Women at the forefront

Scientists are making remarkable headway in MS research.

by Susan Worley

Research in multiple sclerosis continues to move forward at a rapid pace, and women are at the forefront of scientific progress in many areas. With few well-defined career paths to follow, they are discovering their own keys to success.

“It’s incredibly rewarding to contribute to the effort being invested in improving treatments for MS, especially when the science is evolving so rapidly,” says Dr. Jiwon Oh, assistant professor of medicine in the Division of Neurology at the University of Toronto and a practicing neurologist at St. Michael’s Hospital in Toronto.

Inspired by personal experiences and encouraged by generous mentors, these four trailblazers are doing cutting-edge research, exploring areas ranging from advanced imaging of lesions to neuroprotection and myelin repair.

Making things happen

In 2016, Dr. Claudia Lucchinetti became the first woman to receive the prestigious John Dystel Prize for Multiple Sclerosis Research, awarded jointly by the National MS Society and the American Academy of Neurology (AAN). The prize acknowledged her many years of exceptional contributions to the field, particularly with regard to advancing our understanding of the neuropathology of MS and improving the care of people with MS.

Dr. Lucchinetti was honored by the prize and grateful for the “great teachers and wonderful mentors and colleagues" who played important roles in her career.

But she also notes a critical way she contributed to her own success.

"I really never waited for things to happen in my career," Dr. Lucchinetti says. "I've learned that there isn't anything passive about pursuing a career in research. To move forward in the field, it's important not only to be passionate and take advantage of opportunities placed in front of you, but also to reach out and make new contacts and investigate new possibilities. One factor that consistently shaped my career over the years was my tendency to be proactive and make things happen."

Excited by a course on antibodies and immunological disorders in college, she sent letters to investigators at the Mayo Clinic in Minnesota, inquiring about opportunities to work in their labs. One letter was addressed to Dr. Vanda Lennon, a pioneer in autoimmune neurology research and immunology. Dr. Lennon became an important career-long mentor and colleague. In 1983, Dr. Lennon helped arrange a summer research opportunity for Dr. Lucchinetti in the lab of Dr. Moses Rodriguez at the Mayo Clinic.

"While studying a mouse model of MS that first summer, I realized I could combine my interest in clinical neurology with my interest in basic science," Dr. Lucchinetti says. "I also was lucky that Dr. Rodriguez gave me a good balance of freedom and supervision."

After graduating from medical school, she returned to the Mayo Clinic as a resident in neurology. Then, in 1994, while she was chief resident, she had a life-altering encounter with a young mother who had a very rare and terminal type of MS known as Marburg's Variant MS.

"Although she was quite ill during that time, I connected with her on a very personal level," Dr. Lucchinetti recalls. "I committed myself to studying the pathology of MS lesions (areas of damage in the brain or spinal cord) with the hope of finding effective treatments for all forms of the disease."

Dr. Lucchinetti recognized another potential research opportunity during her residency while studying biopsied tissues from people with MS that Dr. Rodriguez had collected over the years. After reading about the research of Dr. Hans Lassmann in Vienna, a world leader in experimental neuropathology, she wrote to him, thus beginning a fruitful collaboration that would help shape her career.

In 2000, Dr. Lucchinetti, Dr. Lassmann and another colleague in Germany, Dr. Wolfgang Brück, published a landmark paper that, for the first time, described four types of lesions, or distinct patterns of myelin destruction, in people with MS. These different patterns of damage to myelin—the material that surrounds and protects nerve fibers in the brain and spinal cord, and which aids in the transmission of nerve signals—were discovered by the team after detailed analysis of tissues from both biopsies and autopsies.

"This had important implications because previously we always treated MS lesions similarly, as if they were all formed the same way," Dr. Lucchinetti says. "Our work suggested that perhaps there are different mechanisms of injury that warrant different individualized or personalized approaches to treatment."

