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INTERNATIONAL PROGRESSIVE MS ALLIANCE



INTRODUCTION

Friends,

Welcome to issue 5 of MS Research.

In this issue we have updates and summaries on two areas of research that attract a huge amount of interest from the MS community – vitamin D and stem cell therapy. Turn to **page 6** to read a review of what the latest research is saying about stem cells and **page 8** for an update from an Irish study into vitamin D.

We have a huge amount of information from the International Progressive MS Alliance on **pages 17 - 23**, including updates from some of the studies they have funded and a report from the Alliance's recent conference in Toronto, which was well-attended by Irish representatives! Many thanks to the researchers who attended for reporting back.

MS Ireland awarded a third Dean Medal Travel Bursary in 2017, and the winner, Dr Sravanthi Bandla, reports back from her trip to Glasgow on **page 9**. See **page 14** too for information about a study into a potential mindfulness intervention for MS, which you may be interested in participating in.

We are also very pleased to be able to report from our very successful second networking event for MS researchers (**pages 3 - 4**) and our very first ever Kiss Goodbye to MS ball, which raised valuable funds for MS Ireland's research fund (**page 5**). This is definitely an exciting time for research in MS Ireland!

We hope you enjoy the issue.



Harriet Doig

Information, Advocacy and Research Officer
Editor of MS Research and MS News



Professor Susan Coote

Chair of MS Ireland's Research Committee

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'MS Research' is the research eZine of MS Ireland. It exists to foster informed debate and comment about issues relating to MS research. The view of contributors are not necessarily those of the Society. No treatments or therapies should be attempted or products used without qualified medical or professional advice.

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World MS Day 2018 'Bringing Us Closer'



World MS Day 2018 took place on Wednesday 30 May and the theme this year was research, with the tagline 'Bringing Us Closer'. This tagline has a double meaning – firstly, research is bringing us ever closer to better treatments and ultimately a cure for MS. Secondly, MS Ireland and other MS organisations around the

world want to bring people with MS closer to the research and the researchers themselves. With this theme in mind, MS Ireland held two events to mark World MS Day, and also launched two new publications on the MS research landscape in Ireland.

Second Networking Event for MS researchers

Following on from the very successful networking event for MS researchers held last November, MS Ireland held a second networking event, organised in conjunction with the Royal College of Surgeons and Novartis. The purpose of this event was for researchers to be able to highlight their areas of current work and discuss opportunities for collaboration and sharing of resources and information.

Harriet Doig, Information, Advocacy and Research Officer with MS Ireland opened the event and highlighted the need for a research network in Ireland. Then Dr Claire McCoy from the Royal College of Surgeons spoke about her research into a molecule called MiR-155 which is believed to play a role in switching immune cells from a pro-inflammatory to an anti-inflammatory state and could thereby play a role in myelin repair. Dr Eric Downer from Trinity College Dublin then presented on his research projects into whether exercise and cannabinoids can be therapeutic targets in MS. Dr Downer also highlighted the importance of researchers focusing on techniques which may improve cognition and slow cognitive decline. Dr Una Fitzgerald from NUI Galway then presented on research techniques using a method called induced pluripotent stem cells (iPSC) which she has recently been studying in Australia and made a case for an MS research network to bring this technique to Ireland.

In the second session, Dr Denise Fitzgerald from Queen's University Belfast presented on her research into oligodendrocytes, the cells responsible for making myelin in the central nervous system. Dr Fitzgerald highlighted how the existence of a research network in Northern Ireland has

supported her work. Then, Jill Moffat, also from Queen's Belfast, spoke about how the research network in NI was developed and how it operates. Then Mary Fitzsimons from Beaumont Hospital talked about how electronic patient records were created for people with epilepsy under the Lighthouse Project and explained how lessons could be learned from this in attempting to do the same for MS. Finally, Alexis Donnelly, MS patient advocate and member of the International Progressive MS Alliance (IPMSA) Scientific Advisory Panel and MS Ireland's Research Committee, presented on the patient perspective on data and privacy and how researchers need to consider these issues carefully when working with patient data.



Some of the attendees from the networking event. Back row, left to right: Marie Fitzgibbon, Novartis; Dr Denise Fitzgerald, Queen's University Belfast; Chiara DeSanti, Royal College of Surgeons; Jill Moffat, Queen's University Belfast; Alexis Donnelly, IPMSA Scientific Advisory Panel member; Dr Eric Downer, Trinity College Dublin; Dr Una Fitzgerald, NUI Galway; Fiona Cullinane, Novartis; Dr Sinéad Hynes, NUI Galway. **Front row, left to right:** Ruth MacIver, Novartis; Dr Kate O'Brien, Genomics Medicines Ireland; Dr Claire McCoy, Royal College of Surgeons; Harriet Doig, MS Ireland.



The speakers from the networking event with the new report 'Making Ireland the Best Place to do Multiple Sclerosis Research'. Left to right: Jill Moffat, Dr Denise Fitzgerald, Alexis Donnelly, Harriet Doig, Dr Claire McCoy, Dr Una Fitzgerald, Dr Eric Downer.

