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Sara Bernstein, Editor,
Research Now

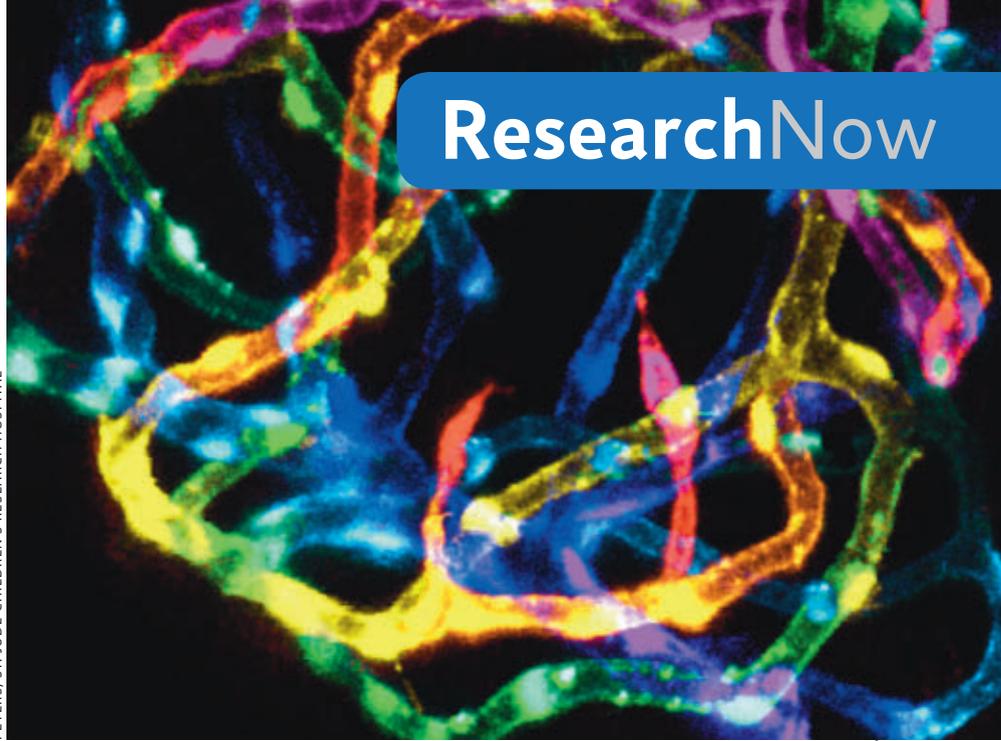
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The National MS Society is proud to be a source of information about MS. Our comments are based on professional advice, published experience and expert opinion, but do not represent individual therapeutic recommendation or prescription. For specific information and advice, consult your personal physician.

COURTESY OF DR. MICHAEL R. TAYLOR AND DR. JENNIFER L. PETERS, ST. JUDE CHILDREN'S RESEARCH HOSPITAL



Researchers created this image of the developing zebrafish brain by labeling brain cells with fluorescent proteins and then using a confocal microscope to snap 3-D images of them. The translucent nature of this model makes it easy to observe how the brain functions and how these processes go awry in diseases such as MS.

MS research under the sea

by Sara Bernstein

The pursuit of all promising avenues is leading multiple sclerosis researchers to interesting places—including the depths of the ocean. Yes, zebrafish and sea anemones are being used to study the origins of MS and to develop novel strategies for stopping the disease in its tracks and restoring function. Here is a sample of such work from grantees funded by the National MS Society.

Zooming in on zebrafish genes

Zebrafish are ideal for studying the early stages of disease development, including MS. Why? Because these small, freshwater fish lay hundreds of eggs at weekly intervals, which means researchers can get information about large numbers of genes simultaneously. The embryos are also translucent,

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PHOTO BY THINKSTOCK

Sea anemones are now the basis of a novel therapeutic strategy for MS.

making it easy to observe the formation of myelin (the substance that surrounds nerves and is a major target for the immune attack in MS) and other processes.

Dr. William Talbot (Stanford University Medical Center, Stanford,

Calif.) is screening zebrafish genes to identify those that may control myelin formation. Dr. Talbot's team has received several grants from the Society to complete this work. The group has identified a string of mutations that may

be important in the development of MS.

One mutation is in the gene that instructs *kif1b*, a “motor protein” that helps nerve cells transport other proteins so they can function normally. Dr. Talbot's team has shown that normal *kif1b* is required for myelin to form properly around nerve fibers and for the proper development of nerve fibers themselves. These findings suggest that disruption of this protein in MS may reduce the capacity for myelin formation and repair in MS (**Nature Genetics** 2009;41:854).

Dr. Talbot and his colleagues are continuing their search using zebrafish models for the genes that are crucial to myelin formation. The discovery of such genes could lead to a new understanding of how to stop MS damage and devise strategies for restoring function.