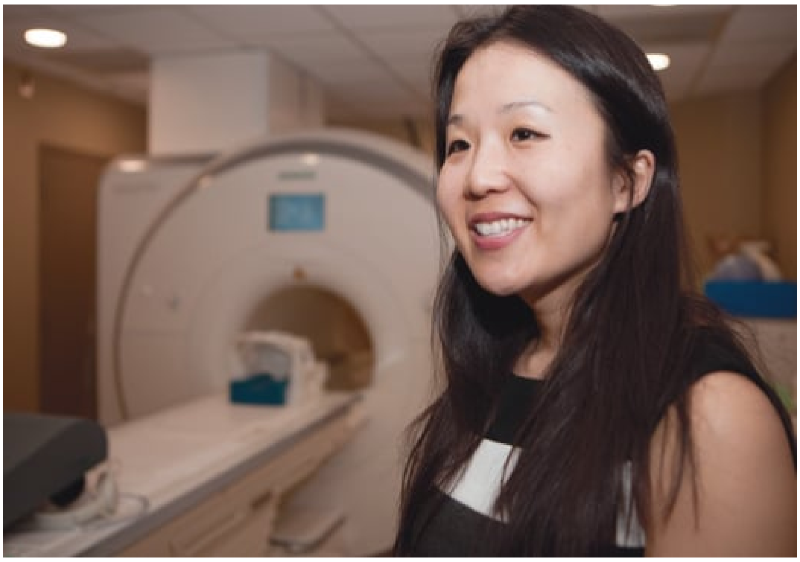
Their findings led to the launch of the MS Lesion Project, an international collaborative initiative jointly funded by the Society and the National Institutes of Health. The project brought together a wide range of experts—including pathologists, immunologists and radiologists—with the aim of better understanding the MS lesion and, in turn, improving treatment of the disease.

The researchers amassed an unprecedented collection of tissue samples from more than 1,000 people with MS, and discovered that unique antibody patterns were associated with different lesion patterns, information that could facilitate some treatment decisions. Dr. Lucchinetti's work today continues to build on her early studies of MS lesions, as well as another groundbreaking study, which showed that the cerebral cortex, or outermost layer of the brain, is targeted early in the MS disease process.

And with a Collaborative MS Research Center award from the Society, which is supported by The Donald C. McGraw Foundation, Dr. Lucchinetti, together with Dr. Chuck Howe, is now leading a team at Mayo Clinic that is studying nerve cells and possible ways to protect them from MS injury. One approach is to reprogram skin cells from people with MS and turn them into stem cells, then grow them in lab dishes to see if they display abnormal energy processes. This would create "MS in a dish," enabling close study of the abnormalities and the ability to test therapies aimed at the problem.

Drawing inspiration from personal experience

Dr. Oh was first drawn to the field of neurology for very personal reasons.



Dr. Jiwon Oh, a neurologist, uses advanced MRI techniques to identify markers that may be used

as outcome measures in clinical trials of MS treatments. Photo courtesy of Dr. Jiwon Oh

“My mother had a stroke while she was in her mid-30s,” she says. “Watching her cope with a chronic neurologic disease at a young age was a formative experience for me. It showed me how a neurologic disorder can completely change the trajectory of a young woman’s life.”

As a young neurology resident, Dr. Oh investigated a number of different neurological subspecialties, including stroke neurology and neuro-oncology, but found she was particularly interested in individuals with MS.

“I met many young women affected by MS, and the challenges they faced really resonated with me,” she says. “In part, that’s because I was a young woman facing challenges related to balancing a career and family, and I recognized how difficult it would be to also have to cope with a chronic neurologic disorder such as MS, and the future repercussions related to a diagnosis of MS.”

As a neurology resident at the University of Toronto, she had exposure to the MS Clinic at St. Michael’s Hospital, one of the largest MS clinics in Canada. She says she was impressed by the rapid changes in MS research.

“MS is one area of neurology in which the field is so dynamic you can actually see it changing right in front of you,” Dr. Oh says. “The management of MS is dramatically different now, compared with when I was a resident.”

During a clinical and research fellowship in neuroimmunology and neurological infections at the Johns Hopkins School of Medicine, Dr. Oh explored the use of magnetic resonance imaging (MRI) technologies under the mentorship of imaging experts Dr. Peter Calabresi and Dr. Daniel Reich. During this time, while also completing her doctorate at the Johns Hopkins School of Public Health, Dr. Oh developed a particular interest in imaging of the spinal cord.

“The spinal cord is commonly affected in MS and is the source of a lot of clinical disability,” she says. “The spinal cord basically is much like a highway, in that it is a conduit for all of the motor and sensory fibers that extend to your arms and legs and torso. It’s an important structure, and yet it is tiny and very difficult to image accurately, so in the past it was largely ignored. Until recently, the brain was the primary focus of MS research.”

The optic nerve, another structure commonly affected by MS, also was inordinately difficult to image until researchers, such as her mentor Dr. Calabresi, were able to use a technique known as optical coherence tomography (OCT). OCT allows experts to examine the layers of the back of the eye (retina) as they shrink or atrophy when affected by MS.

