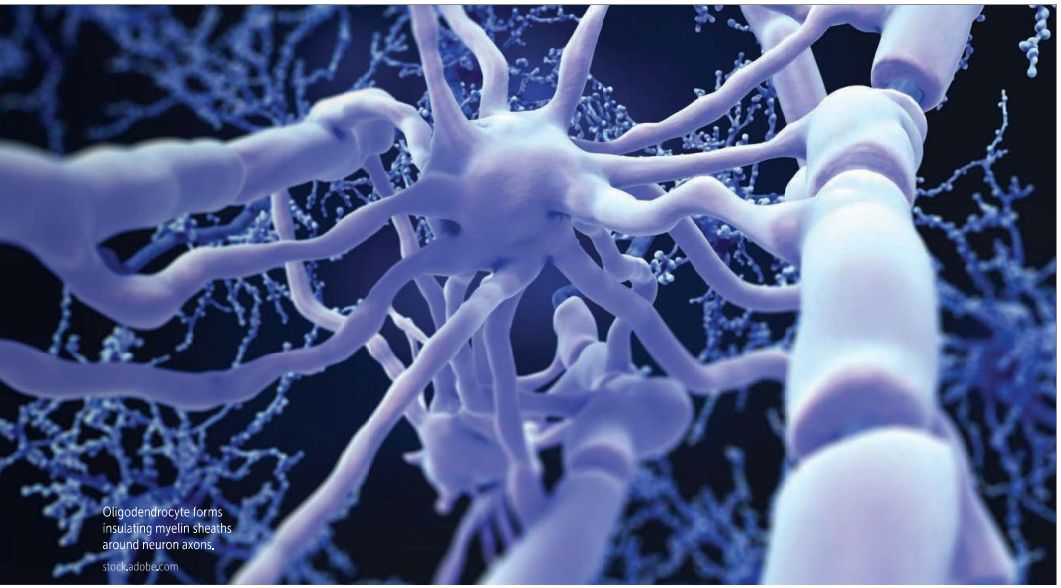

Oligodendrocyte forms insulating myelin sheaths around neuron axons.
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Paradigm-Changing Immunotherapy for Multiple Sclerosis

In multiple sclerosis (MS), the body's immune system attacks the myelin sheath, the protective layer surrounding nerve axons. Current MS therapies act by suppressing the immune system broadly—with sometimes serious side effects, including infection and cancer. However, a team of researchers led by **Abdolmohamad Rostami, MD, PhD**, professor and chair of neurology, has found a way to prevent immune cells from attacking myelin—while leaving the rest of the immune system intact. In mouse models of MS, their approach has halted disease progression.

"One of the biggest hurdles to stopping the attack on the myelin sheath is that science doesn't know which component of myelin is triggering the immune response in MS patients," says Dr. Rostami. "Previous studies have tested the use of single myelin antigens or combinations of antigens to prevent auto-immunity, but those methods have had limited clinical success."

Dr. Rostami's team took a different approach: using oligodendrocytes, the type of cell that produces the myelin sheath that wraps around axons. Oligodendrocytes contain tiny sacs called extracellular vesicles (EVs) that—the researchers found—contain almost all the relevant myelin antigens. The team harvested EVs from cultured oligodendrocytes to create a therapy with the potential to treat the disease without having to know the exact identity of the effective antigen.

> **While the antigens involved in the auto-immune response can differ between MS patients—and even change over time in an individual patient—the fact that our approach was effective in different experimental models shows this could act as a universal therapy.**
>
> —Abdolmohamad Rostami, MD, PhD

"We then injected the EVs intravenously in mice that modeled different stages of MS," Dr. Rostami explains. "When administered before disease developed, the EVs had a prophylactic effect, preventing the onset of symptoms like decreased mobility and paralysis. When given after disease onset, EVs significantly reduced severity of symptoms." Of particular note, the experimental therapy only affected immune cells that were attacking the myelin layer. The rest of the immune system was intact and not weakened at all.

"While the antigens involved in the auto-immune response can differ between MS patients—and even change over time in an individual patient—the fact that our approach was effective in different experimental models shows this could act as a universal therapy," observes Dr. Rostami. "This is one of several major advantages over current therapies."

Working on a parallel research path, Dr. Rostami's team has also found that a compound of naturally occurring elements may both reduce and help reverse MS's damage to the myelin sheaths covering axons. "Although the evidence is preliminary, our studies suggest that ursolic acid—a compound found in the peels of fruits such as apples and prunes, and some herbs—can both halt and repair damage in animal models of disease," says **Guang-Xian Zhang, PhD**, professor of neuroscience. The researchers used a lab-grade purified form of ursolic acid in a mouse model of MS that develops slowly, mimicking human disease; and they began the treatment at an advanced stage, when chronic tissue damage had already affected the nervous system.

"After 20 days' treatment, we began to see improvement in the animals' function; and after 60 days' treatment, those that were initially paralyzed had regained the ability to walk, although with weakness," Dr. Zhang explains.

Analyzing the mechanism for the improvement, the investigators observed that ursolic acid has two important effects: It suppressed Th17 cells—immune cells that help drive the pathological autoimmune response in MS—and spurred maturation of oligodendrocytes, thus enhancing the myelin sheath-making process. "This maturation effect on oligodendrocytes is crucial," says Dr. Zhang. "In MS, myelin sheath-making oligodendrocytes are depleted and the stem cells that produce new oligodendrocytes are unable to mature. This compound helps activate those stem cells and is likely responsible for the reversal of symptoms we observed."

Although ursolic acid is available as a dietary supplement, it could be toxic at high doses. "A number of tests are necessary to ascertain that this compound is safe before initial clinical trials begin," says Dr. Rostami. "However, we are moving forward quickly with this promising approach." ■