How to stop MS: the role of charitable funding

Sir Geoffrey Owen

September 2019

Let's stop MS **together**

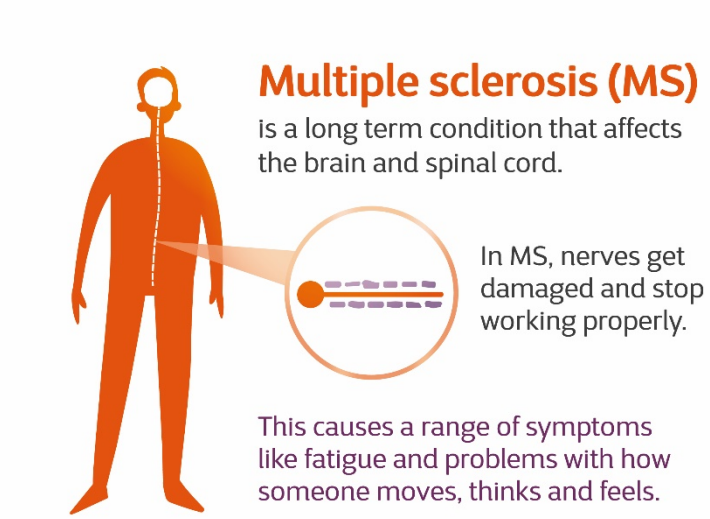
Contents

1. Introduction

This paper has been written in support of the Stop MS Appeal and aims to highlight the importance of charities, and the MS Society in particular, in funding research in Multiple Sclerosis (MS). The paper is based on interviews with scientists engaged in MS research and with officials in the MS Society, the National MS Society in the US and other charities.

Sir Geoffrey Owen

2. A pivotal moment in MS research



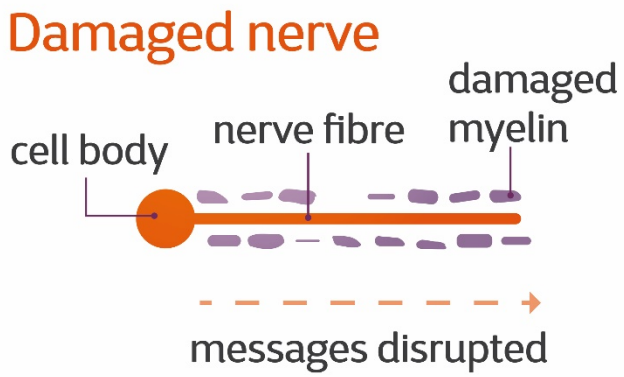
Multiple sclerosis is a crippling disease for which there is no known cure. Over the past thirty years scientists have developed treatments which reduce the frequency and severity of the debilitating attacks which are characteristic of the early stages of MS. These treatments have greatly improved the quality of life for many people with MS. But they are not enough. People affected by MS want to get better. That means having access to treatments that halt and reverse the longer term progress of the disease, restore them to full health and stop further damage from occurring. Today, thanks to recent scientific advances, such treatments are within reach. The challenge now is to accelerate the pace of scientific progress and to bring the new medicines into the clinic. For this to happen, scientists who work on MS have to be adequately funded.

Funding for MS-related research in the UK comes from three main sources: (i) government agencies such as the Medical Research Council and National Institute of Health Research; (ii) pharmaceutical and biotechnology companies; (iii) and charities. The last of these is the main focus of this paper; the aim is to show why the next phase of MS research depends crucially on an increase in funding from charitable sources.

3. Background

Multiple sclerosis was identified as a distinct illness in the late 19th century, but for many years there was little understanding of what caused the disease or how to treat it. In the years following the Second World War some progress was made, thanks in part to the efforts made by newly formed multiple sclerosis societies (notably in the US and the UK) to raise public awareness of the disease and to encourage research. During the 1960s and 1970s, a time of great optimism about the ability of medical science to tackle hitherto intractable diseases, scientists began to explore novel approaches to the treatment of MS. In the 1980s the emergence of new diagnostic tools – most importantly the scanner – enabled researchers to diagnose MS more accurately, to learn more about the biology of MS, and to track the progress of the disease.

MS is an autoimmune disease, in which an abnormal immune system attacks healthy cells and tissues; other diseases of this type include type 1 diabetes and rheumatoid arthritis. It also has a neurodegenerative component; as the disease progresses there is a loss of function in the nerve fibres in the brain, reducing their ability to send signals to the rest of the body. This places MS among other neurodegenerative diseases such as Alzheimer's, Parkinson's and motor neurone disease.



The malfunctioning of the immune system was the target of the first effective MS treatments, the beta interferons, which were launched in the 1990s. Known as immunomodulatory or immunosuppressive drugs, they had the effect of damping down or preventing some immune system attacks. These attacks – characteristic of relapsing remitting MS, the most common form of the disease at onset (Table 1) - vary in type and severity and last for a sustained period of time, at least 48 hours and often for many weeks.

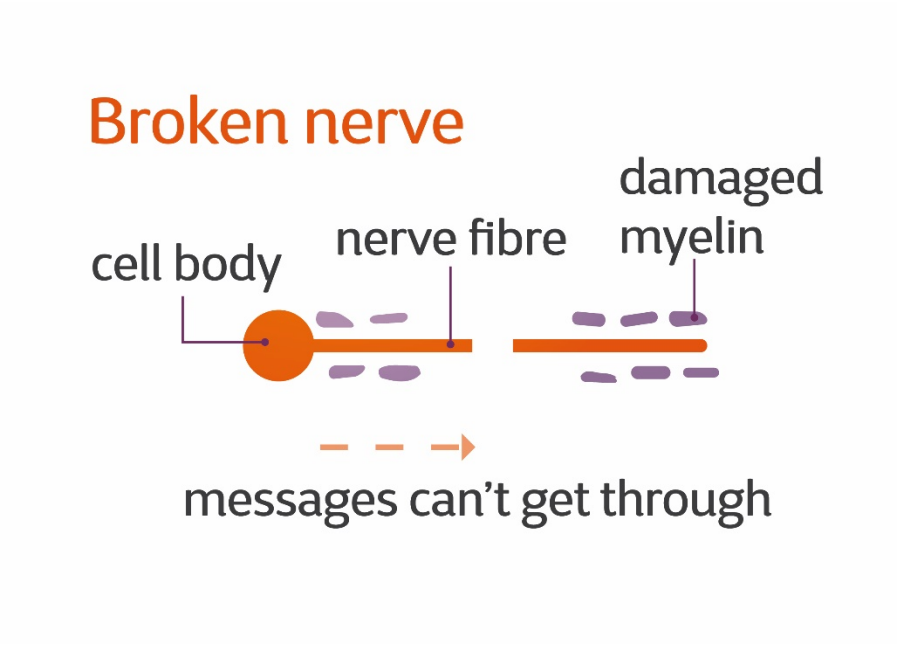
The beta interferons marked a step change in the treatment of MS. Previously doctors had used medicines that relieved some of the symptoms of the disease; the beta interferons showed that the course of MS could be altered by therapeutic intervention. They were followed by other immunomodulatory drugs, based on different technologies. Pharmaceutical and biotechnology firms began to see MS as a treatable disease which offered attractive commercial opportunities; several of them entered the field, often by buying the rights to drugs that had been developed by academic scientists in universities. There are now more than a dozen immunomodulatory MS drugs on the market.

Table 1 Types of multiple sclerosis

Relapsing remitting MS (RRMS)	Characterised by clearly defined attacks of neurological symptoms, followed by periods of recovery - about 85 per cent of people with MS are initially diagnosed with RRMS.
Secondary progressive MS (SPMS)	Most people with RRMS will eventually transition to a secondary progressive course in which there is a progressive worsening of the neurological function.
Primary progressive MS (PPMS)	Characterised by a progressive worsening of symptoms from the outset – about 10-15 per cent of people with MS have PPMS.

Thanks to these drugs, the quality of life for people with relapsing remitting MS has been greatly improved. However, the new treatments are "disease modifying therapies" (DMTs) which, if used in the early stages of the disease, can slow the onset of disability but cannot halt or reverse the progression of MS; they generally have not been shown to work in the later stages of the condition. The fact that the disabilities associated with MS get worse over time is one of the most distressing features of the disease, and one that has been the subject of intense research over the past decade. That research is now bearing fruit.