RESEARCH EVENT REPORTS

MS Research Explored Bringing Us Closer

In the evening, a public event was held in Trinity College Dublin on the theme of 'Bringing Us Closer', co-organised by MS Ireland and Dr Eric Downer from Trinity. Dr Downer opened the event and welcomed everybody, before Harriet Doig from MS Ireland launched a new report 'Making Ireland the Best Place to do Multiple Sclerosis Research' (see right). Then Professor Orla Hardiman, Consultant Neurologist, presented on how clinical research is bringing us closer to understanding MS. She particularly emphasised the need to develop new ways of measuring the impact of MS, aside from the EDSS scale. Next up, Joan Jordan, MS advocate and MS & Me blogger, spoke about the importance of patients and researchers working closer together to better inform and support each other, at every stage of the research process. Joan highlighted a genomics research project that is happening in Ireland right now and is an easy way for people with MS to participate in research. Finally, Dr Claire McCoy from the Royal College of Surgeons in Ireland described what her research team is doing to bring us closer to treatments that may repair some of the damage done by MS. The event then finished with a question and answer session.



Dr Eric Downer from Trinity College opens the event

Research publications

MS Ireland, in conjunction with Novartis, launched a new report, 'Making Ireland the Best Place to Do Multiple Sclerosis Research' at the MS Research Explored event. The report aims to support researchers and provide people with MS and the public with a better understanding of the research process and ongoing research. Some of the recommendations include the establishment of an MS Research Community, improved data and information sharing, greater involvement of people living with MS, potential funding models, and improved dissemination of research findings. The community will help overcome obstacles to research such as gathering samples, establishing a biobank and a patient register. This report was produced following the first networking event for MS researchers held in November 2017, and also includes an analysis of the Research Priorities Survey conducted by MS Ireland last year.



Harriet Doig, Information, Advocacy and Research Officer with MS Ireland, launches the report.

MS Ireland and Novartis also published a booklet called 'Insight Into Ongoing Multiple Sclerosis Research in Ireland', with a selection of abstracts (research summaries) from ongoing MS research projects in Ireland. Topics covered include physiotherapy, falls prevention, cannabis and MS, myelin repair and occupational therapy.

Both publications are available to download from

www.ms-society.ie/pages/living-with-ms/information-centre/our-publications

For hard copies please email Harriet Doig at harrietd@ms-society.ie

Kiss Goodbye to MS Ball



The inaugural Kiss Goodbye to MS Ball was held at The Morrison Hotel Dublin on 26 May 2018. With 140 guests it was a fabulous night raising over €15.5k and putting the Kiss Goodbye to MS campaign firmly on the map in Ireland. The culmination of a month long campaign, the aim of the ball was to raise as much as possible for local and international research projects and services.

Speakers on the night included our own Aoife Kirwin, who spoke brilliantly about what MS research means to her and other young people with MS and our CEO Ava Battles who spoke about her thoughts on the future in relation to MS research.

Our MC on the night was Diana Bunici who did a fantastic job of running the show and was very encouraging when it came to asking people to dig deep for our raffle.

The table raffle and Ring-a-Ruby were a great hit and our silent auction boasted items such as a luxury glamping experience for eight people, signed rugby jerseys and a pair of bicycles kindly donated by our corporate partner SAP. All incredible prizes, which helped us raise much needed funds. The item that caused the biggest stir and a ferocious bidding war however, was the walk-on part on Fair City. Keep an eye out for Colm Murphy – next big thing – you heard it here first!

The Luna boys provided the entertainment, ensuring everyone was up out of their seats and dancing for the night.

Huge shout out and thanks has to go to the KG TMS Ball committee, specifically Helen Murray and Niamh McCarron, who volunteered their time and were key in getting bums on seats and hunting down raffle prizes.

All in all a successful first event with great feedback and we hope to do the same next year on a slightly larger scale.



Stem cells and MS

What does the research say?

By **Harriet Doig** – Information, Advocacy and Research Officer



Few topics attract as much attention in the MS community as that of stem cell treatment. The media regularly features stories about people who have either had the treatment or are fundraising to try and access it. MS Ireland often receives enquiries about when stem cell treatment will be made available to people with MS in Ireland. But what is stem cell treatment exactly, and what is the latest research into this exciting potential treatment saying?

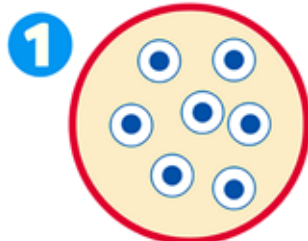
What is stem cell treatment for MS – what does it involve and how does it work?

Stem cells are a type of cell that have the potential to transform into many other types of 'specialised' cells that perform specific functions in the body. Stem cells have been investigated by scientists as potential treatments for various diseases, including heart disease, diabetes and stroke.

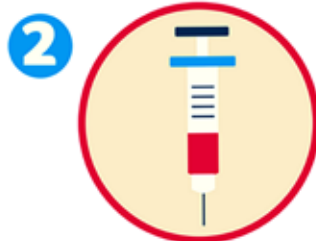
There are currently three main types of stem cell treatments being investigated as potential therapies for MS. They are:

- Autologous Hematopoietic Stem Cell Transplantation (AHSCT) – this type of stem cell therapy was featured in a BBC Panorama documentary in January 2016 and has generated a large amount of media attention since. It has been described as a potential 'cure' for

