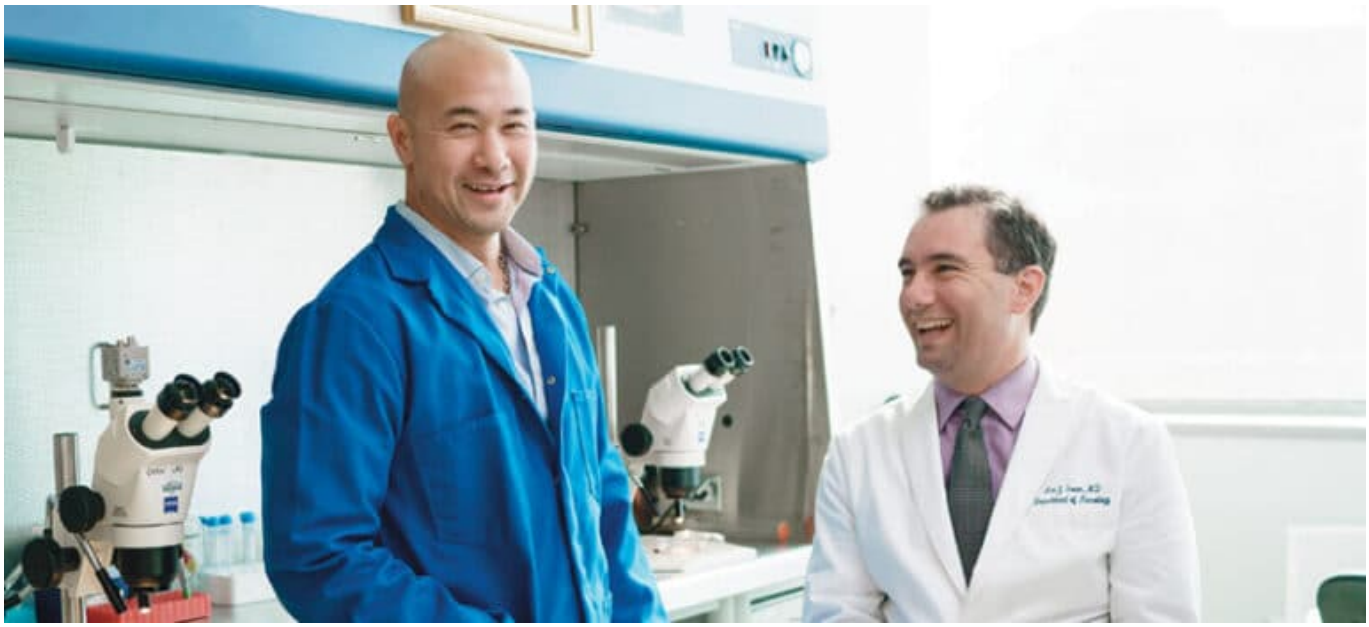
Researchers get closer to myelin repair



Antihistamine and synthetic antibody offer promise.

by Mary E. King, PhD

Stop MS and restore function to people with MS. That's the potential that Dr. Bruce Bebo, executive vice president of research for the National MS Society, sees if new approaches to myelin repair can one day be combined with therapies that regulate the immune system changes of multiple sclerosis.

"Repairing the myelin sheath around nerves is a leading strategy to slow down or stop disease progression," he explains, adding that he has seen an explosion of research in this area. "I think we will have a repair-based strategy in the next five years," Dr. Bebo says.

Dr. Ari Green, medical director of the University of California, San Francisco (UCSF) MS and Neuroinflammation Center, agrees, saying, "I consider myelin repair the most promising area in reparative treatment of MS." That's because stem cells already present in the brain are capable of turning into oligodendrocytes, the cells that produce myelin. These stem cells—known as oligodendrocyte progenitor cells, or OPCs—naturally mature into oligodendrocytes in healthy animals but not so robustly in people with MS, for reasons we don't yet understand, Dr. Green explains. "However, we have now identified a large number of promising leads [that could] unleash the potential of these cells to mature and repair the damage in MS."

Recent results from human trials of an oral antihistamine, known as clemastine fumarate, and of a laboratory-created antibody called anti-LINGO, illustrate the promise of research in myelin repair and the challenges researchers still face.