Dr. Bruce Appel (University of Colorado, Aurora) also is using zebrafish in his work. He is studying the genes that regulate how myelin-making cells wrap myelin around nerve fibers. His team is also evaluating whether mice, whose myelin closely matches that of people, have these same genes. With funding from the Society, his team found eight genes that had not been previously linked with the development of myelin-making cells (**Developmental Dynamics** 2010;239:2041).

Now the Society's funding of his work has been leveraged to

obtain funding from the National Institutes of Health. The team recently published results on the gene that instructs “pescadillo,” a protein crucial to the growth of myelin-making cells. Pescadillo was originally discovered in zebrafish and has subsequently been identified in mice and humans as well. Dr. Appel’s team found that the pescadillo-directing gene is required for the proper number of myelin-making cells to form, and for other myelin-related genes to function normally (**PLOS One** 2012;7e32317).

These experiments should extend our knowledge of the molecular mechanisms that guide the myelin-making process, and inform efforts to find ways to repair myelin damaged by MS.

More potential treatments

A sea anemone common in the Caribbean is known by the scientific name **Stichodactyla helianthus**. In 1995, researchers administered extracts of this anemone to mice, resulting in a toxic reaction. Upon examining this reaction, the team discovered that a protein fragment called “ShK” in the extract blocked ion channels (**Toxicon** 1995;33:603). Ion channels are tiny pores that allow charged particles—sodium, potassium and calcium ions, for example—to pass in and out of a cell. These channels are made up of protein molecules that assemble to form a water-filled tunnel across the cell’s protective membrane.

Dr. K. George Chandy (University of California, Irvine) and his colleagues have focused on ion channels on the surface of immune T cells, which allow T cells to become activated and are thought to lead the immune-system attack against the nervous system. Dr. Chandy discovered a key channel, Kv1.3, and modified ShK molecules to create an experimental treatment, called ShK-186, to block this channel.

In a unique pilot project supported by the Society, Dr. Chandy’s team found that by selectively blocking Kv1.3 and preventing T cell activation, ShK-186 can prevent experimental autoimmune encephalomyelitis (EAE, an MS-like disease) in rats and treat ongoing disease (**Molecular Pharmacology** 2005;67:1369). Dr. Chandy’s team formed a company, Airmid Inc., to develop Kv1.3 blockers as a strategy for MS and similar diseases. Kineta Inc. acquired this portfolio in July 2009. In August 2012, Kineta announced that it had received regulatory approval in the Netherlands to begin studying ShK-186 in human trials.

This novel approach may lead to a therapy that can prevent the activation of immune cells responsible for MS attacks, while leaving the rest of the immune system intact. Research under the sea continues to provide exciting findings that could help us reach the goal of a world free of MS. ■

Harry Weaver Award fuels bright minds in MS research

by Elinor Nauen

Engaging the best and brightest minds is crucial to stopping multiple sclerosis in its tracks, restoring function and ending the disease forever. To do this, we have to attract these minds to the field of MS research. One way the Society accomplishes this is with the Harry Weaver Neuroscience Scholar Award.

Named after the Society’s director of research from 1966–77, this five-year career development grant is given to scientists with a promising future in MS research. Some \$12.5 million has been distributed to 44 individuals and their institutions since the award began in 1981.

Bringing gender research to the forefront

The 1997 Weaver Award supported Dr. Rhonda Voskuhl’s



research on gender differences in MS, specifically regarding whether sex hormones and chromosomes

play a role in MS. In the late 1990s, “People were first getting interested in gender differences in

MS, so it was a good time to be doing this. I was one of the few at the time. The Weaver Award helped me bring this research avenue to the forefront,” she says.

It also helped her win other grants and eventually, an endowed chair. Dr. Voskuhl is now a professor in the department of neurology at UCLA and program director of the UCLA Multiple Sclerosis Program. One outcome of her work is that two different hormone treatments are currently being tested in three clinical trials. She was the first researcher to show that estrogen treatments may protect the nervous system in MS. Now, with funding from the Society’s Fast Forward initiative to expedite the MS drug development process, Dr. Voskuhl’s team is collaborating with ACADIA Pharmaceuticals to determine whether a novel estrogen-like compound can protect the nervous system from damage in mice with experimental autoimmune encephalomyelitis, (EAE, an MS-like disease).

Toward new understanding of the disease process

Dr. Anne Cross, section head of neuro-immunology at Washington University and co-director of the John Trotter MS Center in St. Louis, also believes the



Weaver Award helped her get her current position. “It gave me credibility when I didn’t have that many papers on MS,” she says, adding, “I think the award helped keep me in the MS field. It certainly helped solidify my wish to continue working on MS.” Dr. Cross received her Weaver Award in 1990, when she was studying the trafficking of white blood cells from the bloodstream into the central nervous system. These days her primary focus is on better ways to image the central nervous system. “I would like to be able to accomplish something similar to a biopsy but noninvasively,” she explains. “It would be nice to visualize what’s going on at the microscopic level and how treatments are having an effect—without hurting the patient.” Dr. Cross is incoming chair of the Society’s Research Programs Advisory Committee.