During her work with Dr. Calabresi, Dr. Oh became curious about the relationship between motor (such as walking problems) and sensory (such as numbness) deficits revealed by imaging of the spinal cord and the optic nerve, and became the primary driver behind a study comparing these, which was published in Neurology in 2015.

"My colleagues and I found that measures derived from the spinal cord and optic nerve provide a much better understanding of disability caused by MS," Dr. Oh says. "Whether the focus is general disability or disability in a specific area—for example, vision, or sensation, or weakness in the legs—measures of the retina and spinal cord are actually more relevant to explaining disability than measures of the brain alone. You can't just have tunnel vision and focus on the brain. You really need to sample all areas of the nervous system that MS affects."

Dr. Oh is a co-leader of North American Imaging in Multiple Sclerosis Cooperative (NAIMS), a collaborative group of imaging research centers with expertise in MS. Serving as secretary of NAIMS as well as a steering committee chair, she and colleagues in the U.S. and Canada are beginning large-scale studies to develop reliable image-based markers of disease progression and treatment, and improve our biological understanding of MS.

Splitting her time between St. Michael's hospital in Toronto and Johns Hopkins, Dr. Oh continues to use advanced MRI techniques to identify markers that may be used as outcome measures in clinical trials of MS treatments. She also is trying to gain a better understanding of radiologically isolated syndrome (RIS), abnormal MS-like brain findings identified during the diagnosis of an unrelated condition (such as migraine), which in some cases eventually lead to the development of MS symptoms. And, with funding from the National MS Society, she has launched a new imaging study with mentor Dr. Reich.

Finding your passion

Dr. Ilana Katz Sand, an attending physician at the Corinne Goldsmith Dickinson Center for Multiple Sclerosis in New York, joined the center in 2011 under a fellowship funded by a Sylvia Lawry Physician Fellowship from the Society. An assistant professor of neurology at the Icahn School of Medicine at Mount Sinai in New York, Dr. Katz Sand treats people with MS and other autoimmune diseases that affect the central nervous system, while conducting several MS research studies.

Dr. Katz Sand credits her father, a neurologist, with encouraging her interest in the field at an early age. When she was in high school, she often accompanied her father to see patients. Her interest in MS deepened during her neurology residency.

Dr. Ilana Katz Sand, who is leading a pilot study on the impact of a special plant-based diet on women with MS, discusses the study with patient Jessica Hamilton (left). Photo courtesy of Mount Sinai Health System

“I related well to patients with MS, many of whom are young women,” she recalls. “Also, because MS is a chronic disease, neurologists typically treat patients for a long period of time. The idea of meeting a new patient and carrying that person through potentially difficult years—including reproductive years and early efforts to start a career—and helping the person over time particularly appealed to me.”

Near the end of her fellowship at Mt. Sinai, Dr. Katz Sand was introduced to MS research by her mentor Dr. Patrizia Casaccia, chief of the Center of Excellence for Myelin Repair at Mount Sinai. Dr. Katz Sand credits Dr. Casaccia, a basic scientist and physician and an expert on myelin repair, with shaping her identity as a research scientist and encouraging her interest in translational research, which focuses on the practical application of scientific discoveries.

In one current project, with Dr. Casaccia and colleague Dr. Matilde Inglese, Dr. Katz Sand is examining the potential link between progressive MS and the dysfunction of mitochondria, the structures inside cells that are responsible for producing energy.

“If a cell is not producing enough energy, it will get sick and may die,” says Dr. Katz Sand, co-author of a 2015 article on this topic in the journal Brain. “Our research suggests that this may be a contributing factor in the clinical symptoms that we see in our patients with MS.”

Another early project under Dr. Casaccia’s mentorship involved examination of the role that bacteria in the gut—or microbiota—may play in the development of MS. Dr. Katz Sand became particularly enthusiastic about this project because of questions from her patients, who wanted to know if they could improve their MS symptoms by changing their diet.

