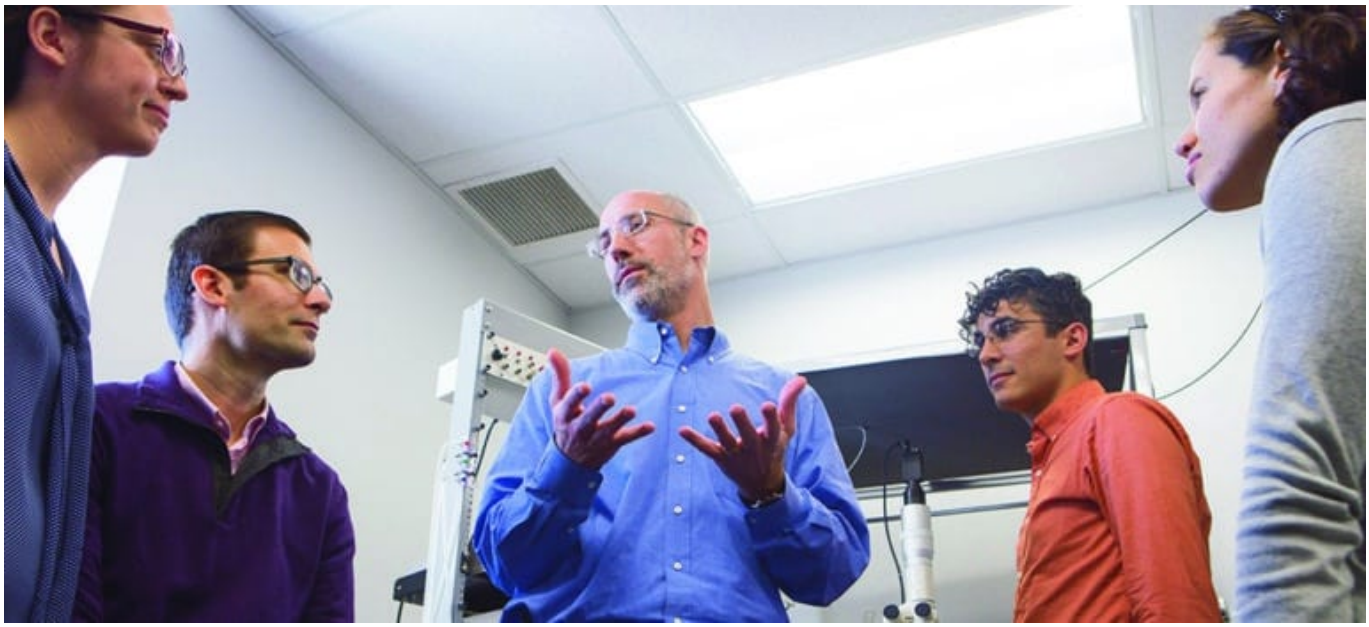
Mysterious cells



Barancik winner’s discoveries upend assumptions about MS and the brain.

by Brandie Jefferson

The expression “You’re born with all of the brain cells you’ll ever have” might have been a fairly common assumption. That is until Dwight Bergles, PhD, professor at the Solomon H. Snyder Department of Neuroscience at Johns Hopkins University, noticed some mysterious cells getting in the way of his postdoctoral research.

The 2021 winner of the Barancik Prize for Innovation in Multiple Sclerosis, Bergles has made several discoveries and innovations that may do more than usher in a new era of myelin-regeneration therapies. His lab’s findings have upended some of the most common assumptions about what happens in the brain.

New tools for research

“In addition to the major contributions Bergles and his team have made to advance myelin repair research, he and his lab have also developed advanced research tools,” says Bruce Bebo, PhD, executive vice president of research at the National Multiple Sclerosis Society, which administers the award. “These tools have made it possible to answer critical research questions that advance strategies to restore function and improve quality of life in people with MS.”

What is the Barancik Prize?

The Barancik Prize for Innovation in Research was created in 2013 by the Charles & Margery Barancik Foundation and is administered by the National Multiple Sclerosis Society. Before their passing in 2019, the Baranciks were major personal supporters of medical research projects in the field of multiple sclerosis for more than 20 years. They developed the Barancik Prize to recognize exceptional scientists who have demonstrated outstanding innovation and originality in MS research. Barancik Prize winners receive $100,000 that can be used at their discretion.

Bergles didn't start his career thinking about MS, but he had been researching the brain as a graduate student at Stanford University and then as a postdoctoral fellow at Oregon Health and Science University, where he used glass electrodes to record the electrical activity of individual cells.

"Occasionally, we encountered these mysterious cells," Bergles says. "At the time, we didn't know about the existence of these cells. We didn't realize what they were, their properties or where they were found."