Bruce Trapp, PhD, a 1986 Weaver awardee, is now chair of the department of neurosciences at Cleveland Clinic Lerner Research



Institute and a professor at Case Western Reserve University. Dr. Trapp’s work changed the face of MS research by showing that nerve fibers are damaged by the disease. His current research aims are twofold: to obtain a better understanding of cell development

and myelin formation in the nervous system, and to understand how myelin and myelin-forming cells are destroyed in autoimmune and inherited diseases. His 1986 Weaver Award funded a study of MS tissue. “Now we have the most sophisticated brain autopsy setup in the world at the Cleveland Clinic, a direct descendant of that early work.”

Dr. Philip L. De Jager, associate professor of neurology at the Brigham & Women’s Hospital and Harvard Medical School, is in the final year



of his 2008 award. His research is focused on understanding how genetic variation affects neuroimmunologic function and susceptibility to MS, and how one goes from having a genetic risk to developing MS. The grant enabled his team to take a close look at one genetic variant and a broad look at many others, to see what causes MS-related alterations in immune responses. “The Weaver Award offered me the flexibility to pursue the original question and grow that question to launch a much broader and more systematic assessment of the consequences of genetic variation in MS,” he notes. “It gives me time to develop innovative research projects and get preliminary data to the point where National Institutes of

Weaver awardees drive progress

Health resources might be forthcoming.”

Dr. Ari J. Green, assistant clinical director of the Mission Bay MS Center at the University of California, San Francisco, is in his first year of the Weaver Award.



His research addresses how MS affects the visual system, using advanced imaging to investigate the retina and optic nerve and how they're damaged by the disease—and thus better understand injury to nerve fibers of the brain and central nervous system.

“I can't express how honored I am to receive the Harry Weaver Award,” he adds. “My hope is to build on what other Weaver awardees have done and to help develop better approaches and treatments for patients.”

All these top-notch investigators are positive about the progress they see in MS research, mentioning advanced technology, emerging therapies to help protect and repair the nervous system, and increased understanding about the types and origins of MS. “It's absolutely an exciting time to be engaged in MS research because we can witness the difference we're making in people's lives,” says Dr. Green. ■

Elinor Nauen is a health writer based in New York City.

Several National MS Society Harry Weaver Neuroscience Scholar Award recipients have gone on to earn **The John Dystel Prize for Multiple Sclerosis Research**. The prize, which is awarded jointly by the Society and the American Academy of Neurology, recognizes outstanding contributions to research in the understanding, treatment or prevention of MS.

- Dr. Richard M. Ransohoff (Cleveland Clinic Foundation) was a Harry Weaver Scholar in 1987 and earned the 2012 John Dystel Prize for pioneering work in MS that led to new insights on immune activity in the brain and spinal cord.
- Dr. David A. Hafler (Yale University) received a Weaver Award in 1985 and the Dystel Prize in 2010 for fundamental discoveries related to MS in fields such as immunology and genetics, and for bringing clinical importance to basic science findings.
- Dr. Stephen L. Hauser (University of California, San Francisco) earned a Weaver Award in 1987, and in 2008 was honored with the John Dystel Prize for his pioneering studies on genetic susceptibility to MS, and for his role in translating findings on the role of immune B cells in MS into clinical trials.
- Dr. Bruce D. Trapp (Cleveland Clinic Foundation) received a Weaver Award in 1986, and was chosen as the 2003 John Dystel prize recipient for his major contributions to our understanding of brain tissue destruction and repair in MS. These findings changed the face of MS research and have had significant implications for the development of new therapies.

The John Dystel Prize is made possible through a special contribution from the Society's John Dystel MS Research Fund. Society National Board member Oscar Dystel and his late wife Marion established this fund in 1994 in honor of their son John Jay, an attorney whose promising career was cut short by progressive disability from MS. John died of complications of the disease in June 2003. To learn more, visit nationalMSSociety.org/dystelprizewinners.

Collaborating on progressive MS

by Timothy Coetzee, PhD

Progressive forms of multiple sclerosis continue to elude effective treatment, increasing our collective urgency to do something now. That's why we've joined forces with the MS Societies of Canada, Italy, the Netherlands, the United Kingdom and the MS International Federation to create the International Progressive MS Collaborative.

The mission of the Collaborative is "to expedite the development of therapies for effective disease modification and symptom management in progressive MS."



While focused and singular, the mission is coupled with significant challenge. We know a lot about treating relapsing-remitting forms of the disease, but we have a long way to go in understanding what's

different about progressive MS and how to treat it.

