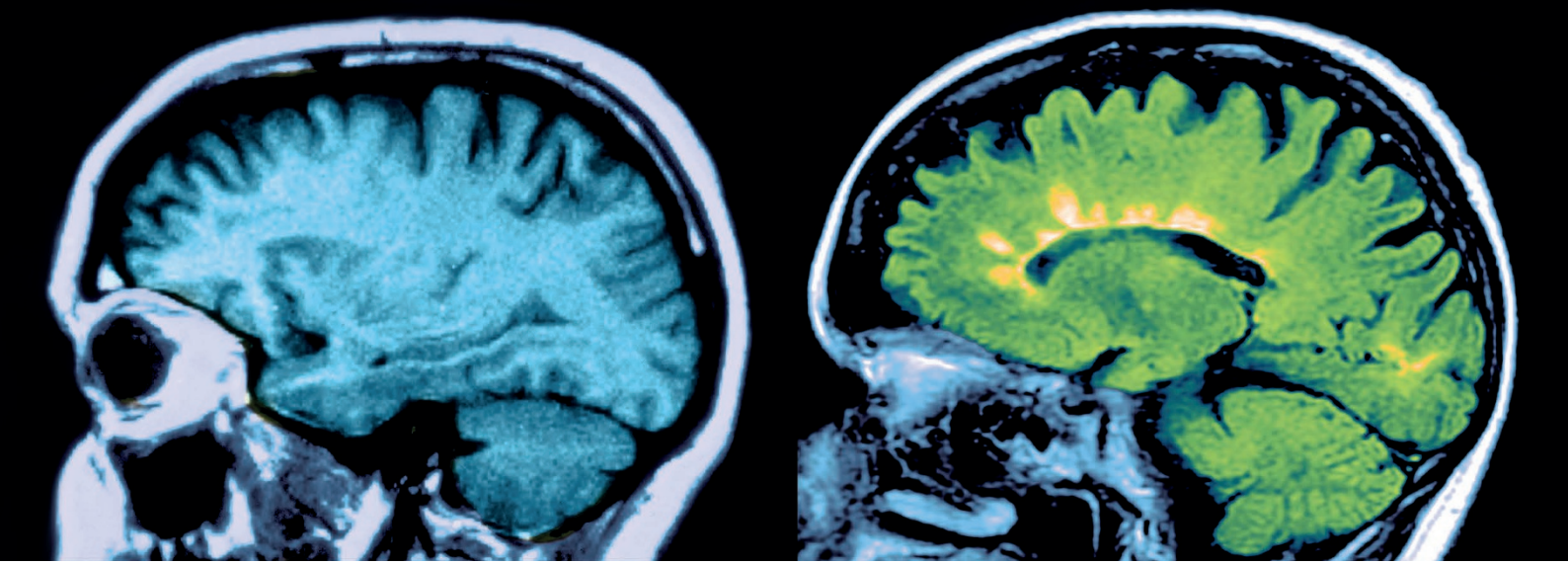
THERAPIES

Progressive steps

New drugs are beginning to show promise for people with one of the less common, and harder to treat, forms of multiple sclerosis.



JESSICA WILSON/SPL

A scan of a healthy brain (left) and one with multiple sclerosis, showing demyelinating lesions (yellow).

BY ELIE DOLGIN

Mitch Sturgeon has tried more than half a dozen therapies to treat his multiple sclerosis (MS), from immune modulators to chemotherapy drugs and vein-widening surgical procedures. None of them seem to have slowed the disease's advance. He did experience a temporary reprieve about a decade ago, thanks to a monoclonal antibody called rituximab, which he received during a clinical trial. But when the two-year study ended in 2007, with the conclusion that the therapy was no better than a placebo[1], it was back to the drawing board for Sturgeon, a former chemical engineer from South Portland, Maine.

The reason that nothing seems to work for Sturgeon is that he has primary progressive MS, a form of the disease marked by steadily worsening neurological function from the onset of symptoms. There are currently 14 drugs approved by the US Food and Drug Administration (FDA) to treat MS, including six that hit the market in the past five years. Yet all these agents combat the clinical attacks associated with the more common relapsing–remitting MS. No medication has ever been shown to help the 10–15% of patients with MS, like Sturgeon, whose physical decline is continuous and unrelenting. And only one drug — a 16-year-old immunosuppressant that is rarely prescribed because of its harsh side effects — has been approved for the secondary progressive form of MS that eventually develops in most patients who first experience the relapsing type.