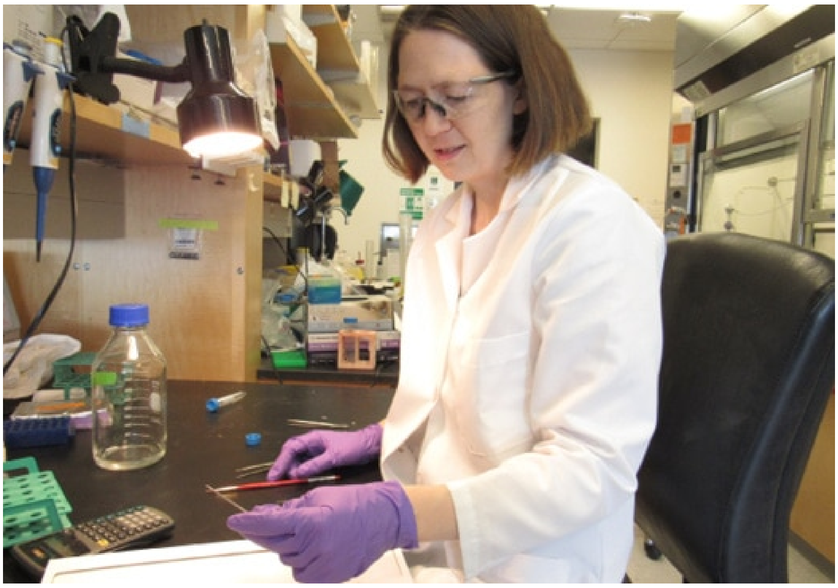
“Questions regarding diet come up all the time, and because there has not been rigorous research in this area, my colleagues and I really have had no way to answer any of those questions.”

Dr. Katz Sand received funding from the Society for a pilot study of 30 women with MS to examine the impact of a diet high in polyunsaturated fatty acids and polyphenols (antioxidants found primarily in plants).

“The diet includes foods that, based on our research, we think may be anti-inflammatory and therefore neuroprotective (protective of nerves at risk for damage from MS). It encourages foods such as fish, fresh fruits and vegetables, and whole grains. It doesn’t permit meat other than fish, and it limits salt intake,” says Dr. Katz Sand, who designed the study.

She hopes the results will contribute to the development of clinical trials, which may ultimately lead to non-pharmaceutical therapies for MS.

Following an unexpected path
When Meredith Hartley, PhD, was completing her doctoral dissertation on the biochemistry of bacteria at the Massachusetts Institute of Technology in Cambridge, she had no idea she would end up pursuing a career in MS research. While searching for postdoctoral research opportunities, she felt particularly drawn to research on a disease known as X-linked adrenoleukodystrophy (X-ALD) led by Thomas S. Scanlan, PhD, now her adviser at Oregon Health & Science University (OHSU), in Portland, Oregon.



Meredith Hartley, PhD, has been researching the role of the drug sobetirome in the treatment of a rare genetic disease. She is now examining the effect of the drug on mouse models of MS. Photo courtesy of Meredith Hartley, PhD

“X-ALD is a disease that is somewhat similar to MS,” says Dr. Hartley, since, like MS, it damages nerve-insulating myelin in the brain and spinal cord. “It’s a rare genetic disease. One severe form primarily affects young boys, who often survive fewer than three years after onset of symptoms. A genetic mutation causes the build-up of toxic fatty acids that result in a number of abnormalities, including [the destruction of myelin] in the brain.”

Dr. Scanlan was interested in looking at the role of a drug called sobetirome in the treatment of this rare disease. During her postdoctoral fellowship at OHSU, sponsored by a grant from the Society, Dr. Hartley examined the effect of sobetirome on mouse models of X-ALD. Sobetirone is very close in structure to the natural thyroid hormone that all people with a normal thyroid gland have.

“Thyroid hormone plays an important role during development because it tells the brain to produce myelin. The hope is that sobetirome can promote repair in places where myelin has been destroyed in individuals with X-ALD and MS,” she says.

In a study published by the Endocrine Society in the journal Endocrinology in 2017, Dr. Hartley and her colleagues showed that sobetirome does indeed help to lower the toxic levels of fatty acids that cause demyelination in X-ALD.

“What’s especially exciting is that we are seeing lowering of these fatty acids in the brain as well, so the drug is working in the brain. No one has ever demonstrated this activity in the brain setting before, so we are pretty excited about the promise of this drug,” says Dr. Hartley.

Dr. Hartley and her colleagues are now examining the effect of sobetirome on mouse models of MS, with a Society grant that is supported in part by the Dave Tomlinson Research Fund.

“Our ultimate goal is clinical trials in MS,” says Dr. Hartley, “We hope that upcoming testing in clinical trials for X-ALD will possibly smooth the pathway to clinical trials for MS.”

Susan Worley is a freelance medical writer in Bryn Mawr, Pennsylvania.

Learn more about MS research.