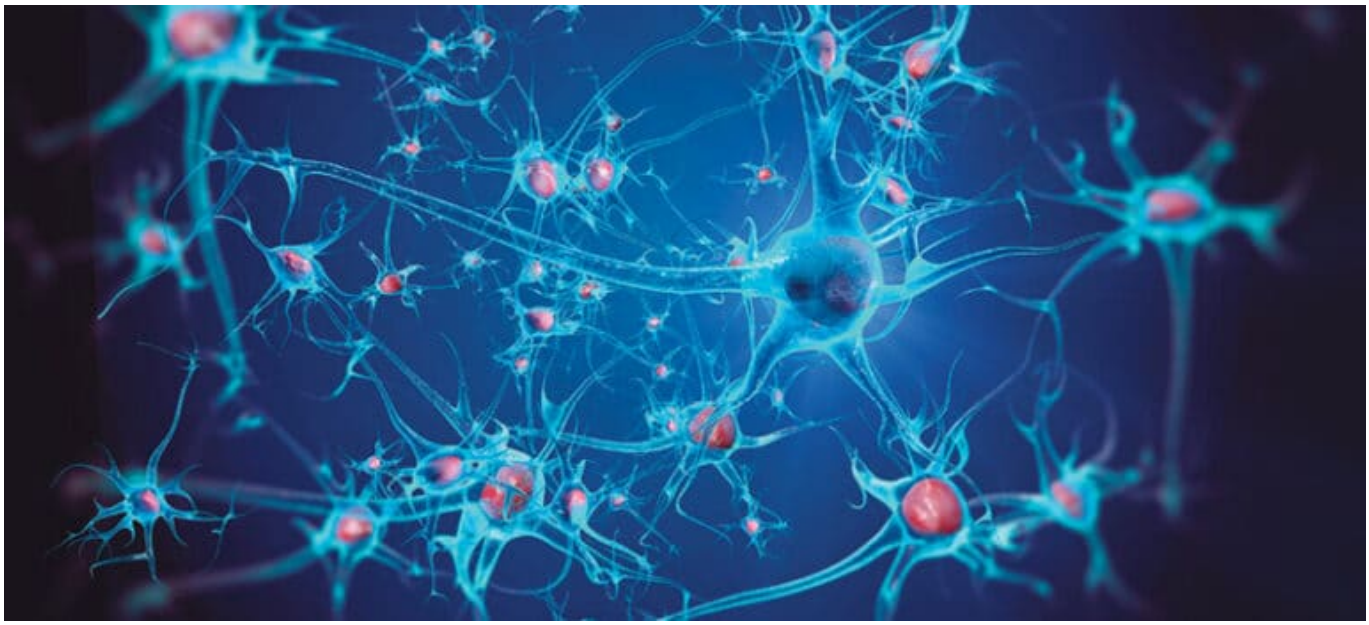
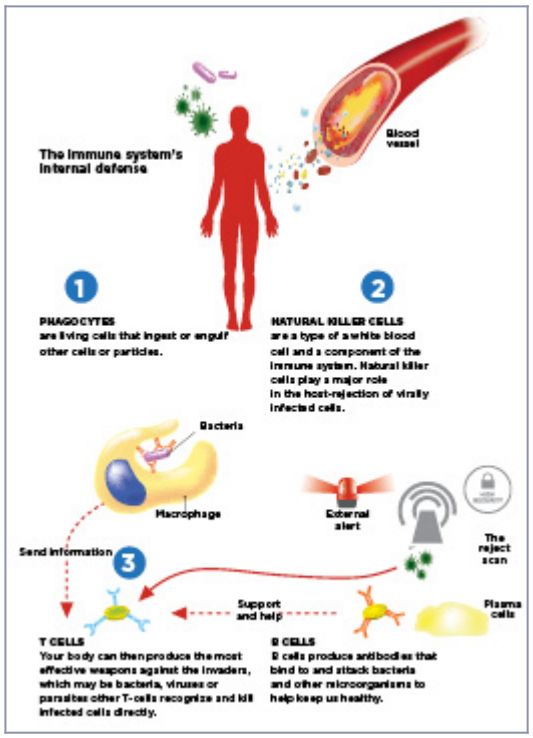
New takes on immune activity in MS



Studies could advance treatment options.

by Mary E. King, PhD



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Researchers are conducting novel studies involving the immune system that could lead to new clues about the cause and cure of multiple sclerosis as well as additional treatments for all types of the disease.

“We encourage early, fundamental research investigations that have the potential to lead to whole new treatment strategies for MS,” says Bruce Bebo, PhD, executive vice president of research for the National Multiple Sclerosis Society, which provided funding for the projects.

One study involves research on a type of immune cells called B cells. MS research had long focused on another type of immune cell, the T cell, a major player in autoimmune attacks on the brain and spinal cord. B cells were better known for producing antibodies that bind to and attack bacteria and other microorganisms to help keep us healthy. In MS, however, B cells appear to play additional roles that contribute to damaging disease activity.

The potential roles of B cells in MS and, in particular, the design of MS therapeutics to target B cells, were being overlooked by granting agencies in favor of what seemed to be much more promising T-cell-oriented studies.

“The National MS Society funded early work on B cells and on anti-B cell agents when no one else was taking the risk to fund this new line of research,” Bebo says. B cell research led to further investigations and eventually to a new treatment for primary progressive MS, ocrelizumab, a B-cell-depleting therapy, he explains.