That dearth of therapies could be about to change. Before the end of December, the FDA is expected to decide on the fate of a new drug called ocrelizumab, which works in a similar way to rituximab by depleting the B cells in the immune system that are crucial for promoting inflammation in MS. The drug is also under review in Europe, Australia and elsewhere. In phase III trials, ocrelizumab proved superior to an existing drug that is commonly used to reduce the frequency of relapses for people who experience them. And promisingly for patients such as Sturgeon, it outperformed a placebo in preserving physical function in primary progressive disease.

If ocrelizumab is approved, Sturgeon expects to try it. For almost two years he has been taking high doses of a vitamin called biotin, even though it has no effect on his disease. "I haven't gotten off it because I have nothing else lined up right now," Sturgeon says. Ocrelizumab could fill that gap — and other drugs might soon be on the way. "The door is ajar for the first time," says Stephen Hauser, a neurologist at the University of California, San Francisco. "But this is only the beginning of effective therapies for progressive MS."

MS is usually thought of as an immune-mediated disease in which misdirected T cells, B cells and other inflammatory drivers infiltrate the brain and destroy the protective myelin coating around nerve fibres, disrupting signalling to and from the brain and spinal cord. But there is also a neurodegenerative component, and this is particularly pronounced in progressive forms of MS, which cause widespread destruction in the brain's white and grey matter.

LEARNING FROM FAILURE

The differences between progressive and relapsing disease remain a matter of debate, but most researchers agree that relapsing MS is characterized by episodes of intense inflammation and demyelination, whereas in progressive MS the inflammation is lower grade and chronic, with neurons dying a slow death from multiple, currently unknown, causes.

Another distinction lies in the integrity of the blood–brain barrier. In relapsing disease, this boundary becomes permeable, allowing immune cells — and the drugs that target them — to pass from the bloodstream into the brain. By contrast, in progressive MS, the blood–brain barrier remains intact, confining the inflammation to the brain, which fuels atrophy and neuronal loss. This firm barrier, and the resulting inability to reach the inflammation with medicines, could explain, at least in part, why nearly every trial of an immune-modulating therapy that works for relapsing MS has failed for patients with progressive

disease — the drugs simply do not reach their target in the brain. An alternative theory is that progressive MS does not result from inflammation at all, but rather from the degeneration that follows the early inflammatory injury.

There is another problem, however. Trials for progressive MS have tended to include everyone with the disease, regardless of whether they show signs of the active, infiltrating type of inflammation that is known to be affected by immune-targeted therapies. This type of inflammatory lesion, which can be detected on a magnetic resonance imaging (MRI) brain scan, is common in relapsing disease but is seen in only a small subset of patients with progressive MS — generally younger people with more recently diagnosed disease. For this reason, drug companies with immune-modulating agents have begun to redesign their studies of progressive MS to enrol more of the patients who are most likely to benefit. This strategy has yielded more success in clinical trials, but it means that these therapies might not be appropriate for everyone with progressive MS.

Ocrelizumab is a case in point. Like rituximab, ocrelizumab targets a protein called CD20 on the surface of B cells. What sets the new drug apart is that it can eliminate B cells with greater efficiency. What's more, whereas rituximab includes mouse components, ocrelizumab has been modified to more closely resemble proteins produced naturally by the human body, making it is less likely to trigger a drug-related immune reaction.

In the study population as a whole, rituximab did not outperform a placebo[1]. But Roche, the Swiss pharmaceutical company behind the drug, noticed some improvements in younger patients with primary progressive MS, particularly in those with active inflammation. Taking those lessons on board, the company adjusted the enrolment criteria and other design features for its late-stage ocrelizumab trial to study younger patients who were more likely to have active disease — and the change paid off.

In 2015, Roche revealed the results of its 732 person trial, which showed that regular infusions of ocrelizumab reduced the risk of disease progression by 24% compared with a placebo. It significantly slowed declines in walking ability, upper-limb function and brain volume for study participants, with no major safety concerns.