Although many aspects of MS are still poorly understood, scientists now have a better insight into the link between the physical deterioration that affects people with MS and the biological processes happening in the brain and spinal cord. The clinical disability observed in MS is caused by a complex interplay between three things; (i) immune attacks on myelin, (ii) failure of the myelin sheath (which protects nerve fibres) to regenerate and (iii) a 'slow-burn' degeneration that is independent of immune attacks often seen early on in the disease course.



The task for MS researchers is to find a way of repairing the damage to myelin and restoring the nerves to their proper function. If myelin can be restored following an MS attack, the nerve fibres can continue to be protected, thus preventing progression of disability. In addition, it is necessary to stop the 'slow burn' neurodegeneration that

appears to contribute to disability progression and is not responsive to treatment by the current DMTs. Leading MS researchers theorise that treating these aspects of MS in combination is likely to lead to significant progress in slowing down and stopping MS.

Following a series of discoveries at the level of fundamental research, scientists have identified the role played by a type of stem cell – known as the oligodendrocyte progenitor cell (OPC) – in remyelination; it is the failure of the OPCs and the myelin-forming oligodendrocytes they generate to do their proper job of repairing the myelin sheath after attack which weakens the nerve fibres and contributes to the disabilities associated with MS. Research is focusing on finding a way of stimulating OPCs and oligodendrocytes to regenerate myelin following damage in MS; several drugs which have the potential to promote myelin repair are being tested in early-stage clinical trials.

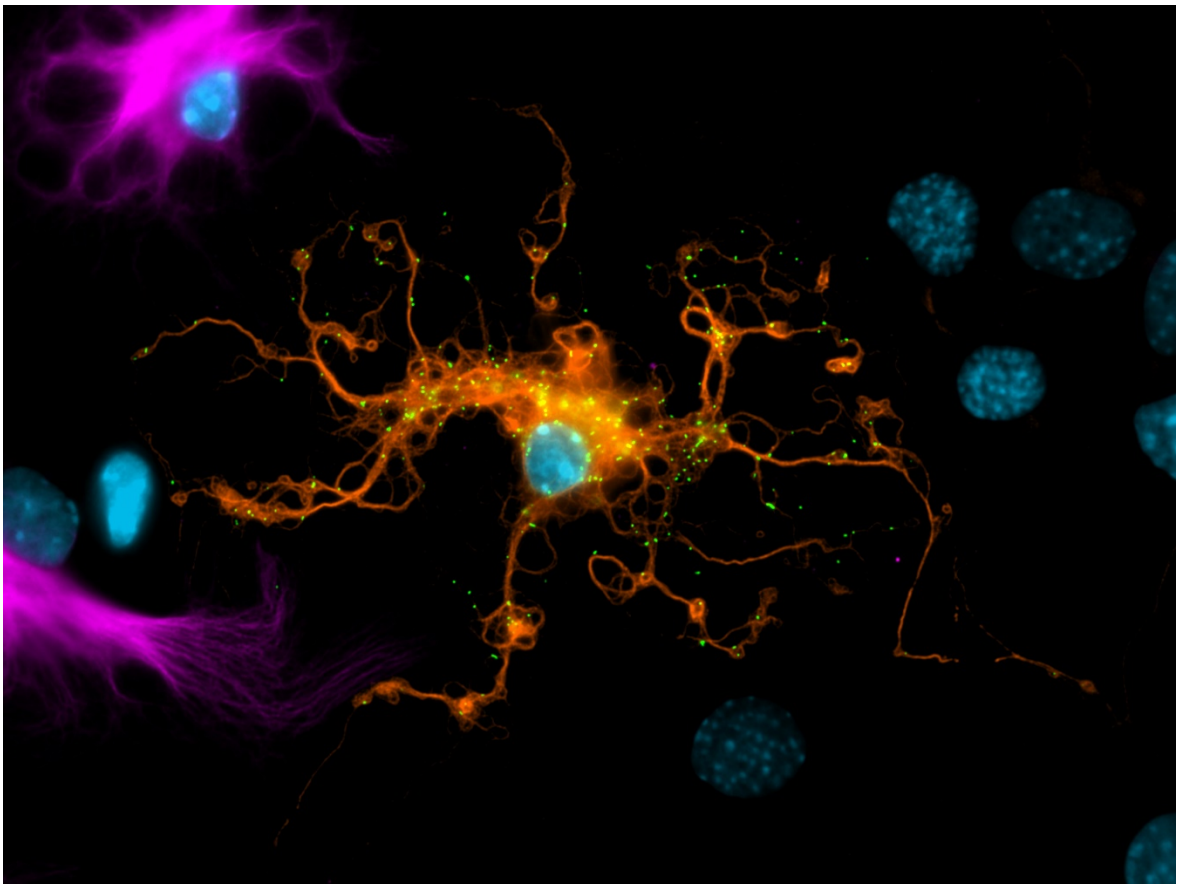


Image author: Colin Crawford. Image of an oligodendrocyte, the myelin-making cell.

While there is still work to be done on improving the effectiveness of immunomodulatory drugs and on optimising treatment response, the biggest unmet need, and the top priority for people with MS, is in developing and testing treatments for myelin repair and neuroprotection. Yet research in this area has not reached the stage which could attract large-scale investment from the pharmaceutical industry. There are still too many gaps in knowledge about myelin loss and axonal damage, and about how the damage can be restored.

4. The drug development process

In MS, as in other therapeutic areas, the development of new medicines generally starts with research conducted in universities and research institutes. The first step is fundamental research, aimed at acquiring new knowledge about the biological processes involved in a particular disease; this often involves experimentation with animal models and human brain tissues. It is followed by translational research, designed to establish whether the scientists' findings might be useful in the treatment of the disease. The next step is clinical research (also called experimental medicine), which tests whether the molecule emerging from the laboratory is safe and effective in humans.

Some of the early-stage clinical research is conducted by universities, especially those in which the biomedical departments are linked to teaching hospitals; this facilitates close cooperation between the scientists who work in fundamental research and the clinicians who deal directly with patients.

When proof of concept has been established and the molecule has been shown to have potential as a marketable drug, development is usually taken on by a commercial firm. The drug may be licensed to an established pharmaceutical company or taken up by a new firm, often spun out from the university responsible for the original research. These new firms are generally described as biotechnology firms (or biotechs), a term that came into use in the 1970s and 1980s to refer to the firms that were created in that period to exploit the latest advances in molecular biology (recombinant DNA and monoclonal antibodies). Subsequently the term "biotechnology" came to be applied to any start-up or early-stage drug development firm, irrespective of the technology it was using.

The pharmaceutical industry is a large spender on research, both in its own laboratories and to a much lesser extent also by supporting research in universities. Some of this research falls into the category of fundamental research, but where such research is undertaken, the motivation is primarily commercial, directed to therapeutic areas in which the company is already active, or which it plans to enter. The bulk of the industry's research effort consists of late-stage research and development, where the commercial potential is clearer. This is the stage at which drug development becomes too expensive for universities or for small biotechnology firms; "Big Pharma" plays an essential role in bringing new drugs to the market.

The process of obtaining regulatory approval for a novel medicine is long and complicated. Once the molecule moves from the pre-clinical stage into full-scale clinical trials, the regulators – of which the most important are the Food and Drug

Administration in the US and the European Medicines Agency in Europe - require the sponsor to put the drug through three phases. Phase 1 involves testing the drug for safety in a small group of healthy volunteers. Phase 2 tests for efficacy and safety in a larger group; this may be divided into Phase 2a and 2b, with the former consisting of pilot studies to test safety and clinical efficacy, and the latter seeking to establish the optimum dosage with the least side effects. Phase 3 tests the effectiveness of the drug in a larger group, which may involve anything from 300 to 3000 patients; this is the most expensive and time consuming part of the process.

The average time between initial discovery and regulatory approval is 10-15 years, but the process can take much longer. Most molecules fail at some stage in the development process, often after the company has spent large sums on the project. Drug development is risky and expensive. Moreover, what matters is not just the amount of funding but its sustainability over time. This is where charities, especially charities which focus on a single disease, make a crucial contribution.

5. How is MS research funded?

In industrial countries such as the US and the UK funding for biomedical research comes from three sources: government agencies such as the National Institutes of Health in the US and the Medical Research Council and National Institute for Health Research in the UK; pharmaceutical and biotechnology firms; and charitable organisations, which in the UK include the Wellcome Trust as well as disease-specific charities such as Cancer Research UK and the Multiple Sclerosis Society.