Six stages of stem cell therapy



1 Stem cells moved from bone marrow to blood stream using chemotherapy and synthetic growth factor



2 Machine collects blood and separates out stem cells



3 Stem cells frozen ready to return to body later



4 More chemotherapy used to fully or partially wipe out bone marrow and immune system



5 Stem cells returned to body using a drip



6 Body recovers over a period of 3-6 months, sometimes longer

mstrust.org.uk/stemcells

MS by the media, although clinicians and other expert groups advised caution. It involves extracting the person's stem cells from their bone marrow or blood, giving them chemotherapy to wipe out their existing immune system and then reintroducing the stem cells to regrow or 'reset' their immune system. Various international trials are currently ongoing in AHSCT. In the United Kingdom, a small number of centres have begun to provide it on the NHS under specific circumstances to a very small number of people

- Mesenchymal Stem Cell Transplantation (MSCT) – this involves a type of stem cell that is usually taken from bone marrow, skin and fat tissue. Some small-scale trials have suggested they can help stimulate re-myelination of nerve cells
- Repairing myelin damage – some scientists are investigating specialist stem cells in the brain that can generate myelin-producing cells

AHSCT is the type of treatment that is most commonly used in MS and has the most research behind it. Centres offering stem cell treatment abroad, which many people with MS engage in fundraising to try and access, will be offering this type of treatment. The infographic on the previous page shows how AHSCT is thought to work in MS.

What does the research say?

AHSCT has been studied as a potential treatment for MS since 1997. The main treatment goals that have been studied in trials are to prevent increases in disability levels, induce prolonged medication-free periods and potentially to improve neurological functioning. A range of studies to date have shown that AHSCT can be effective in inducing remission in people with severe MS, can reduce lesions, can result in improvement in neurological symptoms for people with relapsing-remitting MS and can halt central nervous system inflammation for a period of time. Whilst all these findings have been very promising, there has been a lack of evidence to date on the long-term effects of AHSCT, and whether improvements are maintained over time (Muraro et al, 2017).

A study by Muraro et al, published at the end of 2017, conducted a retrospective cohort study whereby 281 patients who had received AHSCT between 1995 and 2006 were examined to see if improvements had been maintained. The researchers found that "nearly half survived free from neurological progression for 5 years after transplantation". The authors also noted that those who were younger, had relapsing MS as opposed to progressive, had failed on no more than two immunotherapies previously and

had lower disability levels at the outset were more likely to have positive outcomes. The mortality rate of participants was 2.8%, reflecting the risky nature of this treatment. The authors concluded that these results are very promising and that further trials are needed to test the safety and effectiveness of AHSCT against existing DMT treatments over long periods of time.

In summary, current research into AHSCT as a potential treatment for MS suggest that it may be very effective for a particular cohort of patients – those who are younger and have a very active form of relapsing MS. More research is needed to determine whether AHSCT could be similarly effective for other MS patient groups. We also still do not know how safe or effective AHSCT is compared to existing treatments. Consultant Neurologist Professor Gavin Giovannoni, from Barts Hospital in London, summarises the state of the current research as follows on his blog:

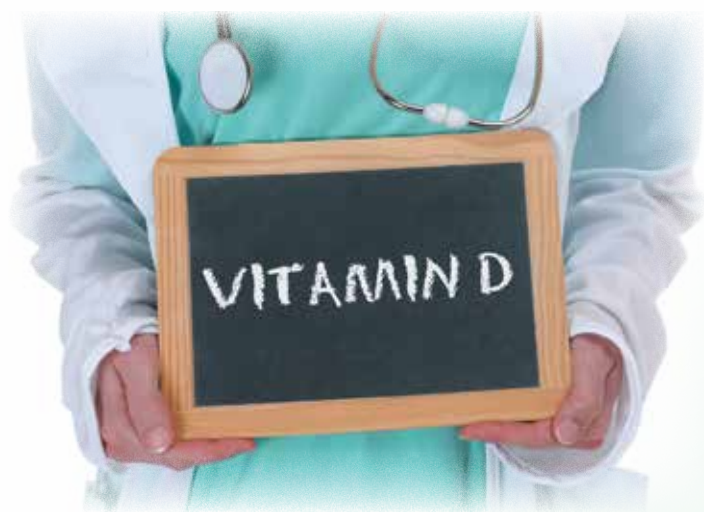
"More and more HSCT procedures (aka bone marrow transplants) are being performed for MS around the world than ever before. Currently, we lack convincing data on the conditioning regimen that best balances efficacy and safety. Patient selection is key and HSCT should be considered as an early option in aggressive cases of inflammatory MS, rather than as salvage therapy in later disease"

MS Ireland's briefing document on stem cell therapy, which contains information for those thinking of traveling abroad for this treatment, can be accessed here:

www.ms-society.ie/pages/living-with-ms/information-centre/our-publications



New Irish study into Vitamin D published



Vitamin D, sometimes called the 'sunshine vitamin' as it occurs naturally in sunlight as well as in various foods, has attracted much attention both for its role in possibly preventing MS and as a potential treatment option. Scientists have speculated that low levels of Vitamin D may contribute to an increased risk of someone developing MS, as higher levels of MS are observed in countries that are further from the equator and therefore receive less sunshine.

Although the exact nature of the link between Vitamin D and MS has never been identified, many studies have investigated whether or not it could be used to prevent relapses and slow disease progression. A number of studies have shown that it plays a role in moderating immune responses and reduces the inflammatory response in autoimmune diseases (Laursen et al, 2016; Guzman de la Fuente et al, 2015; Waubant et al, 2015; Alharbi, 2015, Thouvenot et al, 2014). Other studies have compared patients who were given Vitamin D supplementation alongside a DMT with patients who were given a DMT only and found that Vitamin D may help to reduce both lesions and relapses (Muris et al, 2016; Camu et al, 2016).