Nancie MacIver, PhD, is studying whether calorie intake impacts the immune system in MS. Photo courtesy of Nancie MacIver, MD, PhD

Effects of calorie restriction

Why—and exactly how—does restricting calorie intake affect the immune system? Nancie MacIver, MD, PhD, associate professor of Pediatric Endocrinology at Duke University School of Medicine in North Carolina, and her team observed that fasting or calorie-restricted mice are relatively (but not perfectly) protected against inflammation caused by T cells. Dr. MacIver investigated this in mice that are induced to develop an animal model of MS called experimental autoimmune encephalomyelitis (EAE). These mice, Dr. MacIver learned, are relatively protected from EAE if calories are restricted.

“We then turned our attention to leptin, a hormone secreted from fat cells that is known to communicate nutritional status to immune cells, particularly T cells,” Dr. MacIver says. “The amount of leptin produced by fat cells is proportional to the amount of body fat. Calorie-restricted animals have less leptin in their blood circulation than those of a greater weight.”

“We gave leptin to [calorie-restricted] EAE mice and discovered they lost their protection against EAE. So leptin provides a critical signal to inflammatory T cells that fuels inflammatory function,” Dr. MacIver says.

Dr. MacIver extends this to MS: “Many people with MS make dietary changes [like calorie restriction] in the hope that their disease will improve, because there is some anecdotal evidence that it may help. We want to understand how that might occur. Does calorie restriction really improve disease? If true, does it happen because leptin levels get lowered?” She adds, “If so, we may be able to develop strategies that mimic lowered leptin levels without necessarily restricting food intake.”

“There is some evidence that obesity during adolescence increases risk of developing MS as an adult, particularly in girls,” Dr. MacIver says. “I believe that this may be mediated, in part, through hormones such as leptin. However, there are still many questions to be answered in terms of understanding the connection between nutrition and immunity,” she stresses.

Bonnie Dittel, PhD, is studying B cells in

mice to develop new MS treatments. Photo courtesy of Bonnie Dittel, PhD

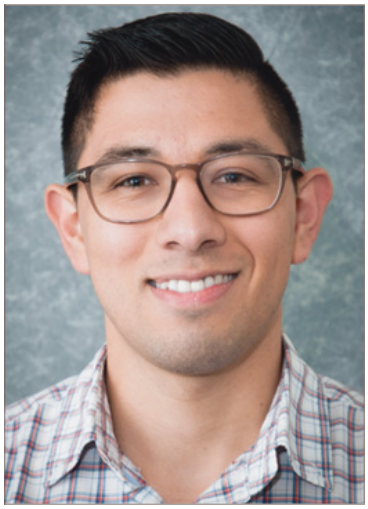
A new type of B cell

Bonnie Dittel, PhD, senior investigator at the Blood Research Institute at BloodCenter of Wisconsin in Milwaukee, now part of versiti, is studying B cells and has discovered that their story is much more complex that initially thought. “Mice whose B cells are completely missing, through either genetic engineering or the use of an ocrelizumab-like agent, cannot recover from EAE,” she explains. This perplexing result triggered Dittel’s curiosity: Why would removing all B cells affect EAE recovery in mice?

The puzzle led Dittel to identify a new B cell population in mice that have protective activity. Removing all B cells removes these protective B cells, too. The net result in mice prevents EAE recovery.

Dittel learned that these protective B cells have regulatory activity. (Cells with regulatory activity are cells that help “regulate” the immune system; that is, they keep the immune system from going too far out of balance in the direction of inflammation.) Dittel has already figured out special techniques to pull out only the protective B cells from the larger B cell population in mice.

Adding just the protective B cells, but not the other B cells, back to B-cell-deficient mice with EAE restores their ability to recover. Dittel is now working to identify, isolate and study human protective B cells, including in people with MS. She explains that learning more about protective B cells may lead to a more specific agent for treating MS—or perhaps to an agent that will work alongside ocrelizumab to protect protective B cells from being removed.



Andrew Mendiola, PhD, is studying the activity

of molecules that may cause inflammation.
Photo courtesy of Andrew Mendiola, PhD

A blood component that inhibits myelin repair

In another project, Bebo explains that in MS, the barrier that prevents components of blood from entering the brain, the "blood-brain barrier," becomes leaky. One of the molecules in our bloodstream is fibrinogen, which normally helps blood to clot. When it leaks into the brain, however, fibrinogen has a different effect—it promotes inflammation, Bebo says.

Andrew Mendiola, PhD, a postdoctoral fellow in the research laboratory of Katerina Akassoglou, PhD, at the Gladstone Institute of Neurological Diseases and the University of California at San Francisco, is studying this harmful activity of fibrinogen.

Mendiola is focusing his research in mice with EAE as a first step. He is using mice in which individual types of immune cells are labeled with fluorescent dyes. "Our lab is able to visualize and record the movement and function of different types of immune cells in the brain and spinal cord of living animals, which lets us study in detail the effects of fibrinogen on these immune cells," Mendiola explains.

He continues, "I am excited to share that we have recently used state-of-the-art technology to identify the actual targets of fibrinogen action in the mouse brain. We think these targets, which we know are part of the mouse's genetic material, may in turn activate disease-causing immune cells."

Mendiola adds, "We hope to test the relevance of these findings in human MS in future studies. I want to use this information to identify new ways to selectively turn off the immune cells affected by fibrinogen that promote and exacerbate MS. It is our laboratory's hope that this research may ultimately provide novel targets for therapeutic intervention in MS."

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

Learn more about MS research.