Investigating Sex-Related Differences in Multiple Sclerosis
Melissa Brown, PhD, professor of Microbiology-Immunology

Q&A

What are your research interests?
As an immunologist, I am interested in understanding the basic mechanisms that allow proper functioning of the immune system. Although immune cells are essential for providing protection from infectious microbes, some diseases are actually caused by an overly robust immune response. My research focuses primarily on multiple sclerosis (MS), an autoimmune inflammatory disease of the central nervous system (CNS). In this disease, immune cells are directed to attack a person’s own tissues — the myelin protein structures surrounding nerves that insulate neuronal axons and facilitate nerve impulse conduction. The ensuing inflammatory damage in the brain and spinal cord leads to a number of sometimes devastating sensory, cognitive and motor deficits.

Like many autoimmune diseases, MS is much more prevalent in women. It has been estimated that females develop MS three to four times more frequently than men. Our laboratory investigates the events that promote CNS inflammation in females, but we are also very interested in determining what confers male-specific protection.

What is the ultimate goal of your research?
Scientists have made great strides in MS research in recent years. Treatments that slow disease progression in patients with relapsing-remitting MS — a form of disease characterized by intermittent periods of disability interspersed with temporary recovery — are particularly promising. However, there are some forms of progressive disease for which there are still no good therapies. Like many scientists in autoimmune disease research, our goal is to identify approaches to effective treatments that do not cause global immune suppression, leaving the ability to fight infection completely intact. There is no cure for MS, and we also hope to uncover pathways that will lead to reversing the damage in the brain and spinal cord.

How does your research advance medical science and knowledge?
It has been recognized for some time that there are striking sex-determined discrepancies in susceptibility to disease. Not only do many autoimmune diseases predominately occur in women, where female to male ratios can approach 11:1, but women also have a reduced incidence of developing some types of tumors and a more vigorous response to infectious microbes. A combination of X chromosome content, microbiota, genetics and hormones contribute to these differences. However, the precise molecular pathways remain largely undefined.

Our most recent work aims to define the mechanisms that promote male resistance to MS. Several previous mouse and human studies have implicated testosterone, a sex hormone present at levels seven to eight times higher in healthy adult men than women, in blocking immune responses and conferring protection from MS. Yet there is still little information available about how this hormone exerts its effects.

Using a mouse model of MS in which females are susceptible and males are resistant, we have identified a molecular and cellular pathway that explains how testosterone works to suppress harmful immune responses, thus providing an explanation for male-biased disease protection. We show that testosterone activates mast cells to produce the cytokine IL-33. IL-33 then acts on another immune cell, the type 2 innate lymphoid cell (ILC2).
Brandon Greene, research administrator in the Office for Research Administration Services, helps Feinberg investigators secure funding for their projects.

Q&A

Where are you originally from?
I grew up in Gresham, South Carolina. It's an extremely small town, roughly 45 minutes from Myrtle Beach, with a population of about 3,000.

What is your educational background?
I attended South Carolina State University, a historically black university, where I obtained an honors degree in accounting.

Please tell us about your professional background.
In college, I was employed as a work study student for the vice president of finance, facilities and management information systems for three years and the office for accounts payable. Working for the vice president of finance was my first job in a professional setting at a university. Post graduation, I was hired by the Office for Sponsored Research (OSR) at Northwestern University, on the Evanston Campus as a grants assistant. I worked in Evanston for a few years before I transferred to OSR’s Chicago office. During my time in OSR, I’ve reviewed many federal and non-federal sponsored proposals and budgets on behalf of numerous departments and schools across Northwestern. I was hired as a research administrator by Research Administration Services at Feinberg in August.

How do you support scientists at the medical school?
In my current role, I’ll be supporting Dermatology investigators with their award management and closeout responsibilities.

What is your favorite part of the job?
What I enjoy most about working in research administration is helping investigators obtain funding for research they are passionate about.

What do you like to do in your spare time?
Though I’ve lived in Chicago for six years, I still feel like a tourist. I enjoy trying new restaurants and attending street fairs and festivals in different neighborhoods. Most of all, I enjoy cooking at home and binge-watching Netflix.

Connect with Brandon on LinkedIn.

Brown (continued from page 3)

ILC2s turn off the harmful immune response and prevent disease development. The lower testosterone levels in females are not sufficient to activate this IL-33 pathway.

