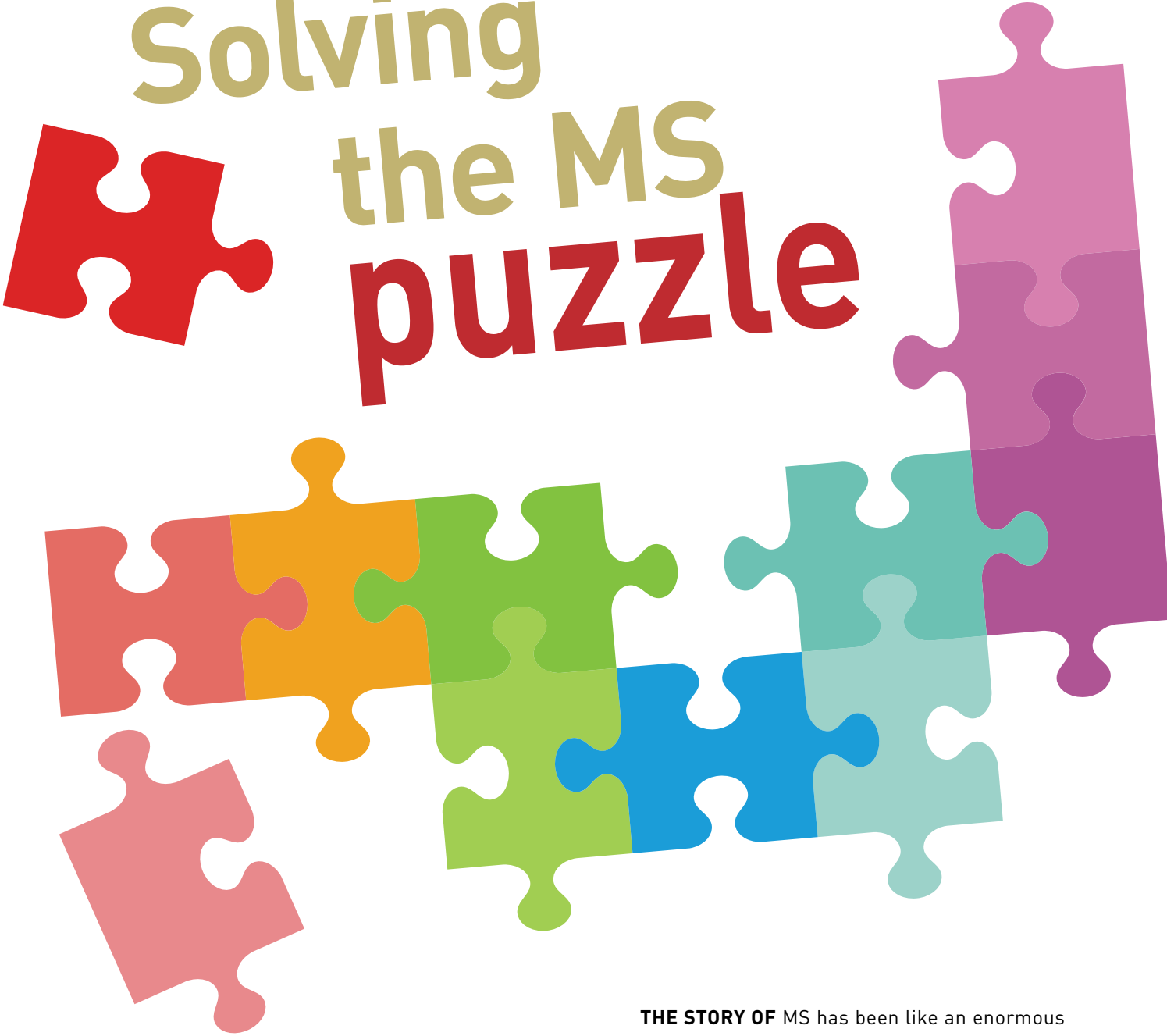


Solving the MS puzzle



MS research is the cornerstone of understanding MS, which will lead to better treatments, interventions and hopefully, one day, a cure. While medical research is the mainstay, quality of life research is now becoming a significant theme as it is seen to make an immediate impact on the person with MS. This article looks at the development of medical research and explores MS Ireland's research agenda.