A new Irish study, led by Dr Karen O'Connell from St Vincent's Hospital and published in the *Multiple Sclerosis Journal* at the end of 2017, looked at whether treatment with Vitamin D would have an impact on inflammation and disease activity in people with clinically isolated syndrome (a term used to describe the first 'attack' of MS symptoms, before a definite diagnosis of MS is made).

Methods

49 people with clinically isolate syndrome and 41 healthy people acting as a control group were randomly assigned to receive either 5,000 or 10,000 IU of Vitamin D daily, or to receive a placebo. The study was double-blinded, meaning that neither the participants nor the treating doctors knew which each participant was getting so as to avoid bias. The study lasted for 24 weeks.

Results

The study found that Vitamin D supplementation was safe and well-tolerated by participants. However, no significant differences were noted in inflammatory activity between the placebo group and those receiving Vitamin D. A slightly higher level of disease freedom was seen in those taking Vitamin D than in those taking placebo, but this was not significant.

Conclusions

This may seem like bad news for Vitamin D as a treatment option, however the researchers noted that the study may have been too short to detect a treatment effect of Vitamin D supplementation and that further, longer studies in this area are needed. They also noted that Vitamin D may only have strong therapeutic effects when used in combination with disease modifying therapies. Another interesting comment by the researchers was that it is possible our existing theories about the relationship between Vitamin D and MS are wrong – perhaps it is not lack of Vitamin D itself which can increase risk of MS, but maybe some other effect of lack of sunlight exposure and low Vitamin D levels are only a marker for this?

Study reference:

O'Connell, K., Sulaimani, J., Basdeo, S. A., Kinsella, K., Jordan, S., Kenny, O., . . . Hutchinson, M. (2017). Effects of vitamin D3 in clinically isolated syndrome and healthy control participants: A double-blind randomised controlled trial. *Multiple Sclerosis Journal – Experimental, Translational and Clinical*, 3(3), 205521731772729. doi:10.1177/2055217317727296

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Thouvenot, E., Orsini, M., Daures, J. ., & Camu, W. (2014). Vitamin D is associated with degree of disability in patients with fully ambulatory relapsing-remitting multiple sclerosis. *European Journal of Neurology*, 22(3), 564–569. doi:10.1111/ene.12617

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2017 Dean Medal Winner

Dr Sravanthi Bandla reports from the University of Glasgow



Since February 2018, I have been working as a visiting researcher at University of Glasgow, Institute of Infection, Immunity and Inflammation. Based in the laboratory of Professor Christopher Linington, I am investigating the effect of recombinant human B-cell immunoglobulin

binding protein (BIP) and a chemical inducer of BIP (BIX) on myelination. The idea for this study arose from previous research carried out in my supervisor Dr Una FitzGerald's research group at NUI Galway, which had demonstrated the significant upregulation of BIP in normal myelination in neonatal rat brain (Naughton et al, 2015, International Journal of Developmental Neuroscience, 47:347-360). In order to determine whether or not BIP is enhancing myelination, we needed to test it using in vitro models of myelination.

The myelinating cultures that are used by the Linington lab are developed from rodent spinal cord explants that are plated onto monolayers of astrocytes. They contain all of the cell types of the spinal cord, such as neurons, oligodendrocytes, microglia, astrocytes and progenitor cells (see Figure 1). After 18 days, myelination starts and can be tracked by dual immunocytochemistry detecting the expression of myelin protein and axonal neurofilament. The possible effect of BIP or BIX on the viability of different cell populations is also being assessed.

Our preliminary results show that BIX has an impact on myelination, oligodendrocytes and microglia. To further investigate this effect, we are planning to perform RNA sequencing on BIX-treated and control samples and we look forward to providing an update once these studies are completed.

I would like to thank all the funding bodies including the MS Ireland Dean Medal Award, the Thomas Crawford Hayes Trust and the Foundation Office of NUIG. I am also grateful to staff at the University of the Glasgow, who have supported this fantastic opportunity, which is helping me to expand my knowledge and skills in the important field of MS research.

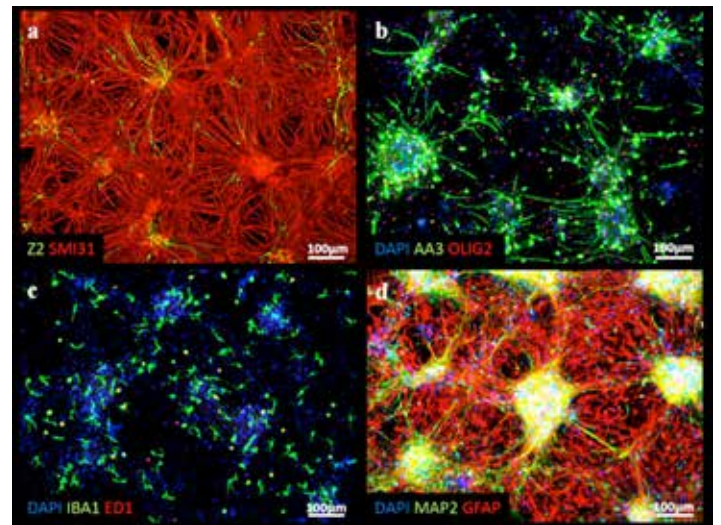


Figure 1: Myelinating cultures on an astrocyte monolayer. **a)** SMI31; staining in red highlights neurons, while, Z2 staining shows neurites; **b)** nuclei; are stained blue and staining of AA3 reveals the myelin sheath. Other cells within the oligodendrocyte lineage are stained red using an antibody to transcription factor Olig2; **c)** nuclei; are stained blue and green cells are positive for IBA1, a marker of microglia. The cells stained red are making the protein ED1, a marker of activated microglia; **d)** cell nuclei; are blue, while MAP-2-expression neurons are shown in red and astrocytes are stained green using an antibody to GFAP.



