators who want to become physician-scientists. The

training of a clinical neurologist includes four years of college, four years of medical school, one year of internship, and three years of residency training in neurology. The average debt of these students tops \$100,000. So there is a lot of pressure to begin practicing instead of continuing on for an additional five or more years of research training. And for those few who do pursue this pathway, the road to independent funding is perilous and uncertain because of the highly competitive nature of research funding. It’s no wonder that the National Institute of Neurological Disorders and Stroke reported a steady decrease in applications and funded awards for physician-scientists from 2005 to 2009.

The problem is not unique to neurology, but it is particularly

distressing given this exciting era in MS research. Progress in immunology, imaging, genetics and neurobiology is giving us a multitude of new leads to follow. As these leads turn into therapeutic possibilities, we need well-trained individuals who understand the complexity of the nervous system and can follow leads out of the lab and apply them to people with MS.

What the Society is doing

The National MS Society has a terrific track record of investing in training both basic scientists and clinicians. The Society joined forces with the American Academy of Neurology (AAN) Foundation in 2005 to launch the NMSS-AAN MS Clinician Scientist Development Award. This two-year, post-residency training award supports promising young clinicians who have potential to make significant contributions to MS research.

The first recipient of this award, Dr. Ari Green, started his MS career under my and Dr.

Applications to NIH for clinician-researcher training awards



Source: NIH IMPAC, Success Rate File

Donald Goodkin's supervision at the Cleveland Clinic. He then moved to the University of California at San Francisco, where—during the term of this fellowship and under the mentorship of another MS physician-scientist, Dr. Stephen Hauser—he revealed new information on the extent of retinal nerve fiber damage in people with MS, and created a neurovisual research diagnostic center. Dr. Green is now the Debbie and Andy Rachleff Chair in Neurology and the Assistant Director of the MS Center at UCSF. This success story speaks to the value of encouraging talented people toward careers as physician-scientists. The Society's Research Programs Advisory Committee has voted this a top priority for the Society's research programs, and we plan to identify new ways to nurture this endangered breed of MS investigator.

The Society also encourages the development of physician-scientists through the Sylvia Lawry Physician Fellowship program, which trains physicians in design and implementation of clinical research. Dr. Ruth Ann Marrie, who completed this fellowship under Dr. Jeff Cohen at the Cleveland Clinic, is now studying genetic and environmental factors that contribute to MS, while directing the MS clinic at the University of Manitoba. She has already published novel findings on many aspects of life with MS, including bone health, mental illness and bladder symptoms.

Others are also responding

The Society is not alone in these efforts. The Consortium of MS Centers also joined forces with the AAN Foundation to create the John F. Kurtzke, MD, FAAN Clinician Scientist Development Three-Year Award. The American Neurological Association has created courses in neuroscience research for neurologists.

In 2002, the National Institutes of Health designed a plan for medical research for the 21st century. Invigorating the training of clinicians who do research was identified as a key need, and this resulted in a multi-million dollar effort called the Clinical and Translational Science Awards. I co-direct the Clinical & Translational Science Collaborative here in Cleveland, funded through this NIH Award. Our goal is to provide Northeast Ohio with full service translational research capabilities, and to help develop future clinical and translational research leaders.

Spreading the word

Funding helps, to be sure, but those of us who are longstanding physician-scientists in the field of MS can do more. We need to speak out about the benefits of this career. They clearly outweigh the disadvantages. The



SUSAN MERRELL, UCSF

Physician-scientist Dr. Ari Green instructs students at the University of California at San Francisco.

next generation of MS drugs—better ones, that will improve the quality of life for people with MS—are waiting around the bend. We need to encourage and train the young men and women who can take us there. The jobs are out there for qualified individuals. Drs. Hauser and S. Claiborne Johnson put it well in a recent editorial (*Annals of Neurology* 2009;66:6): “For the next generation of investigators, the ground is fertile for enduring and highly rewarding careers that combine—as do few other occupations—the application of intellect and creativity in pursuit of a profoundly important societal goal.” ■

Dr. Rudick, Professor of Medicine



and Chair of Neurology at the Cleveland Clinic, is the chair of the Society's Research Programs Advisory Committee.