The MRC, founded in 1920, is now part of UK Research and Innovation, a newly created body which embraces all the research councils as well as Innovate UK, the government's innovation agency. The MRC has laboratories of its own, of which the most famous is the Laboratory of Molecular Biology in Cambridge, where James Watson and Francis Crick worked out the structure of DNA. The bulk of the MRC's research spending – just under half of its total annual spending of about £800m – is channelled through universities and non-governmental research laboratories.

MRC's main focus has traditionally been on fundamental research across all therapeutic areas, and this includes support for several research centres whose work is relevant to MS. In 2008 for example, it set up the Centre for Regenerative Medicine in Edinburgh; this centre supports a number of research groups, two of whom are focused on myelin repair in MS. The MRC is also the joint funder, with the Wellcome Trust, of the Cambridge Stem Cell Institute, which conducts research into neurodegenerative diseases including MS.

More recently the MRC has increased its involvement in translational and applied research. It is a partner with Innovate UK in the Biomedical Catalyst, a fund set up by the government in 2012 to help universities and firms bring their research projects closer to commercialisation. Another initiative, also run jointly with Innovate UK, is the Development Pathway Funding Scheme, which funds the pre-clinical development

and early testing of novel therapies. Innovate UK has a network of research centres, known as Catapults, one of which, the Medicines Discovery Catapult, supports research and development in specific therapeutic areas.

The other big government entity involved in biomedical research in the UK is the National Health Service. Its research arm, the National Institute of Health Research (NIHR), was set up in 2006 to strengthen the links between the NHS in England and the medical research community, including universities, firms and medical charities. Among the NIHR initiatives is the funding of research professorships for scientists working in particular therapeutic areas, including MS.[1]

The second source of funding is the pharmaceutical industry. In MS, as in other therapeutic areas, there are many partnerships through which pharmaceutical firms tap into the skills and expertise of academic scientists, supporting research – including basic research – in fields which are or may become relevant to their commercial objectives. For example, two of the UK's leading MS scientists, Richard Reynolds at Imperial College and Robin Franklin in Cambridge, have had research projects supported by Medimmune, the biologics arm of AstraZeneca, while the Edinburgh groups of Anna Williams and Charles Ffrench-Constant both receive funding from Roche.

Commercial partnerships can be difficult to manage; academic scientists can find it hard to navigate the bureaucracy of a large corporation. There is also the danger, in partnerships with large companies, that changes of strategy or senior personnel can lead to apparently promising programmes being abandoned, often at short notice. Partly for that reason scientists sometimes prefer to work with smaller firms whose culture is nearer to that of academia. In the UK two examples are Canbex Therapeutics, spun out of UCL, which was developing drugs for the treatment of spasticity, and Apitope, spun out from Bristol University, which is working on a novel approach to the treatment of autoimmune diseases. Both these firms have raised funds from venture capitalists and other outside investors, including the Wellcome Trust and both have been supported by Fast Forward (a fund set up by the National MS Society to advance novel discoveries into treatments).

Charities represent the third source of funding for biomedical research. In the UK by far the biggest medical charity is the Wellcome Trust; its spending on research is currently running at about £1bn a year. Wellcome's main focus is on fundamental research in underlying sciences such as immunology, neurobiology and genetics. Through its neuroscience and mental health division it is a major funder of MS-related

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[1] In 2018 Professor Olga Ciccarelli at UCL was given a NIHR award to develop a computer tool that will enable doctors to predict more accurately which of the DMTs are likely to be most beneficial for people with MS.

research in universities, principally Oxford, Cambridge, Edinburgh and UCL. Several of the UK's leading MS researchers have benefited from this support.

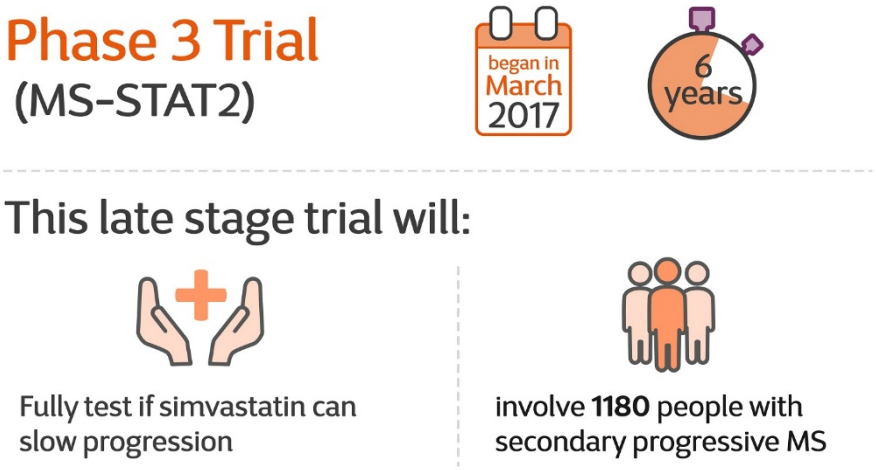
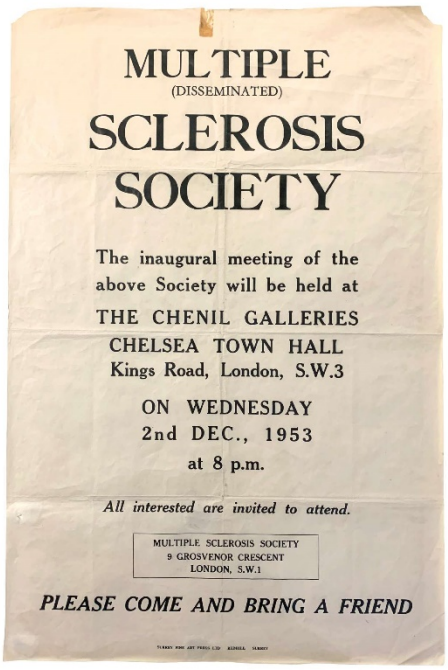


Image: Phase 3 clinical trial of simvastatin

The UK has many smaller charities, often set up by wealthy individuals or families, which support medical research. Some of them concentrate entirely on medicine, while others see the treatment of disease as one of several targets. One example is the Volant Trust, set up by the author, J. K. Rowling, which has supported MS research in Edinburgh University most notably through the building of the Anne Rowling Regenerative Neurology clinic. Another is the Moulton Charitable Trust, set up by Jon Moulton, a City financier, which intervened at a critical stage in the development of Campath, an MS treatment derived from academic research in Cambridge (This drug is now marketed under the brand name Lemtrada). The Moulton Trust also supported a phase 2 clinical trial of high-dose simvastatin as a neuroprotective treatment in progressive MS; that drug is now being tested in a phase 3 trial supported by a partnership between the NIHR, the MS Society in the UK and the National MS Society in the US.

This type of support is opportunistic rather than strategic, and does not necessarily imply a long term commitment to MS research. Such commitment can only come from charities that concentrate on one disease; in multiple sclerosis that is the role of the MS Society.

6. The Multiple Sclerosis Society



MULTIPLE
(DISSEMINATED)
SCLEROSIS
SOCIETY

The inaugural meeting of the above Society will be held at
THE CHENIL GALLERIES
CHELSEA TOWN HALL
Kings Road, London, S.W.3
ON WEDNESDAY
2nd DEC., 1953
at 8 p.m.

All interested are invited to attend.