THE STORY OF MS has been like an enormous jigsaw puzzle, with researchers around the world coming together to find different pieces. Of course, like any jigsaw some pieces have been more difficult to find than others, but gradually those pieces are coming together, and a fuller picture is being developed.

Dr Dhia Chandraratna, International Scientific and Medical Research Officer with the Multiple Sclerosis International Federation (MSIF), says all MS research is important for lots of reasons.

"It is estimated that about two million people around the world have MS. That doesn't sound like a high number but when you look at the social impact it's huge. The cost of MS is enormous, and we still don't know the cause of the disease. Therefore,

continued MS research is essential.”

The story of MS goes back centuries but it was Frenchman Jean-Martin Charcot (1825–1893) who became known as the father of neurology and first found the characteristic scars of MS.

In the 20th century a number of individuals added contributions to the study of MS, including Ian McDonald, Larry Jacobs and Douglas McAlpine, and our own Geoffrey Dean, who was awarded an honorary doctorate by UCD last year for his contribution to MS research. Prof Hans Lassman is also recognised as a pioneer in the fields of neuroimmunology, researching the immune surveillance of the nervous systems and mechanisms of demyelination. Each have helped add to the story of MS, and have helped paint a picture of MS today.

The use of MRI scans had a huge impact on the area of MS research, allowing researchers to track the disease in individuals. It confirmed that MS is often very active even when a person displays no symptoms.

The first successful scientific clinical trial of a treatment for MS took place in 1969, when a group of people who were having acute attacks of MS were given the steroid ACTH. Steroids are now a common treatment to ‘dampen’ the inflammation occurring during a relapse.

While some clinical trials did take place during the Seventies, it was in the Eighties that an explosion occurred. New discoveries were made, including the white blood cell type that can cause the damage to myelin in MS – the macrophage – and the first drug treating MS. During the Nineties a study of some 15,000 people with MS took place and for the first time it was clearly shown that there is a genetic determinant to acquiring MS.

However, one of the biggest success stories of the Nineties was the introduction of disease modifying drugs. The discovery of beta interferon 1b, beta interferon 1a and glatiramer acetate revolutionised the treatment of MS. These proteins form the basis of the four main disease modifying drugs: Betaferon, Avonex, Rebif and Copaxone.

In 2004, after much research, a fifth disease modifying drug, Tysabri, was introduced. Although it was taken off the market for a period due to safety concerns it is now a licensed drug for the treatment of relapsing-remitting MS.

In 2007, scientists identified two genes that may raise the risk of MS. In a large-scale study, international researchers scanned the entire human genome of over 12,000

‘People with MS and the neurologists treating them are acutely aware that there is still no cure for MS’

people for MS risk factors.

According to a report by MSIF, a total of €77m was spent by national societies on all forms of MS research in 2007, 56% of which was spent by the US MS Society and 11% by the Canadian society. The overall investment in research is much greater as the €77m does not include research performed by pharmaceuticals, universities or other private organisations.

Dr Chandraratna believes that the investment is proving worthwhile. “We have a much better understanding of the genetic and the environmental risks of MS, and have made inroads in terms of diagnosis.

“There has been lots of research into the repair and progression of the disease but it’s still important that we understand what’s causing it, so we can eventually find a cure; the two must run concurrently.”

Dr Una FitzGerald, a researcher at National University Ireland, Galway, echoes these sentiments: “People with MS and the neurologists treating them are acutely aware that there is still no cure for MS. Most therapies target the early relapsing-remitting phase of the disease. Symptomatic relief may be given to patients during the later chronic, degenerative phase, but researchers agree that these treatments generally do nothing to address the underlying biological signals.”

The challenges facing MS researchers remain considerable, according to Dr FitzGerald. For example, we still don’t know what triggers the switch from the relapsing-remitting phase of MS to the chronic degenerative phase.

“The notion that a cure for MS is possible would depend on a convergence of evidence from the scientific community, demonstrating a single trigger or causative agent in MS. The bulk of the scientific literature suggests that this isn’t the case. In other words, MS arises in different people, for different reasons,” says Dr FitzGerald. However, both Dr FitzGerald and Dr Chandraratna are optimistic that a cure will be found.