"This is the first positive phase III treatment trial in primary progressive MS," says Peter Chin, group medical director for neuroscience at Genentech, a US subsidiary of Roche. "To show consistency of effect across a number of different disease-progression measurements is a very meaningful result."

But Hauser, who was a trial investigator for the drug, warns that the benefit was "really modest" and that ocrelizumab might not work for older patients in the more advanced stages of disease. "We have to be careful how this is communicated to patients," he says.

Novartis, another Swiss pharmaceutical company, found a similar stratification of benefit in its trial of siponimod for secondary progressive MS. Siponimod is an experimental drug that prevents the transport of immune cells to sites of inflammation in the brain. It targets the same protein on the surface of white blood cells as another Novartis drug called fingolimod, which has been approved for relapsing MS under the brand name Gilenya. In a 970 person study published earlier this year[2], led by Fred Lublin, director of the MS clinic at the Icahn School of Medicine at Mount Sinai in New York City, fingolimod showed no benefit for primary progressive MS. But a 1,651 person trial of siponimod to treat secondary progressive MS found that it reduced the risk of three-month disability progression by 21% compared with a placebo.

"We need to move beyond drugs that work on T cells and B cells."

The overall effect is small, admits lead trial investigator Ludwig Kappos, a neurologist at University Hospital Basel in Switzerland. But "it was reassuring and a positive signal that we also saw a benefit in people who were quite advanced in the progressive phase of MS and already had severe disability," he says. Kappos presented the findings at the 2016 congress of the European Committee for Treatment and Research in Multiple Sclerosis in September.

REUSING DRUGS

Lublin is buoyed by the positive trial results for ocrelizumab and siponimod, both of which he helped to test. "What's really exciting is we've had initial success for two very difficult forms of MS to treat," Lublin says. However, apart from those two immune-modulatory agents, there is not much in the late-stage pipeline for progressive MS.

But there are therapies in earlier stages of clinical testing that are focused on tackling the brain damage that is the hallmark of progressive MS (see 'Therapies in the pipeline'). Some involve stem cells that are designed to restore lost nerve function (see page S11). Most of the investigations focus on neuroprotective agents that have already been approved to treat other diseases and that might be beneficial in progressive MS as well — or at least point to molecular pathways that could be targeted.

The French biotechnology company AB Sciences, for example, is testing whether a cancer drug called masitinib, which is used mainly in dogs, can help patients with primary and secondary progressive forms of MS. And a group led by Jeremy Chataway at University College London is evaluating whether any of three repurposed human medicines — a heart-disease drug, an antidepressant and a treatment for amyotrophic lateral sclerosis (also known as motor neurone disease) — will help with the secondary progressive stage of disease. Chataway explains that the three drugs in his trial were chosen after an exhaustive review[3] of all the licensed neuroprotective therapies that can be taken orally and that have some preliminary data on whether they can help in MS. "We looked at thousands and thousands of reports to really drill down to this short list of drugs that could be useful against the pathology of progressive multiple sclerosis," he says.

One of the drugs that was shortlisted by Chataway's group, but not included in his trial, was ibudilast, which is marketed in parts of Asia to treat asthma and stroke-related symptoms. Ibudilast has previously shown no benefit in people with relapsing MS, but there was some indication that it might protect the nervous system from damage because of its ability to block an enzyme involved in brain inflammation[4]. That observation prompted Robert Fox, medical director of the Cleveland Clinic's MS centre in Ohio, to launch a trial to test ibudilast for primary progressive MS. "This is one of the few molecules that has empirical evidence from MS itself that it slows atrophy progression," Fox says.

The 250 person ibudilast study is exploring the drug's effects on brain shrinkage, which is

THERAPIES IN THE PIPELINE

Several drugs are currently being developed to treat progressive multiple sclerosis. Some are repurposed drugs that are already being used to treat other diseases, and many have a neuroprotective effect.