Repurposing an antihistamine

Clemastine fumarate is an over-the-counter medication commonly used to relieve symptoms of hay fever ("allergic rhinitis"). Clemastine was identified as having possible myelin-repairing properties through innovative preclinical research conducted by National MS Society-funded Jonah Chan, PhD, who went on to become the first recipient of the Barancik Prize for Innovation in MS Research for his pioneering work.

A study conducted by Dr. Ari Green found that the visual evoked potential (VEP) improved slightly among people with chronic optic neuropathy who took clementine. Photo courtesy of Dr. Green

However, a UCSF research group that included Dr. Chan and Dr. Green demonstrated in 2014 that clemastine can also induce OPC stem cells to become mature, myelin-producing oligodendrocytes in a laboratory model of remyelination.

Armed with this knowledge, Dr. Green carried out a clinical trial in people with MS and chronic optic neuropathy (ON) by measuring visual evoked potential (VEP), the time that it takes for a signal to travel along the optic nerve from the eye's retina to the visual cortex area of the brain. This time gets longer as the myelin sheath that insulates the optic nerve is damaged in ON. "If a medication can improve this time, then that is a very good indicator of myelin repair," explains Dr. Bebo.

In a double-blind study, 50 individuals with MS and chronic ON were randomly assigned to take either clemastine or a placebo for three months and then switched to the opposite agent for two months. The VEP improved by a small but statistically significant amount in results reported at the April 2016 American Academy of Neurology annual meeting.

Dr. Green states, “The results of our study are tremendously promising, but caution and a measured approach are critical to our success and to the field of myelin repair. We think these results are some of the most important ever in the history of repair of the adult central nervous system because they rest on a body of preclinical scientific data that strongly indicates that we are witnessing myelin repair. However, more work needs to be done to identify the optimal dosing of medication, potentially improve how we are targeting the receptor so we can limit side effects, and determine the optimal potential timing of when remyelination can be helpful.”

For those reasons, Dr. Green cautions against people with MS taking clemastine at this time. “It would be a mistake for everyone to start taking partially effective therapies at dosing regimens that have not been optimized,” he says. “We need to move together as a field—patients, funders and scientific researchers—to ensure that we deliver on the promise of truly transformational therapies.”

Using a novel antibody

Another recent human trial in myelin repair evaluated a lab-created antibody called anti-LINGO. The protein LINGO is found in nerve cells and oligodendrocytes. Blocking LINGO with the antibody anti-LINGO promoted myelin repair in animal models, and results from a phase 2 clinical trial of anti-LINGO in 82 people who had experienced a first episode of acute ON showed some improvement in visual evoked potential.

A larger phase 2 study is evaluating the effect of intravenous anti-LINGO in a different population: 418 individuals with relapsing MS (including relapsing-remitting MS and secondary progressive MS). This study aims to see if anti-LINGO can improve physical and cognitive function. The study participants took interferon beta-1a (an existing type of MS disease-modifying therapy) and one of several doses of anti-LINGO, or placebo, for 72 weeks. The first results were released in June 2016, and these showed no improvement in the primary outcome measure for the trial, which was a complex, combined assessment of several aspects of physical disability and cognition.

While these results might seem disheartening, especially when compared with the results from the clemastine trial, Dr. Bebo puts them in perspective. Because the damage in optic neuritis is limited to the optic nerve, demonstrating remyelination is going to be more straightforward than in a complex disease like relapsing-remitting MS, he says.

On the other hand, Dr. Bebo emphasizes, the results from the anti-LINGO trial represent the first time that researchers have examined changes in multiple functional outcomes simultaneously in relapsing MS. “Furthermore,” Dr. Bebo adds, “the bar for measuring

improvement in disability was set very high” in the anti-LINGO trial, adding that “additional analyses of the results will help to pinpoint the patient population, dosage and outcome measures that would inform the design of any future trials of anti-LINGO, and additional results may yet reveal a role for anti-LINGO in MS treatment.

The future

Dr. Bebo emphasizes that additional agents and cell therapies for myelin repair are being studied. “We are already learning so much more from the anti-LINGO trial about how to design and carry out clinical trials for myelin repair–promoting therapies, including the best ways to measure this repair.” (To learn more about cell therapies, visit Mesenchymal Stem Cells and iPSCs.)

Dr. Green adds, “The next steps for our clemastine research are continued trials. We are working with other partners to develop new and better therapies for myelin repair. It is an exciting moment! We don’t want to get ahead of ourselves, but as a community we will maintain our excitement—and our skepticism—to help us solve the puzzles that keep us from beating MS.”

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