‘We have a much better understanding of the genetic and the environmental risks of MS, and have made inroads in terms of diagnosis’



A timeline of MS Research

1421	First documented case of MS: St Lidwina of Schiedam
1868	First correlation of MS clinical symptoms with central nervous system. The disease is named 'Sclerose en plaques' by Jean Martin Charcot
1869	First attempts to treat MS with gold chloride, zinc, sulphate, silver nitrate, strychnine and electrical stimulation (by Charcot)
1943	First detailed description of the composition of myelin
1963	First understanding of familial susceptibility to MS
1969	Completion of first controlled clinical trial
1982	First use of MRI to image lesions in living patients
1983	First report of temporary control of chronic-progressive MS with the immunosuppressive drug Cytoxan (widely disputed throughout decade)
1984	First modern documentation of cognitive problems in MS
1988	First demonstration, using MRI, that there is significant lesion activity in MS brain, even when there are no symptoms
1980s–1990s	Numerous clinical trials get under way
1993–2002	Discovery of the beta-interferons and glatiramer acetate which from the four common MS drugs, Copaxone, Rebif, Betaferon and Avonex
2003	First stem cell studies into MS carried out in Italy
2004	Introduction of Tysabri (it is withdrawn in 2004 but later re-introduced in 2006)
2007	Two genes associated with cause of MS found

Source: 1462–1990s – National Multiple Sclerosis Society, USA

Current research

THERE ARE THOUSANDS of MS research projects underway all around the world, so it would be impossible to give an overview of all of them. However, below you will find some information on treatments and developments that MS Ireland members have asked us about over the past year.

MS VACCINE

In MS the body's immune system attacks itself, causing inflammation. Researchers are exploring the possibility of using a vaccine to stop the body from doing this. Prof David Wraith and his team in the Experimental Pathology Department at the University of Bristol have successfully tested the vaccine on animal models. This year, the vaccine is due to be tested on 60 people with MS. Dr Wraith hopes that the research will be completed by 2012.

FINGOLIMOD

This is an oral tablet that works by binding to the surface of immune cells, trapping them in the lymph nodes and preventing them from attacking cells in the central nervous system. There is also some evidence to suggest it has a neuroprotective effect in the brain, which could be helpful in preventing or slowing down disability.

The manufacturers, Novartis Pharmaceuticals, hope to submit the drug for licensing by the end of 2009.

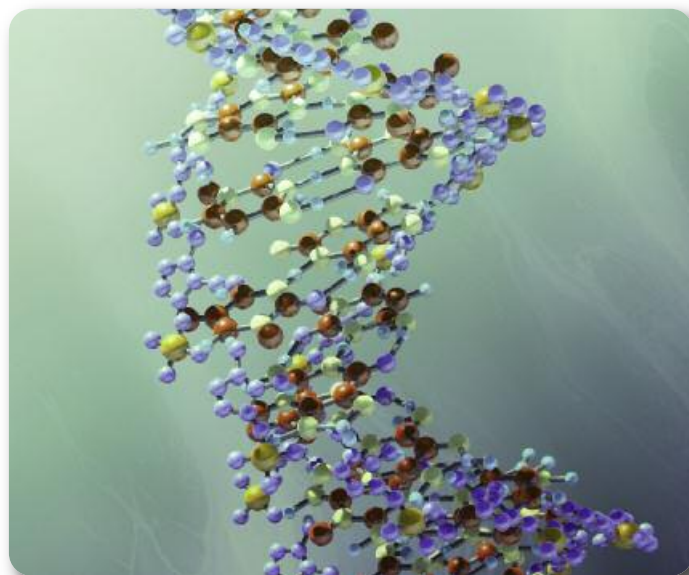
LOW DOSE NALTRAXONE (LDN)

LDN is a licensed drug used in treating AIDS. As MS, like AIDS, is an auto-immune disease, some suggest LDN may have some benefits for people with MS. Anecdotal evidence suggests that MRI lesions halt and some symptoms may be relived. However, there is no clinical evidence to prove LDN's efficacy.