While it is not practical to treat most patients with testosterone, this information may allow us to ultimately treat with IL-33 or locally activate the IL-33 pathway in affected females. Most promising is the possibility that IL-33 may have a role in the regeneration of neuronal cell function.

How did you become interested in this area of research?
My foray into MS research was quite personal. My youngest brother was a sophomore in college when he developed optic neuritis, often a first sign of MS, after a bout of mononucleosis. He was treated with steroids to suppress inflammation and the neuritis resolved, but a year later he had another episode. Subsequently he developed other symptoms, including episodic seizures, loss of sensation and memory problems. He wasn’t definitively diagnosed until several years later. I was already an investigator in immunology, so I had ready access to published scientific information and was eager to learn what was known about MS and what treatments were available to patients.

I was studying the regulation of cytokine production by mast cells, immune cells almost exclusively studied in the context of allergic inflammation at the time. Mast cells are very potent inflammatory cells present in the skin, airways and gastrointestinal tract and are the major source of substances such as histamine and leukotrienes that cause the itching, redness, swelling, mucus production and airway obstruction associated with allergic responses. However, unknown to many, mast cells are also quite numerous in the brain and spinal cord as well as the meninges, structures that are in direct proximity to the brain and spinal cord and enclose the cerebrospinal fluid.

My studies made me realize that mast cells produce many other molecules implicated in the central nervous system inflammation in MS. Although most research had focused on circulating immune T-cells as the orchestrators of brain and spinal cord damage, mast cells have many properties that could significantly increase this inflammation and damage. These ideas were met with a lot of skepticism for many years. However, fast forward and we and others have established critical roles for mast cells not only in MS but in other inflammatory diseases of the central nervous system.

(continued on page 9)
Brown (continued from page 6)

What do you enjoy about teaching and mentoring young scientists in the lab?
Teaching and mentoring are the favorite part of my job. Young scientists bring an enthusiasm and fresh perspective to a project. The majority of the seminal observations our laboratory has published are the direct result of undergraduate and graduate student investigations. There is nothing better than experiencing the joy of a new discovery through their eyes and watching them mature into independent and critical-thinking scientists.

How is your research funded?
My research is funded by the National Institutes of Health and the National Multiple Sclerosis Society.

Latest Podcast Episodes

How to Stop Antibiotic Misuse with Jeffrey Linder, MD, MPH. Listen here.

New Ways to Diagnose Sleep and Circadian Rhythm Disorders with Phyllis Zee, MD, PhD. Listen here.

Subscribe to our podcast and rate it here.

Funding

Ancillary Studies to the NIDDK Inflammatory Bowel Disease (IBD) Genetics Consortium (R01- Clinical Trial Optional)

Sponsors: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Letter of Intent Due: January 21, 2019
Submission Deadline: February 21, 2019
Amount: $200,000 in direct costs per year for a maximum project period of three years

Synopsis: The purpose of this opportunity is to collaborate with NIDDK Inflammatory Bowel Disease Genetics Consortium to expand the number of genes and range of IBD-related phenotypes and physiological domains of previously identified susceptibility loci. Investigators from a wide range of disciplines (e.g., immunology, cell biology, microbiology, bioinformatics, systems biology) are encouraged to respond.

Analytical and/or Clinical Validation of a Candidate Biomarker for Pain (R61/R33 Clinical Trial Optional)

Sponsor: National Institute of Health
Letter of Intent: 30 days prior to the application due date
Submission Deadlines: November 27, 2018; March 7, 2019; November 25, 2019; March 12, 2020
Amount: Budgets are not limited but need to reflect the actual needs of the proposed project.

Synopsis: Eight to 10 grants will be awarded in 2019 in support of the NIH Helping to End Addiction Long-Term (HEAL) Initiative. The goal of this research is to identify biomarkers for pain that define not only how patients experience pain, but also how candidate therapies—including medications, biologics, natural products and devices—engage these molecular targets to ultimately relieve pain.

Clinician-Scientists Transdisciplinary Aging Research (Clin-STAR) Coordinating Center: Synergizing Career Development Toward Improved Care of Older Adults across Specialties and Disciplines (U24 - Clinical Trial Optional)

Sponsor: National Institute of Aging
Letter of Intent Due: January 4, 2019
Submission Deadline: February 4, 2019
Amount: $1 M for a maximum project period of five years

Synopsis: This grant will support the development of a Clinician-Scientists Transdisciplinary Aging Research Coordinating Center that will organize activities and provide research resources for clinician-investigators focusing their careers on aging research.

View more funding opportunities.