MULTIPLE SCLEROSIS SOCIETY
9 GROSVENOR CRESCENT
LONDON, S.W.1

PLEASE COME AND BRING A FRIEND

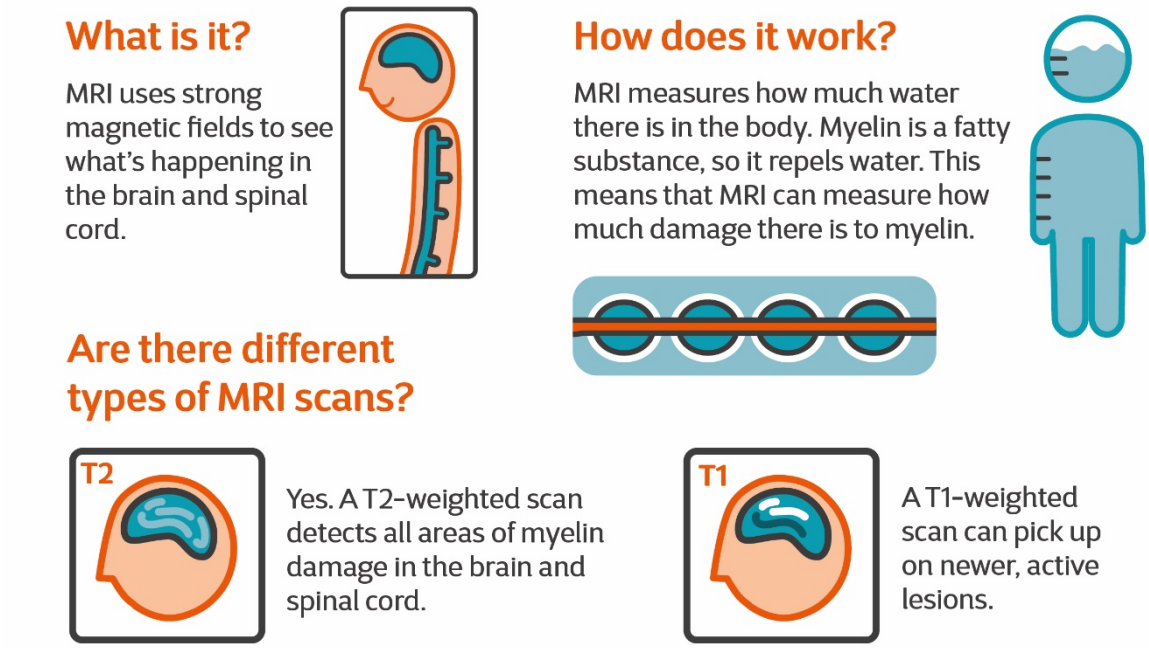
The Multiple Sclerosis Society was founded in 1953. Its sponsors were following the example of the US, where the Association for the Advancement of Research on Multiple Sclerosis, later renamed the National Multiple Sclerosis Society, had been created in 1945. The mission of the US society was to coordinate research efforts on multiple sclerosis in the US and abroad, to collect funds to stimulate and support research, and to act as a clearing house for information on the disease.

The UK society set up a research fellowship scheme in 1958 and started making small grants to academic scientists. The society had a difficult start, partly due to disagreements over how and to whom research funding should be disbursed. At a time when there was no clear view in the scientific community or in the medical profession about how the disease should be treated, it was difficult for the society to formulate a consistent research policy. However, these problems were gradually ironed out, and by the 1970s the society had established itself both as a significant contributor to research funding and as an authoritative source of information on available treatments; the latter role is particularly important in a therapeutic area where exaggerated claims are sometimes made about scientific breakthroughs and miracle cures.

The society is a membership organisation with around 30,000 members and 270 local groups. With an annual income and expenditure of about £30m, it ranks as a medium-sized medical charity, slightly smaller than Diabetes UK (£40m), and much smaller than the two biggest disease-specific charities, Cancer Research UK (£420m) and British Heart Foundation (£130m). About half of the MS Society's income comes from donations and fund raising, another third from legacies.

Much of the MS Society's work is the provision of support to people with MS, their families and carers. Another part is campaigning for access to treatments and services for people affected by MS. The final part of the MS Society's work is support for scientific research. Average research expenditure in the years running up to the Stop MS Appeal was around £4.5m a year. The aim of the Appeal is to enable the MS Society to double this investment over a ten year period.

Within the research budget the main components are: funding for the next generation of MS researchers including PhD studentships; investment in research infrastructure to support the research community in the UK and overseas; funding for research proposals and programmes submitted by individual scientists and research groups; and commissioning research that is of particular strategic focus for the MS Society.



On infrastructure, the society has historically made a big investment in magnetic resonance imaging of the brain (MRI), which has become an essential technique for the diagnosis and management of people with multiple sclerosis. In 1983 the society funded the first MRI scanner in the world to be solely devoted to MS research, at the National Hospital for Neurology and Neurosurgery at Queen Square, London. A leading figure was Ian McDonald, who had previously developed the first set of diagnostic criteria for MS that incorporated laboratory tests; McDonald was one of the first to see the potential of MRI as a diagnostic tool, and he was instrumental in persuading the MS Society to invest in the scanner at Queen Square.

A further £2.5m investment in MRI came in 2009 when a more powerful scanner was installed at Queen Square; this has helped to speed up the process of diagnosis so that people are diagnosed earlier and in a more consistent way, and to develop better outcome measures for clinical trials. The MRI unit in Queen Square has been closely involved in some of the pivotal clinical trials for the anti-inflammatory treatments now on the market, and has played a leading role internationally.

Another infrastructure investment was the creation in 1998 of the MS Society Tissue Bank. Located at Hammersmith Hospital in London and based on a partnership with Imperial College and Parkinson's UK, the Tissue Bank allows people to donate their brain and spinal cord tissue after their death. Study of this tissue is used by researchers in the UK and overseas to identify cells and molecules which may be responsible for the damage caused by MS. The Tissue Bank, which is regarded as one of the best in the world, has been run from the start by Richard Reynolds, professor of cellular neurobiology at Imperial; his research focuses on the mechanisms involved in demyelination and neurodegeneration in MS.

Image: Professor Richard Reynolds at the MS Society Tissue Bank

In 2009 the society funded the UK MS Register, which allows researchers to access information from people with MS and from hospitals and treatment centres around the country. Set up by the Health Informatics Group at Swansea University, the Register has over 17,000 participants submitting patient reported data and over 45 clinical sites across the UK. The Register has the potential to generate valuable information about the impact of MS on individuals and about how best to manage clinical research.

Image: UK MS Register Infographic

In supporting research the society responds to proposals submitted by scientists but it also takes initiatives of its own. In particular, it was quick to recognise the need to concentrate efforts on developing a new approach to treatment with therapies that will work in combination to stop immune attacks, protect nerve fibres from damage, and regenerate lost myelin. Through the Stop MS Appeal the MS Society has developed a focus on the latter two treatments as high priority areas for MS research.

In 2005 the Society set up a centre for myelin repair at Cambridge, led by Robin Franklin. Two years later another centre, focusing on strengthening the interactions between basic and clinical scientists, was established at Edinburgh University; it is led by Charles Ffrench-Constant and Siddarthan Chandran. (In the Edinburgh case substantial funding was also provided by the Volant Trust, the charity set up by the author, J. K. Rowling.) These two centres have an international reputation and have been responsible for much of the pioneering work in myelin repair. In 2005 the groups involved in the Cambridge and Edinburgh centres, as well as other UK researchers, were awarded just under $4m to launch a collaborative effort in myelin repair. They continue to receive substantial support from the MS Society.

In recent years the society has been putting increasing emphasis on translational and clinical research, including the funding or part-funding of clinical trials. For example, in 2017 the society invested just over £1m in a phase 3 trial to test the effectiveness of a repurposed drug, simvastatin (widely used to reduce cholesterol), in secondary progressive MS; it was able to leverage an additional £4m of support from the NIHR and the National MS Society as partners in this ground breaking trial. The results of the trial, which involves 30 trial centres and over 1000 people, are expected in 2023.

This is one of several cases where the society is supporting research into repurposed drugs - drugs that have been already been approved for other diseases, do not require further testing for safety, and might be relevant for MS. One recent case, in which the society was partnered with the NIHR and with the National MS Society in the US, tested whether three repurposed drugs – amiloride, fluoxetine and riluzole – could slow progression and reduce the brain shrinkage that occurs in people with progressive MS. Known as MS-SMART, the trial was led by Professor Chataway from UCL and Professor Chandran from Edinburgh, and incorporated an innovative three active arm design. The outcome of the trial, reported in October, 2018, was disappointing in that none of the three drugs showed potential as treatments for disability progression, but the academic community is committed to learning as much as it can from the trial. In partnership with the MS Society, scientists will continue to identify repurposed drugs that may be effective in MS with a view to putting them through clinical trials.

Partnerships form an important part of the MS Society's research strategy. One of the most ambitious international collaborations is the Progressive MS Alliance, set up in 2013 to accelerate research into treatments for progressive MS. The UK MS Society was a founding member, along with its counterparts in the US, Canada and Italy and MSIF (the international membership organisation of MS charities); membership has subsequently been extended to several other countries including Australia and the Netherlands. Chaired by Professor Alan Thompson, dean of the faculty of brain sciences at UCL, it began by funding 20 small-scale projects on topics ranging from genetics and disease models to pilot studies. This was followed by a larger set of international network grants, including support for biomarker development and the

identification of new treatment targets. The alliance has so far committed nearly £20m to research into progressive MS.