An Italian study will begin trials on LDN in 2009.

ALEMTUZUMAB (PREVIOUSLY KNOWN AS CAMPATH)

A 2008 study showed that after three years 77% of low-dose Alemtuzumab and 84% of high-dose alemtuzumab receivers had experienced no relapses, compared with 52% of people receiving beta interferon 1a. The results also show that Alemtuzumab reduced the risk of sustained disability by 71%. It is now entering phase III trials. The final report is due in 2011.



CLADRIBINE

Cladribine is currently licensed to treat certain forms of leukaemia and appears to interfere with the behaviour and proliferation of cells of the immune system. It can be taken by injection but an oral version is proving more effective in trials. Results released from the two-year CLARITY study in January 2009 showed that Cladribine reduced relapses by 58% among the 1,326 people who took Cladribine tablets for 8–20 days during each year of the trial. Further studies will continue in 2009.

VITAMIN D

Previous studies with vitamin D have shown that Northern Europeans have an increased MS risk if they live in areas receiving less sunshine. This supports a direct link between deficiency in vitamin D, produced in the body through the action of sunlight, and increased risk of developing the condition. A number of trials are currently taking place, including one in St Vincents Hospital, Dublin.

STEM CELLS

On 30 January, The Lancet Neurology published the results of a Chicago trial involving stem cell transplantation in people with relapsing-remitting MS. The results of the study of around 20 people show that the treatment stopped progression of disability and could potentially reverse the damage caused by MS. Further research with larger numbers of people is underway.

To keep up to date with developments in research check out the research section on our website. The MSIF produces a weekly newsletter, 'Making Connections', outlining research developments. Sign up on its website: www.msif.org.

MS Ireland and research

MS IRELAND HAS a long tradition of supporting national and international research. Although modest by international comparisons, its investment represents a commitment by the Society to support, promote and prioritise research.

Since 1982 MS Ireland has invested over €1.2m in MS research. A number of key projects were funded exclusively or jointly by MS Ireland in that period. Much of the research focused on the pathogenesis of MS. (Pathogenesis refers to activities such as epidemiology, genetics, infection and DNA.) Funds have also been used to support international research. In 2003, for example, MS Ireland donated €30,000 to the Sylvie Lawrie Centre, a US MS research centre.

In 2007 MS Ireland implemented a strategic planning consultation process. Contributions were sought from members, the public, staff, sister organisations and others on the work and priorities of the Society. Research was identified as one of five priority areas for MS Ireland.

'Making It Happen' is MS Ireland's strategic plan until the end of 2011. In that plan the Society is allocating a minimum of €100,000 per annum to support and promote research. This, coupled with a commitment to improve information, collaboration and research funding, lays out clear guidelines for the research function of MS Ireland.

The communication of information relating to MS is vitally important to keep people affected by MS up to date with developments. The research section of the website has been revamped to make it more interactive and informative. The news

section contains updates on all research news and the 'participate in research' section gives information on the type of research people with MS can get involved in.

RESEARCH PROGRAMME 2008

MS Ireland's Medical Advisory and Research Committee advertised for submissions in early 2008. Seven suitable applications were sent for peer review. From these, MS Ireland allocated funding to two projects. An overview of each is on the next page.

MS Ireland has also supported a number of scientific conferences in Ireland and has provided some funding and support to St Vincent's Hospital for their research into epidemiology, vitamin D and quality of life.

Its biggest research project in 2008 is the ongoing 'Getting the Balance Right' programme. The nationwide exercise, activity and health promotion research programme for people with MS has enlisted over

1,000 people on the research part of the programme. The aim of the research is to assess the impact various physical interventions may have on people with MS. The interim results look positive, and the final report is due to be published at the end of the year.

RESEARCH PROGRAMME 2009

MS Ireland has just announced a call for applications for this year's fund. Three themes will be adopted:

- Basic and clinical science: Mechanisms of nerve damage, repair and protection
- Quality of life
- Service delivery.

MS Ireland hopes to work collaboratively with the Health Research Board, the Medical Research Charities Group and the MS Society in Northern Ireland. The application, selection and review process will take a few months but we will update you with progress.