An important discovery

The cells were oligodendrocyte progenitor cells (also known as oligodendrocyte precursor cells or OPCs). They make up 5% of all the cells in the nervous system. They are of particular interest to MS research because of what they turn into. As their name suggests, these cells can mature into oligodendrocytes, which make myelin that wraps around axons, the major neuronal communication pathways, insulating and sustaining them in the brain and spinal cord.

OPCs kick into action when myelin has been damaged during the course of MS. And Bergles discovered that they form connections with neurons through synapses — points of contact that scientists previously believed were only for neuron-to-neuron communication.

"This was a very striking observation to many people in the field," Bergles says.

A look inside

Jonah Chan, PhD, the Debbie and Andy Rachleff professor of Neurology at University of California San Francisco School of Medicine, wrote in his nomination letter for Bergles that the discovery led to "a paradigm shift in our understanding of what neuron-glial (other cells in the brain) interactions truly represent."

Since his paradigm-shifting discovery, Bergles has remained at the forefront of research and technological advancements. One of his innovations sounds straight out of a science fiction tale: "We have a window into their brains," Bergles says.

He developed a line of mice with a fluorescent protein built into their OPCs. Then researchers removed a tiny piece of the mouse skull and replaced it with a tiny piece of glass.

That allowed Bergles and his colleagues to watch the movement of a single progenitor cell through the living brain. Using a high-resolution imaging technique, they can now watch these cells move through space in real time — over several months — as they form synapses with neurons, and they can see their transformation into oligodendrocytes unfold "like a caterpillar becoming a butterfly," Bergles says. They have also used the technology to look at the oligodendrocytes.

"The imaging mode we use allows us to see individual oligodendrocytes and every single myelin sheath that each one of those cells forms," Bergles says. "The incredibly high resolution allows us to watch where and when new sheaths are formed and follow the dynamics of individual myelin sheaths." They can also watch them regenerate myelin after damage, mimicking what happens in MS.

Yes, regenerate

"This is one place where OPCs break all the rules," according to Bergles. While most nervous system development and refinement is complete in early life, OPCs stick around and are able to change throughout a lifespan, turning into myelin-making oligodendrocytes in response to injury.

Something about that process is disrupted in MS. But the field is in a place where it may soon understand more fully why OPCs sometimes transform, leading to remyelination, while other times, they do not, thanks to work by Bergles and researchers he has trained and worked with over the years.

Teacher and leader

"If I train an army of individuals who are gifted, extremely committed and highly skilled, then they are the ones who are going to solve this problem," Bergles says. "They will get us to cures for MS. And the National Multiple Sclerosis Society has been crucial because they've provided fellowships for a number of researchers in my lab."

The fellowships allow researchers to earn a living wage while working in Bergles' lab.

"Most came to this lab and weren't thinking about oligodendrocyte progenitor cells or demyelination, but together we've been able to make substantial discoveries," Bergles says. He could be talking about himself. After all, he had little knowledge about myelin or MS when he started, but he followed his curiosity and ultimately changed our understanding of the human brain. Now he watches the future take shape in his lab.

"It is certainly one of, if not the most, valuable things for me to experience that sense of discovery from the trainees in the lab," he says. "When they are the ones saying, 'Look what I found!' … For them to have that sense of ability and confidence, and then continue to do

amazing things in their own labs, is incredibly rewarding.

“I can only do so much, myself. They are the ones who are going to solve this problem.”

Searching for solutions

Bergles foresees the solution to the problems of MS as twofold: a continuation of the therapeutics in use now to suppress the immune system, coupled with the regeneration of myelin spurred, perhaps, by drugs that may be similar to the ones his lab is examining.

Using the imaging platform developed in his lab, combined with therapeutics designed to push OPCs to transform, Bergles has been tracing the arc of myelin recovery. “Some things are very effective,” he says, “but it is not at all a panacea.” In some regions, remyelination occurs. In others, it does not.

Bergles suspects other factors can inhibit the transformation of OPCs, and his next goal is to determine what they are, bringing science closer to reversing MS damage. But OPCs may hold the key to understanding more than myelination in the brain.

“We have the ability to create new oligodendrocytes,” he says, “that may be one way in which the nervous system can adapt to different conditions. It may be a way that brain plasticity works.”

When it comes to the mechanisms at work directing these OPCs and how we might harness them for therapeutics to reverse the damage done to the myelin of people with MS, there is still a lot of work to be done. There are so many questions yet to be answered. Or, for a more positive perspective, Bergles offers: “There is so much left to be discovered.”

Brandie Jefferson is a writer in St. Louis, Missouri. She was diagnosed with MS in 2005.