The Collaborative is tackling this challenge by rallying the global MS research community to help identify the major barriers and potential solutions. This multi-country collaboration of researchers helped us identify key needs for accelerating research in progressive MS. These include:

- **New laboratory models for progressive MS.** Scientists need a way to replicate progressive MS in the lab so that they can sort out what contributes to the disease and potential solutions. We need new tools so that researchers can move more quickly to solve progressive MS.
- **New drug discovery strategies.** Discovering new treatments for progressive MS will require a new approach. We need to see if we can repurpose existing drug treatments, and also find new tools for identifying innovative therapies.
- **Improved clinical trial strategies.** The strategies used to find treatments for relapsing-remitting MS are not going to work for progressive MS. Trials in relapsing-remitting MS often rely on counting relapses or using MRI scans to detect immune activity; the fact that there is no easy way to identify progression quickly is one reason why drug development for progressive MS is lagging. New approaches are needed to test potential treatments faster and with fewer patients.

- **New symptom-management and rehabilitation strategies.** While we're focused on finding effective disease-modifying treatments for progressive MS, we're also committed to finding useful treatments for symptoms associated with progressive MS and to developing better rehabilitation strategies that can improve quality of life.

New approaches are needed to test potential treatments faster and with fewer patients.

By focusing on these key areas, the work of the Collaborative will mobilize the global research community to do something about progressive MS. Together, we will take action and fund innovative and collaborative research initiatives around the world.

We've got some big challenges ahead of us. By working together globally, we will discover the answers and accelerate solutions for people living with progressive forms of MS. ■



Timothy Coetzee, PhD, is chief research officer of the National MS Society.

New MS therapy expands options

by Sara Bernstein

In March, oral Tecfidera™ (dimethyl fumarate, Biogen Idec—formerly “BG-12”) joined the ranks of first-line, disease-modifying therapies approved by the U.S. Food and Drug Administration to treat relapsing forms of multiple sclerosis. This makes it the third oral therapy approved for relapsing MS and the tenth disease-modifying treatment available in the U.S. Taken orally in capsule form twice daily, it expands the range of treatment options now available to people with relapsing MS.

Skin deep

The first use of dimethyl fumarate as a medicine was a leap of faith. German biochemist Walter Schweckendieck took a dose of a related compound, fumaric acid, in 1959, believing that a deficiency of the substance was causing his psoriasis, a skin condition mediated by the immune system. It worked, and although his theory was never proven, fumaric acid showed its effectiveness to treat psoriasis in clinical trials and was approved in 1994 in Germany to treat the disease (Fumaderm®, fumaric acid esters, Fumapharm AG).

Fumarate for MS

Decades later, dermatologist Dr. Peter Altmeyer informed his

colleague, neurologist Dr. Horst Przuntek, that he had noticed that MS symptoms seemed reduced in a couple of people whom he was treating with Fumaderm for psoriasis. The conversation led to a small study in which disease activity on MRI scans was reduced in 10 people with MS who were taking Fumaderm (**European Journal of Neurology** 2006;13: 604).

Biogen Idec acquired the company Fumapharm in 2006, and began developing BG-12, a drug similar to Fumaderm, for treatment of MS. Fumaderm contains the Tecfidera ingredient dimethyl fumarate, and it also contains fumeric acid esters. Biogen Idec specifically created a new, different formulation of dimethyl fumarate alone, which provides a lower dose and comes in coated capsules intended to make it more tolerable to the digestive system.

Small studies led to two large-scale phase III studies called DEFINE and CONFIRM, which were conducted in people with relapsing-remitting MS. In the DEFINE trial, which involved 952 people, there was a significant reduction after two years in relapses experienced by those who were taking BG-12, compared with those on placebo. In the CONFIRM study, which involved more than 1,400 people, the average number of MS relapses in a year was reduced by 44 percent versus the placebo in people taking BG-12 twice daily.

The most common adverse events in these trials were facial flushing and gastrointestinal disturbances such as diarrhea, nausea and upper abdominal pain. In trials, the incidence of these events was highest during the first month of treatment, decreasing thereafter. BG-12 also reduced blood lymphocyte (white blood cell) counts, but no significant or severe infections were reported. Liver enzyme tests were elevated, but there were no reports of significant liver injury or failure. Before starting treatment, the FDA recommends that a person’s healthcare provider assess a recent (within six months) blood cell count and repeat the count annually.

Looking inside

Although its exact mechanism of action is not known, Tecfidera is thought to inhibit immune cells and their messenger signals. Some research also has suggested that Tecfidera may have antioxidant properties that could be protective against damage to the brain and spinal cord. Further research is necessary to fully explore this potential. ■

To read more about Tecfidera and other disease-modifying therapies available for MS, visit nationalMSSociety.org/aboutMS and click “Treatments.”