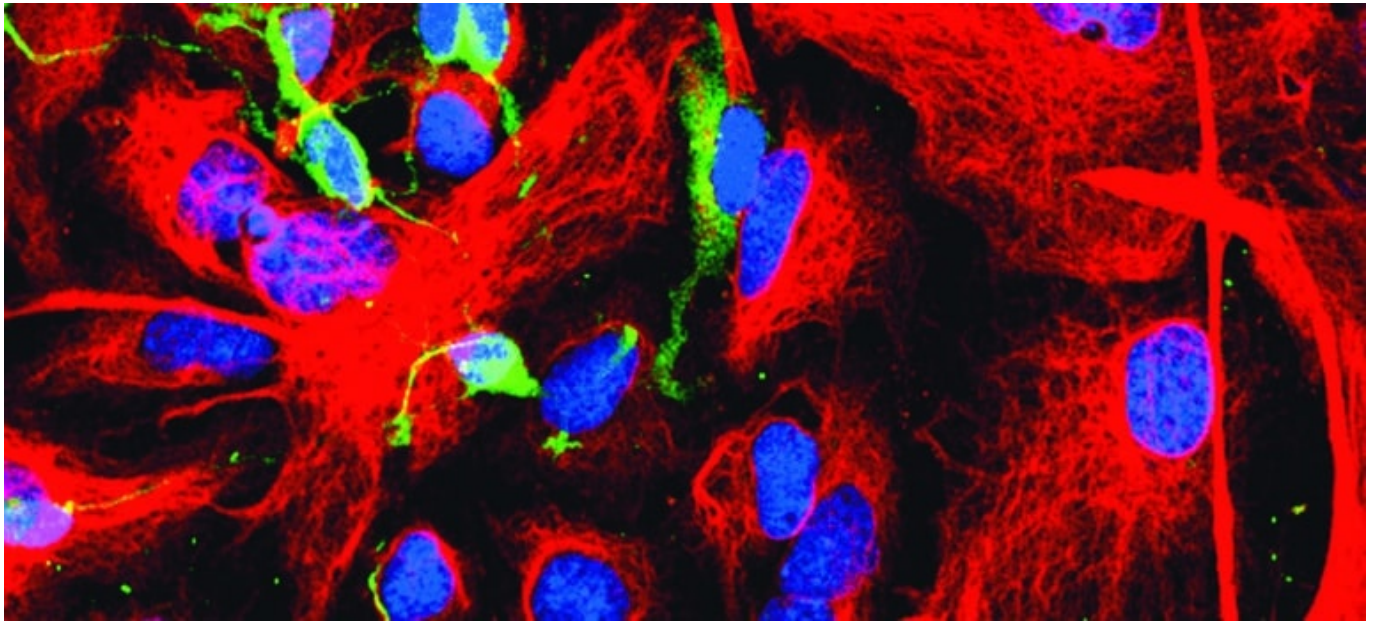


# Hope on the horizon



## **International collaboration accelerates the development of effective treatments for progressive MS.**

by Lori De Milto



**Robert Fox, MD, is part of an alliance aiming to develop treatments for progressive MS.**

Nearly half of all people with multiple sclerosis have or will develop progressive MS. Yet researchers have struggled to understand and develop treatments for this form of the disease.

The FDA has approved only one medication for treating primary progressive MS and has

provided retroactive approvals for all relapsing MS drugs to include secondary progressive MS with disease activity (clinical relapses or new lesions on MRI). No treatments are approved for secondary progressive MS without disease activity. Even so, additional treatment options are needed for progressive forms of the disease.

There's been a sense that progressive MS has been overlooked, says Robert Fox, MD, a staff neurologist at the Mellen Center for MS and vice chair for research at the Neurological Institute at the Cleveland Clinic.

The International Progressive MS Alliance aims to change that by accelerating the development of effective treatments for progressive MS. "We are working hard and seeing some promising early signs of success," says Fox, who also is vice chair of the Alliance's Scientific Steering Committee. This global collaboration is made up of MS organizations worldwide, such as the Society, along with researchers, healthcare professionals, the pharmaceutical industry, donors and people affected by progressive MS.

### **A global collaboration**

Bringing together researchers, health professionals, industry experts, patient advocacy organizations and people affected by MS with a range of perspectives, talent and experiences worldwide is key to understanding progressive MS and developing effective treatments. "Unmet needs in progressive MS are a bigger problem than a single MS organization can grapple with. The Alliance has brought together the best people from around the world to tackle this challenge," Fox says.

Gianvito Martino, MD, the principal investigator of the Alliance's BRAVEinMS collaborative drug discovery network, agrees. "Based on advances in science and technology, it is impossible to have everything state-of-the-art in each single institution. By bringing together experts from different institutions, we can get a better view of what is going on with progressive MS," says Martino, a professor of experimental biology and vice rector for research at San Raffaele University in Milan, Italy.

BRAVEinMS is one of two international drug discovery collaborative research networks funded by the Alliance, where leading MS researchers from multiple countries have been working together since 2017 to understand, prevent and reverse the progression of progressive MS. BRAVEinMS focuses on finding compounds that can protect and repair the brain. Compounds are substances that could be made into medications. The other drug discovery network focuses on preventing brain damage in progressive MS by understanding how the immune process affects disease progression and identifying compounds that use this understanding to treat progressive MS.

"We didn't quit during the COVID-19 pandemic. We continued to work, taking advantage of bioinformatics tools, so we could work remotely during the lockdown," Martino says.