Thanks to its close interaction with patients, doctors and researchers at all stages of the drug development process, the MS Society plays a unique role in the MS funding landscape. As a single disease charity, it is better able than other funders to identify gaps that need to be filled and to take the lead in opening up new areas, through its own funding and by negotiating partnerships with other funders. The view of scientists interviewed for this paper is that funding from charities has made a bigger contribution than government or commercial funders to the fundamental research on which recent advances in the understanding of MS are based. Collaboration between the UK and US societies has been especially productive. [2]

The question now is whether the combined efforts of academic scientists, charities, government agencies and the pharmaceutical industry can meet the next big challenge. Can the substantial progress that has been made in immunomodulatory treatments be repeated – if possible at a faster pace - in addressing the problem of progressive MS? The next two sections look first at how that earlier success was achieved, and then at the current phase of MS research.

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[2] This view is supported by a detailed study, published in 2006, of the history and current state of MS research. The authors described the British and US societies as the "default funders" for the scientific work which has laid "the modern foundation for our understanding of the disease". Alastair Compston et al, McAlpine's Multiple Sclerosis, Fourth Edition, Elsevier 2006, p24

7. Treatments for MS: the immunomodulatory drugs

Most major medical advances take place when there is a coming together of a serious, widely recognised, unmet medical need with a scientific breakthrough which shows how that need might be met. The initial breakthrough is often followed by a wave of further innovation, as scientists in academia and industry look for ways of building on and improving the discovery made by the pioneer. Just as the development of penicillin sparked a search for other micro-organisms which might have therapeutic value, setting in train the antibiotic revolution, so in MS the introduction of the beta interferons opened up a new opportunity for treating a disease for which at that time no effective drugs were available, Table 2 shows how the number of immunomodulatory drugs has increased since the 1990s.

Table 2 Principal anti-inflammatory drugs for MS

Trade name (generic name)	Date of regulatory approval	Marketed by	Mode of administration
Betaseron (Interferon beta-1b)	1993	Bayer	Injection
Avonex (Interferon beta-1a)	1996	Biogen	Injection
Copaxone (Glatiramer acetate)	1997	Teva	Injection
Rebif (Interferon beta 1a)	1998	Merck KgaA	Injection
Novantrone (Mitoxantrone)	2000	Immunex	Infusion
Tysabri (Natalizumab)	2004	Biogen	Infusion
Extavia (Interferon 1b)	2009	Novartis	Injection
Gilenya (Fingolimod)	2010	Novartis	Oral
Aubagio (Teriflunomide)	2012	Sanofi/Genzyme	Oral
Tecfidera (Dimethyl fumarate)	2013	Biogen	Oral
Lemtrada (Alemtuzumab)	2014	Sanofi/Genzyme	Infusion
Ocrevus (Ocrelizumab)	2017	Roche/Genentech	Infusion
Mavenclad (Cladribine)	2017	Merck Serono	Oral

The research that led to the beta interferons was based on the hypothesis that MS was caused or exacerbated by a viral infection. Interferon is a naturally occurring protein which "interferes" with or guards against viral infections; the introduction of the recombinant DNA technology, starting in the 1980s, made possible a substantial increase in the supply of "cloned" interferon that could be used in drug development. After testing different types of interferon scientists were able to show in clinical trials that interferon beta produced a reduced relapse rate in people with relapsing remitting MS. The beta interferons are administered by injection, as is glatiramer acetate (Copaxone), another early entrant in the market for anti-inflammatory treatments. This drug is a copolymer made up of four amino acids, and, like the beta interferons, was shown to be effective in reducing the frequency of relapses. Since their launch in the 1990s new formulations have been introduced which have made these drugs more acceptable to patients, including a reduction in the necessary dosing frequency; a generic equivalent of Copaxone was approved by the FDA in 2015.

The next major advance came with the launch of the first monoclonal antibody for MS, natalizumab (Tysabri). Monoclonal antibodies, based on a technology which was invented in the UK in the 1970s; provided a means of developing drugs which targeted one component of the immune system while leaving the rest of the system intact. Following the approval of natalizumab (Tysabri) in 2004, several other monoclonal antibodies were tested and approved in MS including alemtuzamab (now marketed as Lemtrada) and ocrelizumab (Ocrevus).

Of these three drugs, Ocrevus is the only one to be approved not just for relapsing remitting MS but also for the primary progressive form of the disease.[3] (It was approved for PPMS in the US and for early stage PPMS in Europe). Whether Ocrevus will have a major impact on the PPMS population is still debated; the treatment effect size in clinical trials was small but significant and it is not yet clear how many people will be eligible to receive Ocrevus on the NHS. But the academic community is united in its view that the approval of Ocrevus opens the door for developing and testing new treatments for progression in MS.

Another major advance in the field is the development of oral immune modulatory drugs – first fingolimod (Gilenya), followed quickly by teriflunomide (Aubagio) and dimethyl fumarate (Tecfidera); a fourth oral drug, cladribine (Mavenclad) was approved in 2017. These drugs transformed the treatment of relapsing remitting MS, "The option to use oral rather than injectable therapies for equal or greater therapeutic benefit reduced the burden of treatment, thereby increasing both patient satisfaction and compliance".[4]

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[3] In September 2018 the National Institute for Health and Care Excellence (NICE) ruled against the use of Ocrevus as a treatment for PPMS in England and Wales, on the grounds that the benefit of the treatment did not justify the cost.

[4] Megan Cully, Oral drugs expand therapeutic options, Nature December 2018

8. Lessons from the immunomodulatory story

The evolution of anti-inflammatory treatments since the 1990s is widely regarded as one of the great successes of modern medical science. It has involved a range of different technologies, with different risk profiles and different therapeutic mechanisms. But the story also highlights several aspects of the drug development process that are relevant to the current phase of MS research. These are: the crucial importance of basic scientific research; the extent to which drugs originally aimed at other diseases have proved later to be useful in MS; the role played by small, often newly created firms in bringing academic discoveries nearer to the market; and the need for patience on the part of both researchers and their funders - the willingness to keep going during the inevitable setbacks in the research process.

Basic research

In the case of the beta interferons, the starting point was the discovery in 1957 of interferon, a naturally occurring protein which is capable of "interfering" with viral infection in cells. The process of converting the discovery into effective treatments for disease took many years of further research. In the 1970s and 1980s interferon was thought to hold the key to a cure for cancer, and several of the new biotechnology firms raised money from investors on that premise. Although the idea of interferon as a cure for cancer proved to be illusory, the protein was found to have therapeutic value in other diseases, notably multiple sclerosis. Some of the early work on interferons was funded by the National MS Society in the US, which had been investigating the role of viruses as potential causes of MS. All of the interferons were tested, showing that beta-interferon was most likely to have a beneficial effect in MS. This paved the way for further work by academic scientists.

One of the pioneers was Kenneth Johnson, based first in the University of California San Francisco, and later at the University of Maryland. Johnson's work on beta interferon was taken up by a small biotechnology firm in California, Triton Biosciences. Triton formed a joint venture with another small firm, Cetus, to develop what was intended at the start to be a broad- anti-cancer drug. That project failed, and the research focus switched to MS, leading (after several changes of ownership) to the approval of Betaseron by the FDA in 1993.

Another American neurologist, Lawrence Jacobs, based at the University of Buffalo, started work on beta-interferon in the 1970s. Again the initial target was cancer, but Jacobs devoted most of his research to neurological diseases, principally MS. By the end of the 1980s his research had reached the point where he was able to persuade Biogen, then a small biotechnology firm, to back a large-scale clinical trial. The outcome was Avonex, which was approved in 1996.

The third of the beta-interferon drugs, Rebif, approved in 1998, was the product of research at the Weizmann Institute in Israel. The principal inventor was Michel Revel, who had worked for the Pasteur Institute in Paris before moving to Israel in 1968. At the end of the 1970s the Israeli group found a commercial partner in Serono, the Swiss pharmaceutical company, which agreed to share the development costs and to build a plant in Israel. The Weizmann Institute also played a leading role in development of Copaxone; in this case commercialisation was handled by an Israeli pharmaceutical company, Teva.

As these examples show, the drug development process almost always starts with breakthroughs at the level of fundamental science. In the mid-1970s two scientists working in the MRC's Laboratory of Molecular Biology in Cambridge, Cesar Milstein and Georges Kohler, found a way of making monoclonal antibodies - proteins which recognise and attach to specific molecules, marking them for destruction. This technology (for which both scientists won Nobel prizes) opened up a new approach to drug discovery which has had a profound impact on the world pharmaceutical industry; a third of all the drugs on the market are based on monoclonal antibodies, including top-selling drugs such as Humira for rheumatoid arthritis and Herceptin for breast cancer. But before that could happen, further scientific work was necessary. A key advance was made by Greg Winter and his colleagues, also based at the Laboratory of Molecular Biology, who invented a technique for "humanising" monoclonal antibodies; the effect was to reduce the murine content of the drug and make it less likely to be rejected in humans. (Winter is the latest British scientist to win the Nobel Prize; he was given the prize for chemistry in 2018).