MS Ireland's 'Solving the MS Puzzle'

MS Ireland is committed to supporting research but we need your help to do so. We need to raise €100,000 and more each year. We are asking all our friends and supporters to join our 'Solving the MS Puzzle' campaign and donate money to the fund. Research is the best way to find better treatments and interventions and will hopefully lead us to a cure for MS.

MS may be big puzzle, but we can all be part of the solution, one jigsaw piece at a time. Please support us today!

You can download your jigsaw piece at www.ms-society.ie or send your donation to MS Ireland Research Fund, MS Ireland, 80 Northumberland Road, Dublin 4.

Solving the MS puzzle

We can all be part of the solution.
One jigsaw piece at a time.

Promising projects



There are two projects currently funded by MS Ireland.

PROJECT 1: In-vitro assessment of the efficacy of the nootropic nefiracetam to enhance plasticity after experimental demyelination.

Dr Mark Pickering of the Conway Institute, University College Dublin

Difficulties with memory and cognition are problems experienced by many people with MS, and there is no specific treatment available for this effect of the condition at present. It is most likely that these problems occur when the loss of myelin affects a part of the brain known as the hippocampus.

In this project, a tissue culture model of the hippocampus will be treated to cause a loss of myelin, and the effect this has on the plasticity will be measured. Tissue will also then be treated with nefiracetam, a drug previously shown to protect memory, to investigate if this alleviates the effects of demyelination. If any benefits are shown in tissue culture with this drug, it may open the door for clinical investigation of this drug for people with MS.

PROJECT 2: Endoplasmic Reticulum as a component of neurodegeneration in MS grey matter lesions.

Dr Una FitzGerald, National Centre for Biomedical Engineering Science at the National University of Ireland, Galway

In a joint collaboration with Professor Stephen McQuaid of Queen's University, Belfast, Dr FitzGerald will examine the pathology of lesions occurring in the grey matter of MS patients, i.e. lesions in the outermost layers of the brain. This area of the brain is increasingly under the spotlight as it is known that lesions develop all over the grey matter and these may be responsible for chronic neurodegeneration occurring in the later stages of MS.

Many researchers believe that factors that trigger pathology in the grey matter are different to those that cause damage elsewhere.

To examine this, post-mortem material will be obtained from the UK MS tissue bank and the archives of the Belfast Bank. Tissue sections will be stained with appropriate antibodies and the pattern of staining analysed. This work will add to the body of knowledge surrounding how grey matter lesions are generated.

Irish research in action

UNA FITZGERALD has been a recipient of MS Ireland research funding. In 2005, Dr FitzGerald received 'seed' money from MS Ireland that helped to fund a -80 degree freezer. This is a secure freezer that the labs in Galway use to store precious MS tissue samples. Its presence has been crucial to the setting up of tissue studies there. This year she was awarded €15,000, which will allow expansion of the Endoplasmic Reticulum (ER) stress-related work, which follows on from a past collaboration with Dr Stephen McQuaid of Queen's University Belfast.

Dr FitzGerald got involved in MS research when she was working as a postdoctoral researcher in the laboratory of Professor Sue Barnet at the University of Glasgow.

"I was fortunate to spend over four years working on a brain cell called the oligodendrocyte. The oligodendrocyte produces myelin, the fatty substance that insulates nerves, accelerating the speed of nerve impulse conduction tenfold. It is this cell which fails or is under attack during MS.

"Having learned how oligodendrocyte life and death can be controlled in the lab, I developed a strong desire to understand how oligodendrocytes behave in the brain of MS patients. It was for this reason that I initiated the study of ER stress signalling in post-mortem brain samples."

For all researchers, Dr FitzGerald says financial support from organisations like MS Ireland is essential.

"Although Science Foundation Ireland and the Health Research Board have been providing significant levels of funding to researchers all over Ireland, competition for this money is fierce. The current economic climate is making many researchers very nervous and apprehensive about future sources of funding. Continuing support from charities such as MS Ireland may be the safety net that helps to maintain smaller research groups who have limited funding opportunities.

"Data from this research can be used as the basis for future grant applications, further emphasising the long-term impact of the financial support provided by MS Ireland," she says.