# The International Progressive MS Alliance

The National Multiple Sclerosis Society is a leading agency for The International Progressive MS Alliance, providing financial support, operational management and scientific staff support. Cyndi Zagieboylo, the Society's president and CEO, serves as chair of the Alliance's executive committee, its decision-making body. As an original member of the scientific steering committee, Robert Fox, MD, helped set the research agenda for the Alliance and was the Society's first scientific representative to the Alliance before becoming the steering committee's vice chair earlier this year.

The Alliance is also supporting the creation of tools to speed up and improve clinical trials, so more treatments can be studied faster and at less cost. For example, researchers are studying biomarkers that can identify changes in the brain if a treatment is effective and potentially predict the course of the disease. A biomarker is a characteristic of the body that can be measured to show how the body is doing. A protein from a blood test can be used to diagnose a heart attack, for example. In clinical trials, biomarkers are often used to measure the effects on people of the drug being tested.

## International drug discovery networks

BRAVEinMS comprises 13 investigators from Italy, France, Germany, Europe, Canada and the U.S. The team is identifying compounds that may protect nerve cells and promote myelin repair. Protecting nerve cells would prevent further damage and disability from progressive MS while repairing myelin would allow people with progressive MS to recover some function.

The BRAVEinMS team started with more than 1,500 compounds. Using sophisticated bioinformatics tools, the researchers created a virtual model of MS. They then screened these compounds for their ability to protect nerve cells or promote myelin repair in laboratory tests. Results of many laboratory tests led to seven compounds that could potentially become drugs, two of which appear to be the most promising, according to Martino.

"We are confident these two compounds will be the right ones to progress to clinical trials if they are effective in the animal models," Martino says. Testing of progressive MS in animal models began in March 2021. Martino hopes to have the results of the testing by the end of 2021. If the compounds work in animal models, the next step would be clinical trials in people.

## The role of the immune system

Francisco Quintana, PhD, professor of neurology at Brigham and Women's Hospital, Harvard Medical School, is leading the network focused on developing a drug discovery pipeline for progressive MS. He and his team of eight investigators from the U.S., Canada, Israel and Sanofi Genzyme are studying the immune system's role in the central nervous system to find effective treatments for progressive MS. While the immune system normally protects the body from infections, Quintana and other researchers have previously found that immune

cells in the central nervous system may promote disease activity in MS and other diseases.

Quintana's team has identified biological pathways that control the immune response in MS. They also found that manipulating the biological pathways using genetics can stop nerve damage and alter disease progression in animal models.

Next, the team found a type of brain cells called astrocytes that can turn off inflammation based on signals emanating from bacteria in the gut. They are studying how the anti-inflammatory functions of astrocytes could be harnessed to develop new treatments for progressive MS, such as customized probiotics to alter the balance of gut bacteria to turn on the anti-inflammatory activity.

"Both networks have identified candidate molecules that look promising for application to progressive MS. They are finishing the validation stage. The next steps will be to take these molecules into clinical trials," Fox says.

The Alliance is funding projects to improve clinical trials and speed the development of new treatments. These include developing a routine blood test that could predict and measure disease progression. Other projects include creating tools that use MRI images as a biomarker of disability progression for use in clinical trials. The blood test project explores whether the protein Serum Neurofilament light chain (NfL) can function as a biomarker, help predict the future course of progressive MS and show whether a treatment is preventing nerve damage.

Neurofilaments are structural proteins in nerve cells in the central nervous system. NfL is a type of neurofilament released when there is damage to the brain that occurs in MS. NfL then passes into the blood where it can be measured with a blood test.

Scientists have found that NfL in the blood is a plausible marker for measuring damage to the brain. More work is needed before an NfL blood test can be used routinely for personalized medicine, including developing standard procedures for collecting and analyzing blood samples. An Alliance expert panel is developing recommendations for using an NfL blood test as a biomarker in clinical trials. The panel will be working with regulators to address challenges to doing this. Fox and Kathryn E. Smith have been leading this panel.

The MRI network is developing imaging tools and computer programs to predict changes in the brain as MS progresses. These tools could be used in clinical trials as biomarkers to measure if a treatment is slowing or stopping disease progression.

This network is led by Douglas Arnold, MD, professor and neurologist at McGill University in Canada, in collaboration with investigators from the Netherlands, U.K., U.S. and Switzerland. The team uses cutting-edge advances in artificial intelligence and machine learning to develop imaging tools and computer programs. So far, they have processed and analyzed more than 72,000 MRI scans from 13,500 people.

MRI biomarkers of disease progression would reduce the time and cost of developing new treatments. Researchers would know much sooner whether a prospective treatment is working and need far fewer patients to participate in clinical trials.

### **Working to improve quality of life**

Current treatments for many of the worst symptoms of progressive MS are insufficient, and people affected by these symptoms experience diminished quality of life.

The Alliance focuses efforts to jumpstart research on several key symptoms: fatigue, impairment of mobility and upper limb function, pain and cognitive impairment. An expert panel published a paper outlining critical knowledge gaps and research priorities for these symptoms. Priorities include the need for better ways to measure symptom severity, best treat these symptoms, and sustain the benefits of treatments to provide relief and improve function for people with progressive MS. “The International Progressive MS Alliance provides hope for a pathway forward in accelerating the development of treatments to stop progressive MS and improve the lives of those affected,” Fox says.

**Lori De Milto is a Sicklerville, N.J.-based freelance writer.**