Underlying mechanisms

Dystel Prize winner focuses on immune responses that drive MS.

by Mary E. King, PhD

It was a personal connection — a nephew with an autoimmune disease — that inspired Vijay K. Kuchroo, DVM, PhD, to follow a career path that led to research focusing on the underlying immune mechanisms that drive multiple sclerosis. Now, Kuchroo, the Samuel Wasserstrom Professor of Neurology at Harvard Medical School, Boston, is the 2021 recipient of the John Dystel Prize for Multiple Sclerosis Research for his work. The prize is awarded jointly by the National Multiple Sclerosis Society and the American Academy of Neurology.

“Professor Kuchroo’s research lays the groundwork for stopping the immune response in its tracks,” said Bruce Bebo, PhD, executive vice president of research for the Society. “This work is crucial to advancing the most promising pathways to MS cures.”

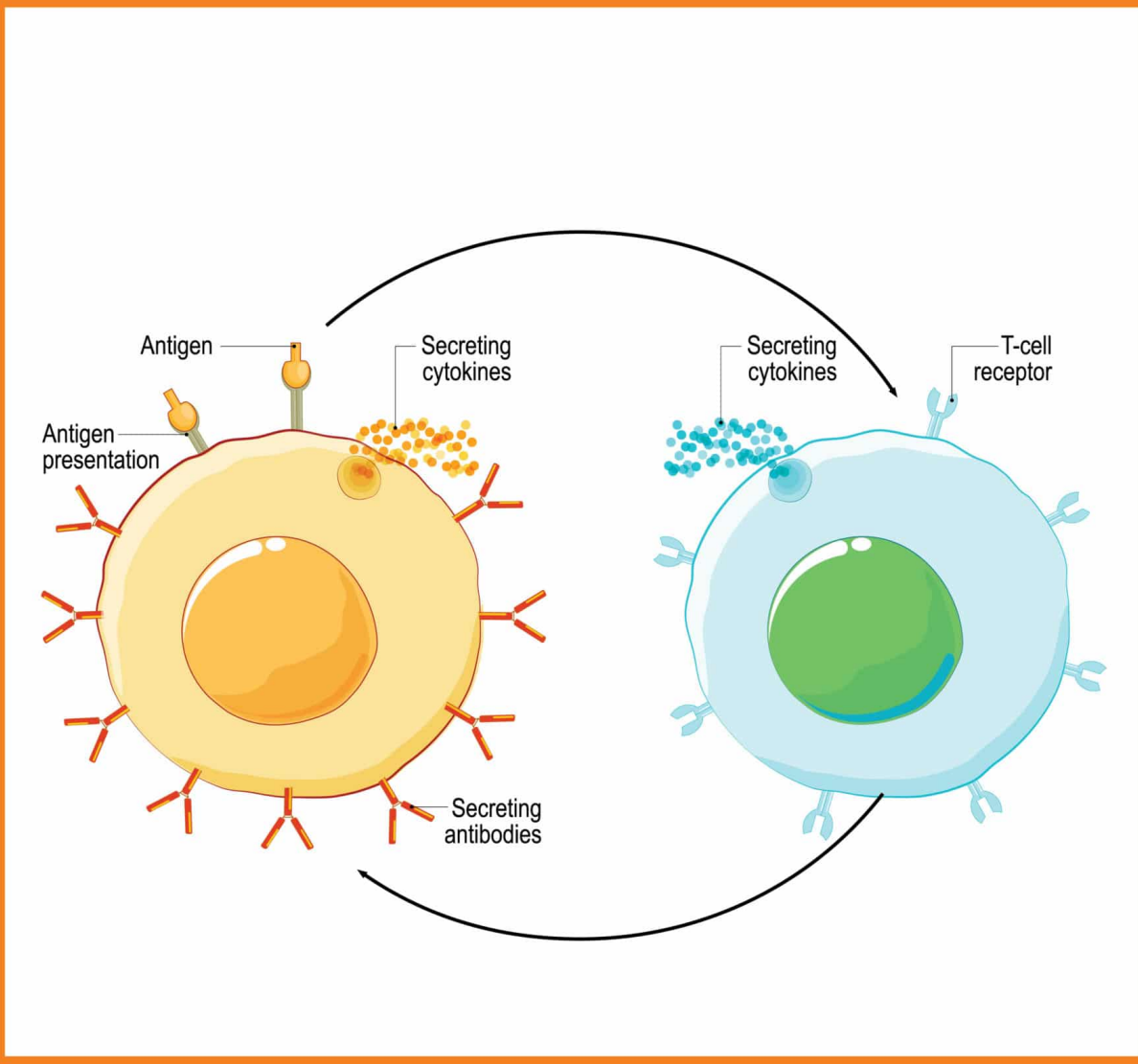
Early curiosity about autoimmune diseases

Kuchroo trained in immunology and veterinary medicine. “I was fascinated by autoimmune diseases, especially because my nephew had a very serious case of inflammatory bowel disease [IBD],” he recalls. “So I wondered, why would the human body ‘break tolerance,’ as immunologists say — that is, why do we develop immune reactions against our own proteins? I wondered why we could develop the types of immune reactions to the brain that underlie MS when the brain is so isolated from the immune system.”