Dean Medal Travel Bursary



Above: Dr Geoffrey Dean

Left: Dr Bandla receives the Dean medal cheque from Aidan Larkin, Services Development Manager, MS Ireland.

Geoffrey Dean was an internationally regarded epidemiologist who in several seminal studies established the importance of environmental influences on the pathogenesis of multiple sclerosis. His work continues to have relevance to this day. Active in research up to his death, Dr Dean published a total of 120 papers during his illustrious career. His last was published in 2008 at the age of eighty-nine.

The Dean Medal award, established in 2010, is intended to enable new MS researchers to travel to centres of excellence to enhance their understanding and knowledge of MS. MS Ireland wishes to encourage the dynamic and innovative work so keenly exemplified by Dr Geoffrey Dean. MS Ireland makes an award of €2,000 every two years.

MS Ireland would like to thank Merck Serono for their kind sponsorship of the 2017, 2019 and 2021 Dean Medals.

MS patient registries – what are they and why are they important?

By **Harriet Doig** – Information, Advocacy and Research Officer



What are patient registries?

A patient registry is defined as a “framework for collecting and analysing data on a particular disease that aims to cover the whole national population of that disease” (MRCG & IPPOSI, 2011, p.5). Individual patients are recorded only once in a registry and are not duplicated.

Within the framework of the concept of registries, four different sub-types or categories have been identified as follows (MRCG & IPPOSI, 2011, p.5):

- **Patient Registry** – the ‘gold standard’ in the registries framework is a well-resourced national patient registry that captures a wide variety of high-quality data and interacts with registries in other countries to contribute to an international body of research on a particular disease. A properly resourced registry will generally employ dedicated staff to capture and analyse the data. Data from a registry is not generally used to influence the treatment of individual patients, but rather exists to inform research into treatments and therapies, and plan for current and future service delivery to meet the needs of a particular patient population
- **Patient/Electronic Health Register** – these are generally developed and operated primarily by clinicians as a means for monitoring and managing individual patients’ conditions. As such, whilst they can capture very high quality data, they tend to contribute less to overall policy and practice in relation to the management of particular diseases than a full registry. Patient/Electronic Health Registers can be important building blocks on which a full registry can be developed

- **Patient databases** – these are smaller data sets of particular patient groups, such as those held by patient organisations to inform the development and delivery of their services, and data sets held by pharmaceutical companies to monitor the efficacy and safety of particular medications
- **Electronic Patient Records** (hospital level) – these are records held by individual hospitals of particular patient populations attending their clinics. Currently in Ireland, Electronic Patient Records are optional add-ons to traditional paper-based recording and are not operated consistently between hospitals and disease groups. It is widely recognised that, if developed and implemented properly, Electronic Patient Records form the most useful basis from which to transfer data to a national Patient Registry.

Why are patient registries important?

The Medical Research Charities Group (MRCG) and the Irish Platform for Patient Organisations, Science and Industry (IPPOSI) released a report in 2011 entitled ‘Towards a National Strategy for Patient Registries in Ireland: Considerations for Government’. This report states that:

“Patient Registries should be central to the planning, delivery and review of health care in Ireland as they provide data and analysis to:

- Observe the trends and course of a disease
- Enable the more effective use of limited resources
- Inform clinical and policy decision-making at a national and institutional level
- Illuminate practice patterns and variations in practice patterns
- Assess clinical outcomes: effectiveness and safety
- Explore the impact of the disease and treatment on patients, including health-related quality of life and other patient-reported outcomes
- Assess health economic inputs, outcomes and impact”

A 2012 report from the MRCG identified the following benefits of patient registries (MRCG, 2012, pp.12-24):

- The facilitation of multi-disciplinary working and integrated care for patients with complex needs. Registries can also help with the development of funding models whereby ‘money follows the patient’
- Improvement of management of chronic diseases and reduction in unnecessary hospitalisations, thus allowing more efficient use of healthcare resources
- Improvement of relationships and communications between healthcare professionals, e.g. emergency department staff and consultants

- Improvement in patient outcomes – specific examples given in the report include two diabetes registries and two stroke registries in the US which recorded notable improvements in patient outcomes since the development of the registries
- Allowing physicians with a particular clinical interest to network with each other, share best practice and contribute to research
- Examining disease trends in populations over time including incidence rates and prognoses. This can be extremely important for research, including helping to generate hypotheses about possible causes of diseases like MS
- Supporting research into genetic susceptibility to diseases and helping to identify genetic markers that may increase or decrease the risk of developing diseases like MS
- Supporting surveillance of the efficacy and safety of medications
- Helping identify gaps in service provision, evaluate service delivery and plan for the future delivery of services
- Supporting the health technology assessment process by providing data on the cost effectiveness of treatments
- Providing a source of participants for clinical trials and data to calculate sample sizes for trials
- Examining the translation of information from randomised controlled trials into clinical practice

Additionally, patient education programmes such as EUPATI (European Patients' Academy for Therapeutic Innovation) report that registries can be a positive force in empowering patients to be involved in their disease management.