The MRC's monoclonal antibody technology was widely licensed around the world. The first drug of this sort to be approved for MS was Tysabri, launched in 2005. It was followed by Ocrevus from Roche/Genentech and Lemtrada (formerly Campath) from Sanofi/Genzyme.

The repurposing of drugs

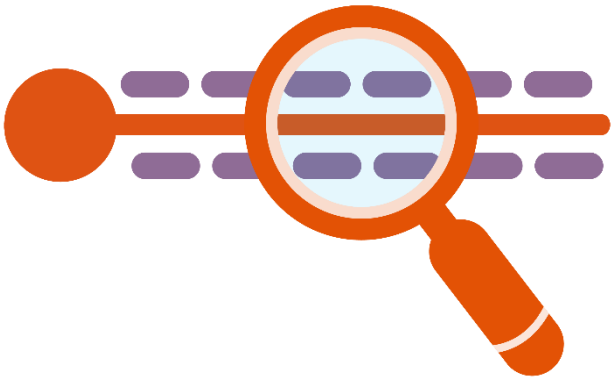
As noted above, interferon was initially seen as a possible cure for cancer; it was only later that scientists began to explore its possible relevance to MS. This has been a common experience in MS research. For example, cladribine (Mavenclad) was developed in the 1980s by scientists at Scripps Research in the US as a treatment for a rare form of leukaemia; it was licensed by the FDA as an orphan drug for this disease in 1994. But because the drug targets T and B lymphocytes, which play a role in MS, Scripps scientists began to explore its possible application to this disease. After more than a decade of further research, including the formulation of the drug in oral form, and an earlier rejection by the EMA on safety grounds, cladribine was finally approved in 2017 as an oral treatment for MS.

The case of Lemtrada is another example. Herman Waldmann, an immunologist in Cambridge University's Department of Pathology, began work on monoclonal antibodies in the late 1970s; his initial research was funded by the Medical Research Council. His first plan was to develop a drug that would counter organ transplant rejection, and this drug, known as Campath, was used for that purpose during the 1980s. In 1985 Campath was licensed to Wellcome Biotech, a large British

pharmaceutical company (later merged with GlaxoSmithKline). The drug was tested for its effectiveness in several diseases, but after seven years' work Wellcome gave up the rights to Campath. In 1997 development was taken on by a small US firm, LeukoSite, whose chief executive had previously worked with Waldmann in Cambridge.

The use of Campath for chronic lymphocytic leukaemia was approved by the FDA in 2001, but MS was a larger and more profitable market, and this was part of the reason why, after several changes of ownership, control of Campath was acquired by Genzyme, a large Boston-based biotechnology company, and then by Sanofi, the French pharmaceutical group, which bought Genzyme in 2011. Renamed Lemtrada, the drug was approved for MS in 2015, some thirty years after Waldmann had started work on monoclonal antibodies in Cambridge.

The role of small firms



A third theme in the history of MS treatments since the 1990s is the role played by small, often newly created firms, in beginning the process of converting discoveries made by academic scientists into marketable drugs. Biogen today is no longer a small company, but, when it was founded in 1978, it was a paradigm case of a science-driven company looking for niches in the market which were unlikely to interest Big Pharma. It was Biogen, not one of the established pharmaceutical companies that took the risk of supporting Lawrence Jacobs' research in 1990, leading to the launch of Avonex.

The large, established pharmaceutical companies were slower to invest in MS, and when they have done so their entry has often taken the form of buying the rights to a drug that a smaller firm, or a university, has already taken some way towards commercialisation. Fingolimod (Gilenya), the first oral disease modifying drug for MS, was developed by scientists at Kyoto University in Japan and then by Yoshitomi Pharmaceutical Industries, which sold the rights to Novartis in 1997.

The early development work on what became Betaseron was done by Triton Biosciences, a San Francisco-based company that was later acquired by Schering a German pharmaceutical company. In the case of Tysabri (formerly Antegren), the initial development was done by a small US company, Athena Biosciences, working with scientists at Stanford University. Athena was taken over by Elan, a Dublin-based pharmaceutical company, in 1996, and it was a partnership between Biogen and Elan that brought Tysabri to the market.

Campath was licensed initially to Wellcome, and then to LeukoSite in the US, which believed that Campath could be the basis for a range of novel drugs; it was given the right to explore the use of the drug in several diseases including multiple sclerosis.

Several Big Pharma companies, including Roche, Novartis, and Sanofi, are now competing in the MS market. But for early stage development academic scientists often find it easier to work with small biotech firms. In these firms, as Waldmann has written, "the ethos is more akin to our academic culture and the management is closer to our level. To us, Big Pharma…seem daunting and impersonal; our main point of contact is with lawyers who appear obsessed with detail we find trivial".[5]

The need for patience

The final message from the immunomodulatory story is the length of time that is frequently involved between the initial discovery in the laboratory and regulatory approval. This is not a problem unique to multiple sclerosis, but MS, like other neurodegenerative diseases such as Alzheimer's and Parkinson's, has posed especially difficult challenges for researchers and firms because of the complexity of the factors that appear to play a part in the onset of the disease – and the risk of side-effects.

This underlines the importance of consistent funding, and again Campath highlights the challenges that have to be overcome. The development of Campath as a treatment for multiple sclerosis began in the early 1990s, with some modest support from the MS Society. The clinical scientists involved in this effort, led by Alastair Compston and Alasdair Coles, were funded in part by the MRC and Wellcome Trust, but they had difficulty obtaining funds for clinical trials. At a critical stage when the programme might have run out of funds, they were able to persuade the Moulton Charitable Trust to provide some £250,000 to fund a clinical trial of Campath in combination with another drug. Commercial interest began to pick up in the early 2000s after development was taken on by LeukoSite and its partner, Ilex, in the US, and there was also support from charitable funders, including Moulton again and later the MS Society, which supported a study to determine how to manage the side effects of Campath. The Medical Research Council came in at a later stage, after Lemtrada had been approved, to support a trial designed to test ways of reducing the side effects from Campath.

Campath could almost certainly have been brought to market earlier as a treatment for MS if the funding of the programme had been more consistent. An important question for the MS research community is whether that kind of extended timescale can be avoided in the search for drugs that promote myelin repair and prevent neurodegeneration.

The next phase: tackling progressive MS

The current state of MS research is in many ways far better than it was in the early 1990s, before the launch of the beta-interferons. More is known about the disease, and the prospects for further breakthroughs are more promising than is the case in other neurodegenerative diseases such as Parkinson's and Alzheimer's. In the case of

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[5] Geoff Hale and Herman Waldmann, From laboratory to clinic: the story of Campath-1, Methods in Molecular Medicine, Vol 40, 243-266, 2000

myelin repair and neuroprotection, although there are no drugs on the market that are directly aimed at these targets, scientists have identified a number of promising lines of development. The research that is now under way is built on scientific advances that were made in the 1980s, 1990s and 2000's, some of them in British laboratories.

Basic research

A major contribution to knowledge about myelin repair was made by Martin Raff, a Canadian-born immunologist who came to the UK in 1968 to work first at the National Institute for Medical Research and then, for the rest of his career, at UCL. His initial research was funded by the MRC, a grant that was renewed five times over the next thirty years. Raff's work focused mainly on the cells of the immune system, and he was the first to describe the role played by oligodendrocyte progenitor cells in generating oligodendrocytes and in producing the myelin sheath.

Another pioneer, whose research was supported by the MS Society, was William Blakemore. Working at the Centre for Myelin Repair in Cambridge, Blakemore described how remyelination could occur in the adult Central Nervous System and what might promote or inhibit it. He theorised that axon damage in MS was caused by a failure of remyelination.