Drug	Mechanism of action	Disease course under investigation	Phase
Ocrelizumab	CD20 antagonist	PPMS	Regulatory filing
Siponimod	Sphingosine-1-phosphate receptor modulator	SPMS	III
Masitinib	Tyrosine kinase inhibitor	PPMS, SPMS	III
High-dose biotin	Vitamin B7	PPMS, SPMS	III
Ibudilast	Phosphodiesterase inhibitor	PPMS, SPMS	II
Idebenone	Coenzyme Q10 analogue	PPMS	II
Amiloride	Potassium-sparing diuretic	SPMS	II
Riluzole	Glutamate-release inhibitor	SPMS	II
Fluoxetine	Selective serotonin reuptake inhibitor	SPMS	II

PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

MOUNT SINAI HEALTH SYSTEM

Fred Lublin (left) is pleased with the progress being made to treat progressive multiple sclerosis.

the standard approach in mid-stage clinical trials of MS therapies that are seeking proof of principle that the drug is working in the brain. But unlike most trials of its kind, this study also includes several advanced imaging techniques and tests of disability so that, even if ibudilast shows no benefit, the investigators will learn something about their outcome metrics through direct head-to-head comparisons.

Another idea for improving outcome measures comes from Bibi Bielekova, head of the neuroimmunological diseases unit at the US National Institute of Neurological Disorders and Stroke in Bethesda, Maryland. Bielekova's team statistically compared 58 outcome measures in a group of 98 untreated people with primary progressive MS, and concluded that most brain-scanning metrics are unreliable surrogates for symptom progression (see page S10). The researchers integrated four different clinical scales into a single disability score called CombiWISE, and it outperformed other measures for detecting clinical deterioration[5].

"I have zero doubt that CombiWISE is the best thing we currently have for screening treatments," says Bielekova, who is currently using the metric in an 85 person trial of the antioxidant idebenone for primary progressive MS.

BACK TO BASICS

Most researchers who study progressive MS remain cautiously optimistic that at least some of the experimental therapies for this form of the disease will prove their worth. But the challenges are daunting, largely because so much remains unknown about the basic pathology of progressive MS. "We still need to better understand the mechanisms of progression," says Tim Coetzee, chief advocacy, services and research officer at the US National Multiple Sclerosis Society in New York City.

To address these knowledge gaps and accelerate progress in new therapeutic directions, the society teamed up in 2013 with other research and advocacy non-profit groups from around the world to launch the Progressive MS Alliance. This €22.4 million (US$24.0 million) initiative will be "a catalyst that brings together the best institutions worldwide", says Alan Thompson, dean of brain sciences at University College London and chair of the alliance's scientific steering committee. "This has never happened in the world of MS before," he says.

In 2014, the alliance funded a series of 20 small-scale research projects on topics ranging from genetics and disease models to proof-of-concept trials. And earlier this year it handed out three larger grants worth a total of €12.6 million for drug-discovery efforts and biomarker development. Francisco Quintana, an immunologist at the Brigham and Women's Hospital in Boston, Massachusetts, has received both kinds of award.

Quintana used his €75,000 grant from the Progressive MS Alliance to demonstrate in a mouse model of MS that miglustat, a drug currently used to treat Gaucher's disease, can stop the activation of astrocytes, a type of immune cell that promotes inflammation in the brain. Now, thanks to a four year, €4.2 million award, Quintana is trying to find more drugs that can cross the blood–brain barrier and block astrocyte function or disrupt a metabolic pathway involved in the activation of astrocytes.

"We need to move beyond drugs that work on T cells and B cells," Quintana says. Modulating those cells may help to treat relapsing MS, but progressive disease is driven by innate immune cells such as microglia and astrocytes, and it's "those cells we should be targeting to arrest chronic progression," he says.

Research efforts such as Quintana's could eventually help the million plus people worldwide who live with the disability of progressive MS. But as the years pass and his condition continues to deteriorate, Sturgeon, who now relies on a powered wheelchair and voice-controlled devices, is losing hope of researchers finding a therapy that can help someone in his advanced disease state. He plans to take ocrelizumab next year after its anticipated approval, but he realises that the likelihood of it working for him is "pretty low".

"I'm walking a fine line between hope and acceptance," says Sturgeon, who chronicles his experiences in a blog called *Enjoying the Ride*. But there is one reason to maintain hope. "We don't seem to be the forgotten group anymore," he says. "There's some attention coming our way — and that helps." ■

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5. Kosa, P. *et al. Front. Neurol.* **7,** 131 (2016).