Patient registries in Ireland

Ireland currently lacks a strategic framework for patient registries. Registries for some disease groups exist (such as cancer and cystic fibrosis), and others are in the process of being established (such as a dementia registry), but there is no national oversight and no single body within the Health Service Executive (HSE) that has responsibility for managing, funding or regulating registries (IPPOSI, 2015).

Current challenges to the development of patient registries in Ireland include a lack of a specific funding mechanism to set up and sustain registries, lack of necessary IT infrastructure, concerns regarding impact on clinicians' time for updating records, lack of standardisation of data captured in existing data sets, the lack of a single centralised body to which researchers and data collectors can apply to for ethical approval and a general lack of awareness of the importance of registries among key stakeholders including Government organisations and patient organisations (MRCG & IPPOSI, 2011; IPPOSI, 2015).

A recent report by IPPOSI highlighted that lack of registries is a major problem in terms of attracting clinical trials to Ireland (2015, p.12):

“Without good quality data available, Ireland is not on the map for industry-led clinical trials. If industry cannot identify and track patients and their outcomes, they simply will not conduct clinical trials in Ireland”.

There is currently no national registry for multiple sclerosis in Ireland. Electronic Patient Records for people with MS exist in some individual hospitals and pharmaceutical companies hold databases on particular MS medications. Multiple Sclerosis Ireland, as the only national MS patient organisation, holds a non-medical database on people with MS who interact with the organisation and use their services (MS Ireland, 2015).

The National Clinical Programme for Neurology Model of care, launched in September 2016, also references the need to establish an MS registry (HSE, 2016, p.177):

“To support the effective and efficient management of DMT's the Neurology Programme would support the development of a national treatment registry for all MS patients in Ireland. The aim of such a registry would be to encourage regular reviews of MS patients where their clinical progress is assessed”.

Multiple sclerosis registries internationally

Multiple sclerosis registries exist in a number of countries internationally and there are now some collaborative efforts underway to conduct cross-border data collection. For example, the European Multiple Sclerosis Platform's European Register for Multiple Sclerosis project (EUREMS) ran from 2011 to 2014 and collected data from MS registries in 12 European countries. Data collected from EUREMS fuelled four studies on incidence of MS, disease modifying treatment use and efficacy and the economic burden of MS (EMSP, 2014). Similarly, the Big Multiple Sclerosis Data network includes MS registries from a number of countries and allows researchers to pool data and collaborate on research projects (European Medicines Agency, 2017).

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The Genomic Basis of Multiple Sclerosis in Ireland

By Kate O'Brien, PhD – MS Programme Manager, Genomics Medicine Ireland

Overview of the study

Genomics Medicine Ireland (GMI) is running a nationwide study examining the genetic contribution to Multiple Sclerosis (MS). The study aims to identify patterns in genes in people with MS so as to develop new diagnostic tools, treatments, and better our understanding of disease progression. Currently, four hospital sites are recruiting volunteers with MS:

1. St Vincent's University Hospital, Dublin led by Prof. Chris McGuigan
2. Cork University Hospital led by Dr Brian Sweeney
3. Tallaght Hospital, Dublin led by Drs Sinead Murphy and Richard Walsh
4. Altnagelvin Hospital, Derry with Dr Fergal McVerry run through the Clinical Translational Research and Innovation Centre (C-TRIC)



The study is expanding across the island of Ireland and has ethical approval at University Hospital Limerick and Mercy University Hospital, Cork. In addition, ethics applications have been submitted to Sligo and Letterkenny University Hospitals.

If you have MS and are interested in volunteering to take part in the study, please contact your consultant neurologist and register your interest at <http://genomicsmed.ie/interest-in-ms-study/>.

Exploring Advances in Multiple Sclerosis

Summer Research Forum

Friday, 6th July, 2018, 08.30 – 16.00
Royal College of Physicians of Ireland, Dublin

Keynote speakers:

Professor Stephen Sawcer,
University of Cambridge

Dr Howard Jacob,
AbbVie Inc.

Dr Sherman Jia,
University of California, San Francisco (UCSF)



For full agenda and to register visit:
<http://genomicsmed.ie/summer-ms-forum/>

Background

The role of genetics in MS has been widely accepted since the human leukocyte antigen (HLA) class II region was first identified as a “risk” region in 1972⁽¹⁾. These genes produce proteins that are located on the cell surface of immune cells. One of the largest MS genetic screens has since identified 52-different genomic regions of interest, where it is proposed that disease-causing or risk variants are present. In that first genome-wide association study (GWAS), the interleukin-7 receptor alpha and interleukin-2 receptor alpha genes were identified as being strongly associated with MS⁽²⁾. More recently, the International Multiple Sclerosis Consortium (IMSGC) also identified an additional 48 susceptibility variants, bringing the total number of MS risk variants up to 110⁽³⁾.

The development of next-generation sequencing techniques has resulted in the ability to track down additional disease-causing variants in individual patients. Recent studies have begun to identify some of the genetic factors that can predispose an individual to MS. One example is the identification of a variant in the CYP27B1 gene (associated with vitamin D metabolism)⁽⁴⁾. However, further variants remain to be discovered.