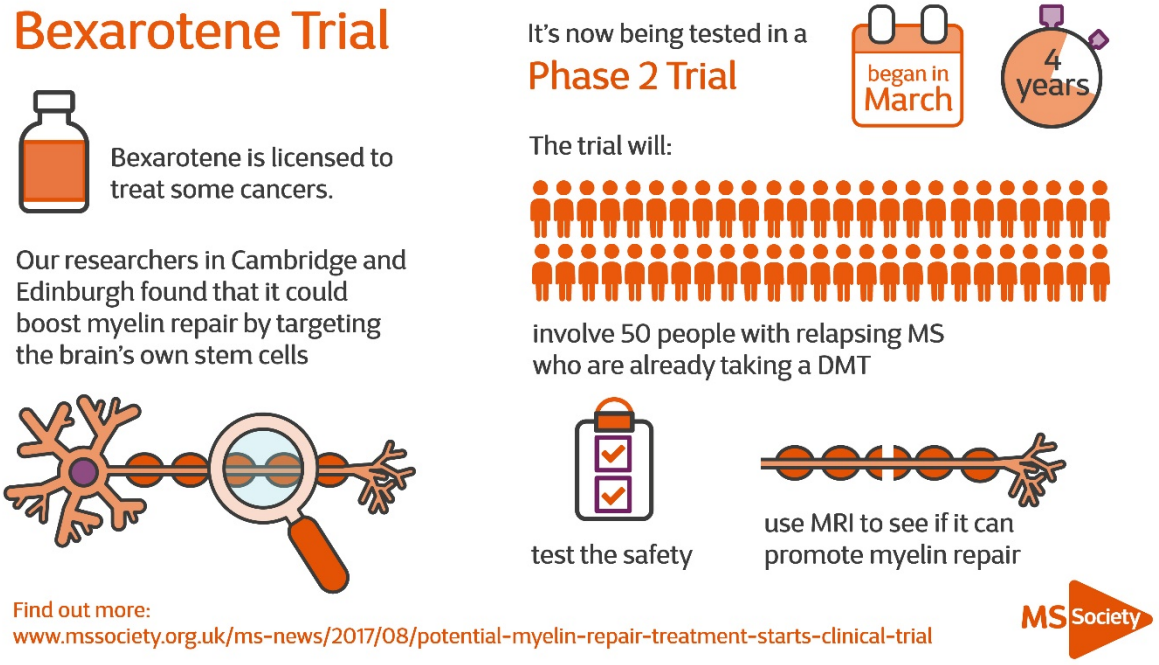
In the field of neuroprotection, new insights into the causes of axonal damage, in MS and other neurodegenerative diseases have come from the work of many researchers. Important work on the biology of remyelination has been done in Robin Franklin's laboratory at the Cambridge Stem Cell Institute. Working closely with Charles Ffrench-Constant (who moved from Cambridge in 2007 to become director of the MRC Centre for Regenerative Medicine in Edinburgh), both researchers have contributed to a fuller understanding of the cells and signalling pathways that are responsible for remyelination. Both Franklin and Ffrench-Constant have been consistently supported by the MS Society. (In 2017 Franklin won the Barancik Prize, a prestigious US award administered by the National MS Society, for innovation in MS research.)

Clinical trials

Building on these advances scientists have sought to find ways of promoting or accelerating myelin repair, and this has now reached the stage of early stage clinical trials.

In the UK Franklin, Ffrench-Constant and their colleagues, using samples from the Tissue Bank, identified retinoid X receptors (RXR) as having a role in the development of oligodendrocyte progenitor cells into myelin-producing oligodendrocytes. Further research showed that RXR-gamma was the receptor type that was the most likely target. The next step was to find a drug that would stimulate RXR-gamma and thus promote remyelination. The drug selected for this purpose was bexarotene (Targretin), which had been approved in the 1990s as a treatment for skin cancer. With financial support from the MS Society the Cambridge group, together with colleagues in Edinburgh, has initiated a Phase 2a clinical trial, led by Alasdair Coles,

which will examine the safety of bexarotene in 50 people with MS, together with its potential effectiveness as a myelin repair therapy. The results of the trial are expected in 2019.



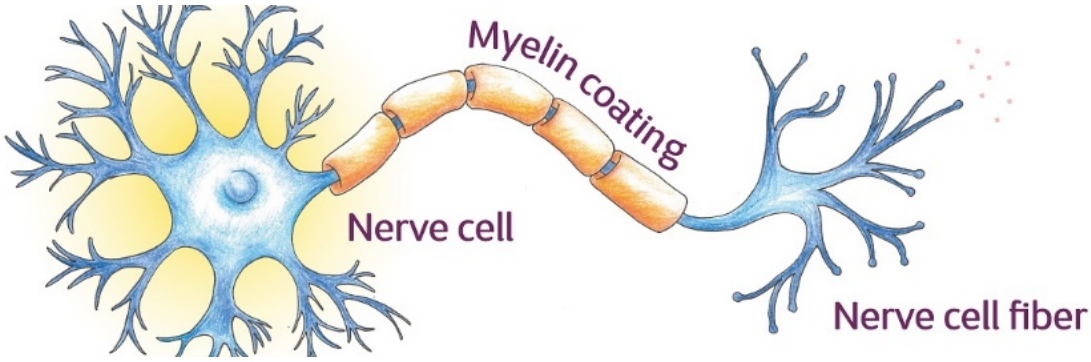
Two other trials, using different drugs but with a similar overall objective, have been taking place in the US. One of them, financed and managed by Biogen, focused on Lingo-1, a protein which is thought to play a role in preventing oligodendrocytes from protecting the myelin sheath. Biogen used a monoclonal antibody, opicinumab, which had been developed in its own laboratories, to counter the actions of Lingo-1; the drug was administered together with Avonex, Biogen's beta interferon drug. Initial results looked promising, but in 2017 the company announced that the anti-Lingo trial had failed to meet its primary goal of improving disability in relapsing and secondary progressive MS.

The other American trial was undertaken by scientists at the University of California San Francisco, with support from the National Institutes of Health and a private foundation. They used as the myelinating agent clemastine fumarate, an anti-histamine drug which had been approved in the 1970s as a treatment for allergies; a technique called visual evoked potentials was used to test clemastine's therapeutic effects. As in the anti-Lingo trial, the drug was delivered to patients together with an anti-inflammatory drug. The initial results of the trial were promising but not conclusive, and a larger trial is now being planned.

Further trials of drug-based therapies for remyelination are planned, showing that research in this area has reached the stage of experimental medicine.

The role of pharmaceutical firms in myelin repair and neuroprotection

Of the leading pharmaceutical and biotechnology firms, Biogen had led the way in developing treatments for MS; it is also actively searching for new treatments for progressive MS. Most other companies, even those that are marketing anti-inflammatory drugs, have taken a cautious stance in the area of myelin repair and neuroprotection. Their focus has been on immunology rather than neurobiology, and where they have ventured into neurodegenerative diseases such as Alzheimer's, the results have been disappointing. Pfizer has recently withdrawn from in-house neuroscience research, although it has also established a venture capital fund to invest in neuroscience start-ups. Neither of the two big UK-based pharmaceutical companies, GlaxoSmithKline and AstraZeneca, has active programmes testing therapies for MS.



There are, however, some promising early stage firms which are targeting myelin repair. In the US, for example, Convelo Therapeutics was formed by scientists at Case Western University who had identified a number of compounds (including a common anti-fungal treatment for athlete's foot, miconazone) as having the potential to enhance myelin formation; trials are set for 2019. Another company active in regenerative medicine is Frequency Therapeutics, formed in 2015 by scientists from MIT and the Harvard Medical School. Based on what the company calls its Progenitor Cell Activation platform, the aim is to develop a new category of therapies for degenerative diseases. Venture capital firms are also taking an interest; Versant Ventures, a leading health care investor, is supporting a San Diego-based firm, Pipeline Therapeutics, which is seeking to commercialise discoveries made at UCSF.

Given the size of the potential market for a remyelinating therapy it would not be surprising if one of the big pharmaceutical companies decided to enter the field, perhaps by acquiring one of the start-up firms. As things now stand, however, the risks and costs associated with developing an experimental myelin repair drug and taking it through clinical trials appear to be holding Big Pharma back.

