

Breakthroughs in B cells



Dr. Anne H. Cross receives Dystel Prize for advancing MS research.

by **Mary E. King**

Dr. Anne H. Cross received the 2019 John Dystel Prize for MS Research for her far-reaching work in several areas of multiple sclerosis: from clarifying the role that B cells play in the disease, to advancing new imaging techniques, to understanding how diet affects MS. Cross is professor of neurology and the Manny and Rosalyn Rosenthal – Dr. John Trotter Multiple Sclerosis Chair in Neuroimmunology at the Washington University School of Medicine in St. Louis.

The prize is awarded jointly by the National Multiple Sclerosis Society and the American Academy of Neurology in memory of John Jay Dystel.

The John 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. The late Society Board Member Oscar Dystel and his wife, Marion, established the prize to honor their son, John Jay Dystel, an attorney who died of complications from MS in 2003. 2019 marked the 25th anniversary of the prize.

“The selection committee of her peers enthusiastically chose Cross on this 25th anniversary of the Dystel Prize,” says Bruce Bebo, PhD, the Society’s executive vice president of research. “She epitomizes the goal of this prize: to recognize someone who has changed the way we think about MS. She has certainly done that, namely for her pioneering work on the role of immune B cells in driving MS immune attacks and her use of new imaging techniques to detect disease activity.”

“I think it’s notable that the Society recognized Cross’ potential early in her career, first with a postdoctoral fellowship and then with a prestigious Harry Weaver Neuroscience Scholar Award [in 1990], given to junior faculty judged to have promising futures,” Bebo adds.

Dr. Emmanuelle Waubant, director of the Pediatric MS Center at the University of California San Francisco, who nominated Cross, describes her as a giant in the field of MS research. “Cross’ research has always been at the forefront of the field. She very boldly investigated the role of B cells at a time when most other research focused on T cells. She made the key observation that B cells are in fact critical for MS progression.”

A passion for her work

“Receiving the John Jay Dystel Prize is an incredible honor. It is probably the biggest honor of my career,” Cross says. “To be named as one of a small group of scientists and clinician-researchers for whom I have much respect and admiration is extremely validating and has renewed my motivation to keep working to figure out the puzzle of MS.”

Cross’ passion for her work is twofold. “I was very interested in immunology and neurology. I tried to combine the two in MS,” she says. “My other reason to go into MS is that it is so common and prevalent. I was distressed when, as a resident, I was often called upon to make the diagnosis of MS. But in those days, the 1980s, there were no treatments to alter the long-term course for the better.”

And she has a personal stake as well. “I pursued neurology as a career because of several family members, including my only sibling, a younger brother, with neurological diseases,” Cross says. “I also had two friends who were diagnosed with MS before I decided to do MS research myself. One was a fellow medical student at the University of Alabama in Birmingham and the other was a co-resident with me at George Washington University in D.C.”

B cell focus led to new drug

Asked why she pursued the study of B cells in MS when most researchers were so focused on T cells, Cross replies: “I had a talented postdoctoral fellow named Jeri-Anne Lyons who worked with me in the 1990s. She and I both thought it might be interesting to look more at the role of B cells, precisely because they were, at the time, not being studied much.”

They discovered that B cells were, in fact, very critical in an animal model of MS, a first step toward defining a role for these immune cells in human MS.

“At approximately the same time, rituximab was being studied as a treatment for B cell malignancies,” Cross says. (Rituximab is a specialized antibody that binds to the surface of B cells and leads to their removal.) “I realized it might be used for treating people with MS to determine whether B cells had a role in MS,” Cross says. “I began to try to figure out a way to put together a study using it in MS.”



Dr. Anne Cross turned her focus to B cells and made a crucial discovery. Photo by Whitney Curtis

Cross then led the first clinical trial of rituximab in people with MS who did not benefit from other available treatments. Its use in MS at the time was an exciting and innovative approach to MS treatment.

Dr. Peter Calabresi, director of the Johns Hopkins MS Center, supported Cross' nomination. "Dr. Cross' phase 2 trial, published in 2010, showed that adding rituximab [to beta interferons or glatiramer acetate] reduced gadolinium-enhancing brain lesions [detected by MRI] in people with MS, foreshadowing the positive phase 3 trial results." Gadolinium, a contrast agent, helps clinicians identify areas of new inflammation in the brain.

Bebo says this important work also helped lead the way to the development and eventual FDA approval of ocrelizumab (Ocrevus) for primary progressive MS in 2017, and later for relapsing forms of MS.

Additional groundbreaking research

Cross has also pioneered other investigations in MS. She is trying to solve the problem of how to better identify early nerve damage in progressive MS. "Cross has contributed to the

development of new MRI techniques in collaboration with her Washington University colleague and professor of radiology Sheng-Kwei ['Victor'] Song," Waubant says. The Society helped fund this research to detect MS progression before damage can be detected in a clinical exam.

Waubant notes that Cross has also been a pioneer in understanding the effect of diet on MS progression: "She identified how diet can modify the immune response and the progression of EAE, an animal model of MS." Dr. Dennis Bourdette, chair and Roy and Eulalia Swank Family research professor and executive director, Multiple Sclerosis Center Department of Neurology at the Oregon Health & Science University also notes Cross' research in this area. "There is growing interest now in the role that diet may play in treating MS. Dr. Cross was one of the first serious investigators in this field. Her research formed the basis for clinical trials of caloric restriction in MS being conducted at Washington University and elsewhere."

Calabresi calls Cross "a creative, productive and humanistic leader" who has excelled as a clinician educator. "In addition to being an outstanding researcher who has made many contributions to the field of MS, her expansive knowledge of MS combined with her outstanding creativity and mentoring skills have allowed her to build a world-class MS center that is now making major contributions to several other unique domains of research," he says.

Future directions

Cross plans to continue her work in neuroimaging in the hopes of finding ways to assess neuropathology in MS without a brain biopsy. "I think this is important because we don't yet have very good treatments for progressive MS," she says. "Part of that is because we don't have good biomarkers to assess progressive MS." Cross also plans to pursue research in the immunology of MS that involves some clever genetic testing. "Together with several colleagues, we are sequencing the genes expressed by invading CNS inflammatory cells, obtained by spinal taps, in people with MS and comparing those to the genes expressed in inflammatory cells in healthy controls and people with other neurological diseases." She will also continue to look at the mechanisms of actions of B cell depleting therapies "in the hope that this will help us better understand the disease process."

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

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