We are further investigating the totality of genetic causes of MS that ultimately should lead to better diagnostics and therapeutics. Specifically, our investigations are studying the underlying genetic changes using whole genome sequencing techniques to identify both common and rare variants associated with MS.

1. Jersild C, et al. HL-A antigens and multiple sclerosis. *Lancet*. 1972;1:1240-1
2. Hafler DA et al. Risk alleles for multiple sclerosis identified by genomewide study. *N Engl J Med*. 2007;357:851-62
3. International Multiple Sclerosis Consortium (IMSGC), et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet*.2013;45:1353-60.
4. Ramagopalan SV, et al. Rare variants in the CYP27B1 gene are associated with multiple sclerosis. *Ann Neurol*. 2011;70:881-6.

President Higgins Presents Future Research Leaders Award to Dr Claire McCoy

President of Ireland, Michael D. Higgins, honoured Dr Claire McCoy with the Science Foundation Ireland - President of Ireland Future Research Leaders Award at a special ceremony in Áras an Uachtaráin on the 25 January 2018. Claire was among one of five recipients for this prestigious award and receives a total of €1.5m for her research focused on the immune system in multiple sclerosis.

The research of Dr Claire McCoy is based in the Molecular and Cellular Therapeutics Department at the Royal College of Surgeons Ireland. Her research is focused on significantly advancing current therapeutic strategies for the treatment of multiple sclerosis (MS), where Ireland has the highest global incidence. Speaking of her award, she said "Obtaining this SFI Future Research Leaders award is the highlight of my career to-date. Not only does it enable me to lead a growing research team, it will also significantly contribute to the cutting-edge research being conducted at RCSI. Most importantly, it helps to place Ireland at the forefront of multiple sclerosis research worldwide."

Congratulating the awardees at the event in Áras an Uachtaráin President Michael D. Higgins said, "I am delighted to receive the wonderful scientists who have been granted SFI Future Research Leaders Awards. This award celebrates their scientific achievements and significant dedication. Their work is evidence of the ongoing world-class research being carried out in Ireland, positioning us as a global leader for scientific excellence."

Congratulating the awardees, Prof Mark Ferguson, Director General of Science Foundation Ireland and Chief Scientific Adviser to the Government of Ireland, said "The President of Ireland Future Research Leaders Award is designed to attract to Ireland outstanding new and emerging research talent. In supporting these talented and innovative individuals, we are delighted to recognise early career researchers who have already displayed exceptional leadership potential at the frontiers of knowledge. The development of leadership skills in these researchers early in their careers is vital to ensure research and innovation in Ireland continues to progress. Our investment highlights the importance that Science Foundation Ireland places on supporting all stages of academic careers, and on the attraction and retention of star researchers."

Dr McCoy leads a research team of six scientists in RCSI, Dublin. She has been the recipient of major national and international awards from Science Foundation Ireland, the Irish Research Council, Marie Curie, the Australian National Health and Medical Research Council and the Multiple Sclerosis Research Australia. She has published >21 highly cited and seminal publications in Nature Immunology, Nucleic Acid Research, Journal of Leukocyte Biology and Journal of Biological Chemistry. To find out more about her research and upcoming job opportunities go to: <http://pi.rcsi.ie/pi/clairemccoy/index.asp>



Pictured (L-R): Professor Mark Ferguson, Director General of Science Foundation Ireland and Chief Scientific Adviser to the Government of Ireland; President Michael D. Higgins; Dr Claire McCoy (MCT dept, RCSI), Dr Francis O'Keefe (Claire's Husband).

Researchers from Queen's University Belfast shortlisted for MS Society UK's Research of the Year Award

The award recognizes a world-class research project, based in the UK, working towards stopping MS. Researchers Yvonne Dombrowski, Denise Fitzgerald and colleagues have been nominated for their project entitled "Regulatory T-Cells promote myelin regeneration in the central nervous system".

In MS, the immune system attacks the myelin coating that protects our nerves. These researchers investigated whether other parts of the immune system also play a role in repairing myelin. They showed for the first time that a group of immune cells, called regulatory T-Cells, helps to grow new myelin in mice. Mice without regulatory T-cells showed less myelin repair than mice with regulatory T-Cells. These results open up a new area for the development of treatments for MS.

Mindfulness for MS Research Conducted by the Centre for Pain Research at NUI Galway

By Bevin Malone MSc, Laura O'Connor MSc.IT & Christopher Dwyer PhD



been described as paying attention in a particular way in the present moment, on purpose, non-judgementally, which can potentially promote additional helpful coping responses. Online-based interventions have emerged as a popular platform for such practice, as many people have access to the internet and, perhaps more importantly, because people can log in and practice mindfulness from the safety and comfort of their own home, without needing to schedule appointments and meet face-to-face with an instructor.

Multiple Sclerosis (MS) is a lifelong disease of the nervous system including the brain, spinal cord and optic nerves, affecting 2.3 million people worldwide with 9,000 of those living in Ireland. Symptoms of MS range from mild sensory problems to severe disability. The cause of MS has not been identified and, currently, there is no cure.

Diagnosis of MS generally occurs between early and mid-adulthood - a time where family and career plays a major role in an individual's life. MS can also have a major impact on people's social relationships, lifestyle and careers due to mobility issues, sexual dysfunction and difficulty in finding/maintaining employment. As a result of these environmental and physical stressors, the psychological well-being of those living with MS is of utmost importance as rates of depression, anxiety and fatigue are distinctly high among this population.