Outlook

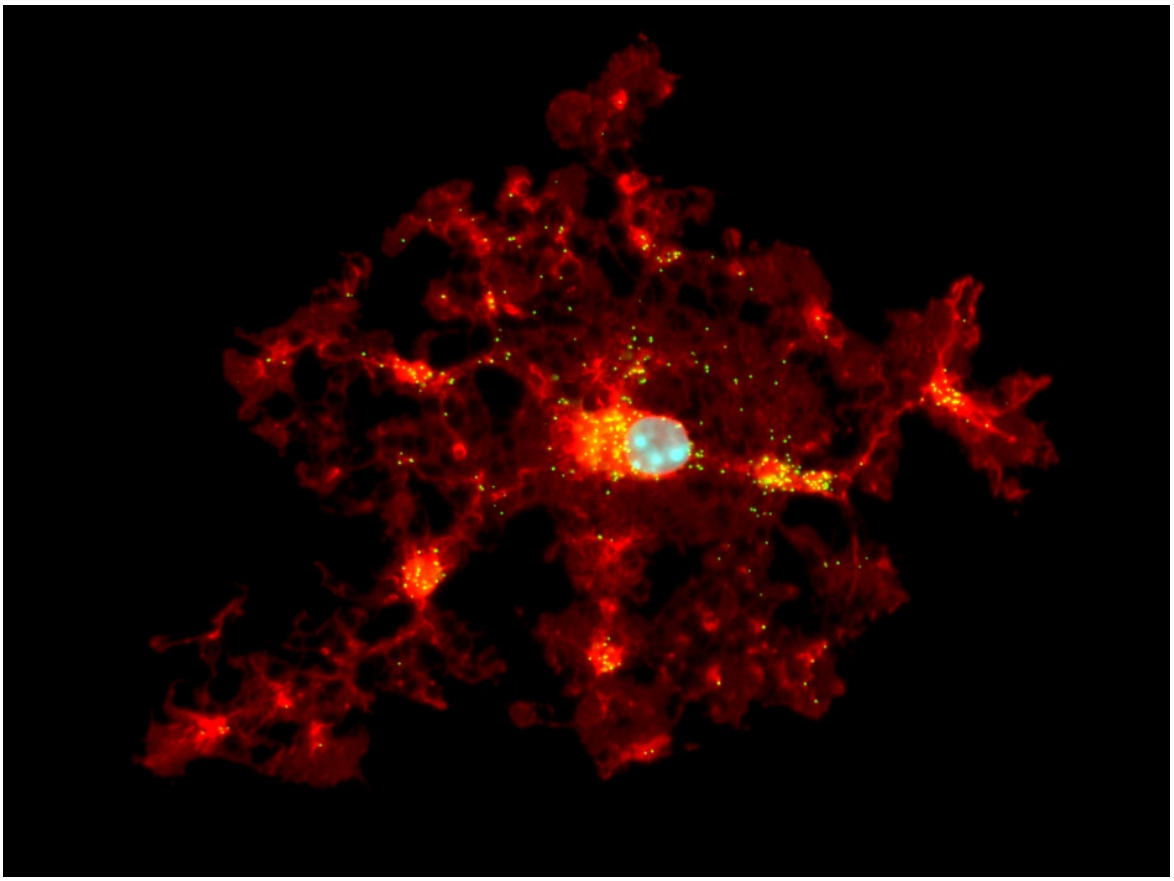


Image author: Colin Crawford. Image of an oligodendrocyte.

As the search for effective therapies for progressive MS continues there are several questions which remain to be fully answered – for example, whether myelin repair, even if successful, will completely prevent axonal damage, whether other measures that work directly on axons are also necessary, and at what stage in the disease a remyelinating therapy should be started. Further research is also needed to improve understanding of how ogliodendrocyte progenitor cells evolve into oligodendrocytes capable of protecting the myelin sheath. The use of animal models is essential, but that technique has some shortcomings, since remyelination capacity appears to be more limited in humans than in rodents. As two scientists have written, "Understanding the time course of remyelination in human MS, which will be different from in experimental models, will be critical here, but this is where we find another hurdle; remyelination in humans cannot yet be reliably measured directly".[6]

This point was underlined in a recent paper by Franklin and Ffrench-Constant.[7] The paper emphasised the importance of outcome measures that are sensitive enough to detect the regenerative effects of the drug under trial, and to ensure that a positive effect is not missed. In addition to MRI, the authors suggested that another imaging

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[6] E. Jolanda Munzel and Anna Williams, Promoting remyelination in multiple sclerosis – recent advances, Drugs 2017 73 (16) 2013

[7] Robin J. M. Franklin and Charles Ffrench-Constant, Regenerating CNS myelin – from mechanisms to experimental medicines, Nature Reviews Neuroscience, Vol 18, December 2017

strategy, positron emission tomography, may also be helpful in quantifying remyelination.

Once biomarkers for regeneration are in place, the two scientists wrote, "we predict that the 'bench-to-bedside-to-bench again' approach will lead to genuinely effective regenerative therapies that complement the immunomodulatory drugs developed over the past two decades for MS and thus provide effective treatments for progressive MS".

9. The funding challenge

Multiple sclerosis affects over 100,000 people in the UK and has to compete for attention and funds with other diseases which are far more prevalent, For example, there are thought to be about 800,000 people in the UK suffering from Alzheimer's disease. Dementia in its various forms has a higher public profile than MS. It was an initiative from David Cameron, then Prime Minister, which led to the creation in 2015 of the Dementia Discovery Fund, supported to the tune of £150m from the government, with further finance coming from charities, investment firms and pharmaceutical companies. Mental health is also high on the political agenda, attracting finance on an increasing scale from government and charitable funders.

MS, unlike cancer, is not a life-threatening disease, although it can shorten the life span of those who have it; some people affected by the relapsing/remitting form of the disease are able to lead relatively full lives for some years before the onset of more severe disabilities.

Partly for these reasons, MS has not been a high priority for the government agencies that fund medical research. Although the Medical Research Council funds fundamental and translational research in neurobiology, generating knowledge that is relevant for MS and other neurodegenerative diseases, it does not have a fund earmarked specifically for MS. The same is true of the Wellcome Trust. As for commercial sources of funding, the pharmaceutical industry, as noted earlier, has invested large sums in the development of anti-inflammatory medicines, but has generally steered clear of early-stage neurological research. In these circumstances MS researchers in academia have looked to philanthropy as an essential source of funding.

As a location for MS research the UK has some advantages and some disadvantages. Compared to the US, the most obvious disadvantage is that of scale. Government funding of medical research, principally through the National Institutes of Health, is at least ten times as much as in the UK; the number of US universities committed to biomedical research is much higher than in the UK. The US also has a larger pharmaceutical industry, and, thanks to the strength of the venture capital sector, early stage drug development firms have easier access to capital than their counterparts in the UK. Another distinctive feature of US biomedical research is that the philanthropy habit is more deeply entrenched than in the UK. Universities rely heavily on donations from wealthy alumni, and some of these are directed towards medical science.

Against that, the UK has some advantages of its own. One, perhaps not yet fully exploited, is the National Health Service. The NHS infrastructure, together with

support from its research arm, the NIHR, helps to make clinical trials cheaper, faster and better coordinated than in other countries. Links with the NHS have been strengthened by the MS Society's recently created Clinical Trials Network.
An interesting development in the UK this year has been the announcement that LifeArc (a charity that originated from the Medical Research Councils Technology Transfer arm) has monetised its royalties in Keytruda (a therapy owned by Merck) for over £1billion. The money positions LifeArc as one of the UK's largest medical research charities and will be invested in partnerships and approaches to advance UK health research[8].

The biggest single British asset is the high quality of biomedical science in British universities. As several examples mentioned in this paper have shown, UK-based scientists have made an outstanding contribution to some of the fundamental discoveries which have made possible a fuller understanding of MS.
That research has been supported, especially in fundamental science, by the Medical Research Council and the Wellcome Trust. But there are limits to what these two funders, covering as they do the full range of therapeutic areas, can do to support a specific, middle-ranking disease such as MS, and that is why disease-specific charitable funding is so important.

The MS Society – and the same is true of its US counterpart - plays a pivotal role in funding research programmes which, because of high risk or for other reasons, government agencies are unable or unwilling to support; there have been several occasions when a research project has been rejected by the MRC, leaving the MS Society to provide the initial funding, and then for the government agency to come in at a later stage. The MS Society also differs from other funders in its close and continuous interaction with patients, providing insights into which areas of research need to be given the highest priority.

The role of the Society is particularly important at the present time, when recent scientific advances have opened up new and highly promising avenues of research; in that sense MS is in a different situation from other neurodegenerative diseases. As the leading scientists see it, MS research has reached the foothills in a mountainous journey which should end in the development of truly transformative treatments for the disease. A big push now, involving scientists and clinicians at all stages of the drug development process, will take research higher up the mountain, bringing nearer the ultimate goal, which is to stop MS.

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[8] https://www.lifearc.org/lifearc-monetises-keytruda-royalty-interests-20052019/

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