He started working with Marjorie Lees, PhD, (now deceased) at the National Institutes of Health. She was the first to identify a certain protein in myelin called proteolipid protein (PLP)

in the early 1950s and show its possible importance in MS. Working with one of her postdoctoral fellows and a pathologist, Lees had identified a series of small portions of PLP which, when injected into mice, led to a paralytic MS-like disease.

“Because PLP was known to exist in the brain but not in the rest of the peripheral nervous system, I felt it would be ideal for expanding this research to understand how autoimmunity could develop in the brain. That might lead to a better understanding of how autoimmunity can develop to other proteins in the body, too,” Kuchroo says.



B cell and T cell interactions are thought to be critical contributors to central nervous system damage that causes MS. Photo: iStock

Development of a critical research tool for MS

"Because I trained as a veterinarian as well as in immunology, I started developing animal models of disease, including MS," Kuchroo explains. He developed an essential MS research tool, a variation of a mouse model that develops spontaneous MS-like disease, which is used worldwide to study MS in the laboratory. His lab work has also helped researchers explore the essential role of B cells, a major type of immune cells, and proposed that T cells and B cells play a role in the development of MS. Therapies that target B cells are commonly used to treat MS.

He credits the Society for helping him launch his MS research. "I didn't know how to get funding for my work initially," he explains, "but I saw that the Society was supporting small pilot grants, and I thought my early mouse model work would be a fantastic topic. I wrote a grant proposal that was accepted, and this funding got me started. Otherwise, I would not have gotten into this field."

Passion for his work

Kuchroo recalls the effect his first encounter with people with MS had on him. Howard L. Weiner, MD, chief of the Division of MS and Neuroimmunology at Brigham and Women's Hospital in Boston, with whom he was working at Harvard, insisted Kuchroo come to his MS clinic even though Kuchroo wasn't a clinician. "The first time I saw people with MS was heart-wrenching," Kuchroo says. At that time, there were no disease-modifying therapies for MS. Beta interferon, the first, wasn't introduced until a couple of years later.

"The more I talked with these patients and saw the struggles they had, the more passionate I became about understanding this devastating disease. We have now come a long way with the development of a variety of disease-modifying treatments, fortunately."

Numerous other advances in MS

Kuchroo has continued to make numerous advances in the field of MS. "He has made many outstanding contributions to our understanding of the mechanisms that drive MS," says Weiner, in supporting Kuchroo's nomination for the Dystel Prize.

"Kuchroo is a pioneer in the field of T cell biology and central nervous system autoimmunity as it relates to MS. The immune system and autoimmunity are at the heart of MS. His work has had a major impact and has opened up pathways that will lead to better treatment and ultimately a cure for MS."

Kuchroo has contributed to the following advances:

- Defining the role of specific proteins in nerve-insulating myelin as targets driving the immune response. He developed a mouse model showing that myelin oligodendrocyte glycoprotein triggered inflammation of the optic nerve, often the first symptom of MS.
- Identifying "TIM-3," a molecule on the surface of T cells, which can distinguish inflammatory cells from T cells that can regulate inflammation. Kuchroo identified the

whole TIM family of genes, which have a very important role in regulating immune responses.
- Defining distinct steps in how T cells that drive the immune response are activated and the specific immune messenger proteins involved, providing targets for developing immune-modulating therapies.
- Advancing understanding of the role of immune B cells in MS. Kuchroo found a molecule on B cells that regulates tissue. These observations are now being investigated in people with MS in collaboration with Weiner.

Kuchroo also elucidated the role of high salt intake as an environmental trigger of MS. “We found that increases in certain T cells called Th17 cells, which are critical to the development of autoimmune diseases, are linked to high salt intake,” he says.

As Weiner explains: “It is becoming increasingly clear that MS and other autoimmune diseases are on the rise in the West. It is known that an individual’s genetic background predisposes the person to the development of MS; however, it has been suggested that environmental factors are required to trigger the disease. Kuchroo’s work identifies a high salt diet as a potential trigger for MS and other autoimmune diseases.”

The Dystel Prize

Each year the National Multiple Sclerosis Society and the American Academy of Neurology jointly award the John Dystel Prize for MS Research to recognize outstanding contributions to the understanding, treatment or prevention of MS. This prestigious honor was established by the late Oscar Dystel, a member of the Society’s National Board of Directors, and his late wife, Marion. They established this prize in 1994 in honor of their son, John Jay Dystel, an attorney who died from complications of MS.

Appreciation for the Dystel Prize

“I am so appreciative of this award,” Kuchroo says. “The Dystel Prize is one of the pinnacles of recognition in MS research. I’m honored to be grouped with the prestigious individuals who previously received this award. It is recognition by your colleagues that the quality of your work is making a real difference in the lives of people with MS.”

Kuchroo plans to continue research into B cells and their role in MS, pointing out that the current therapeutic approach involving B cells is to eliminate all of them, not just the deleterious ones. He would like to identify and develop ways to remove only the subset of B cells involved in initiating MS. That might preserve other B cells such as those that are so important for developing antibodies, for example, in response to vaccines. That way, he hopes, people with MS can better maintain a healthy immune system.

Mary E. King, PhD, is a freelance medical writer in Boulder, Colorado.