MS affects each individual differently; however, understanding how MS impacts people both physically and psychologically; and how they use the supports available to them plays a role in coping strategies for overcoming symptoms. In recent years, mindfulness has emerged as a popular strategy for psychological well-being and research has shown that mindfulness-based psychological interventions can be used to help ease MS-related symptoms, including fatigue and anxiety. Mindfulness refers to the observation and non-judgmental awareness of ongoing thought processes; and the approach has

The Centre for Pain Research at the National University of Ireland, Galway is developing one such online mindfulness programme for people living with Primary or Secondary Progressive MS (i.e. PPMS or SPMS). The programme consists of eight weekly sessions, in which participants engage with various videos, information and mindfulness exercises. The Centre for Pain Research will be collecting data through a series of questionnaires: prior to beginning the programme, upon completion of the programme and again three months after completion of the programme. This data will then be analysed and subsequently reveal the clinical and cost-effectiveness of the programme.

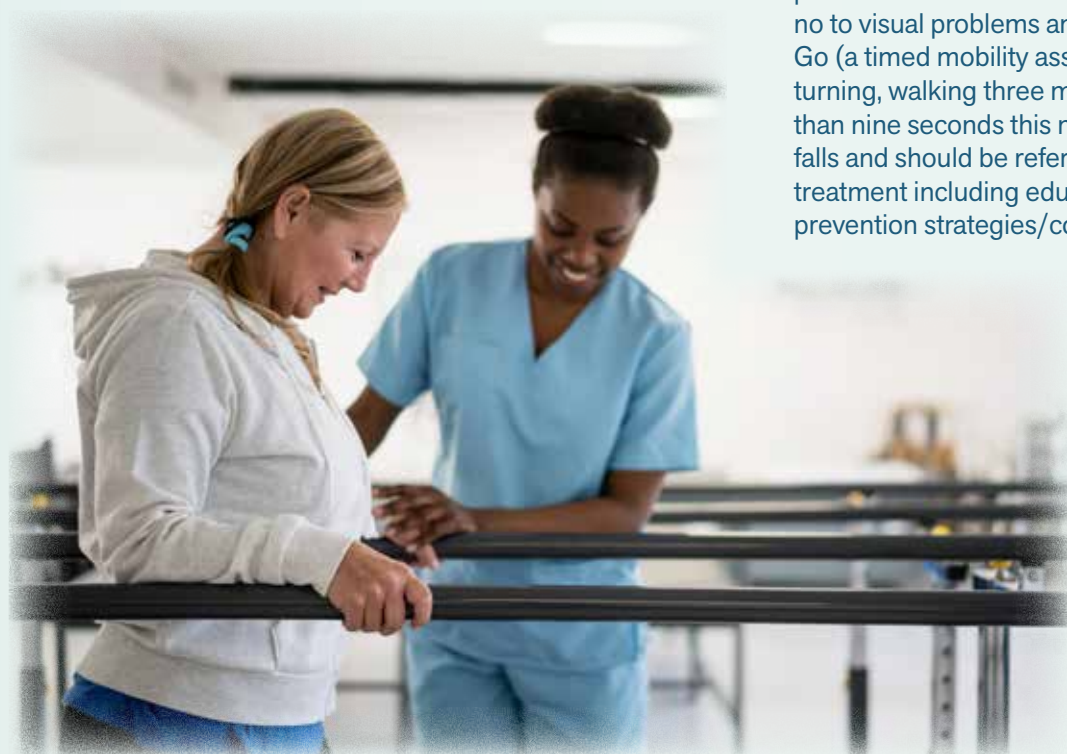
Participants will be randomly allocated to a treatment group - who will complete the programme; or to a control group - a group who do not participate in the programme during the research period. However, the 'control group' will have the opportunity to gain access to the programme after completion of this research. The findings from this study will provide a valuable contribution to research in this area, inform MS researchers and enhance the development of cost-effective practices for improving the well-being of individuals living with MS.

If you or someone you know might be interested in participating in this study, the Centre for Pain Research is now recruiting. Alternatively, if you have any queries, please contact Dr Christopher Dwyer via email at painresearch@nuigalway.ie

Development of a Falls Prediction Tool for People with MS

By Gillian Quinn – PhD candidate, University of Limerick. Supervisors: Prof Susan Coote, Dr Rose Galvin (UL), Prof Chris McGuigan (St. Vincent's University Hospital)

I work with the MS research team in UL, led by Prof. Susan Coote, and my overall research interest is in the area of falls in MS. It is known that people with MS fall frequently and a range of factors are associated with falls such as problems with balance, weakness in the legs, fatigue and mobility aid use. Falls have serious consequences such as increased fear of falling, activity curtailment, physical deconditioning and increased healthcare utilisation which can result in time off work and a further decrease in quality of life. Many of these risk factors are modifiable and can respond well to falls prevention interventions carried out by a physiotherapist or occupational therapist. While it is known that falls are a serious problem for people with MS, the best way to identify fallers has not yet been identified and current clinical measures of balance that are used in both research and clinic settings are not reliable or sensitive enough to use as a falls screening tool.



The aim of this research study was to develop a simple falls risk screening tool for use in a busy clinic setting. As the treating doctor or MS nurse often has limited time for each clinic appointment and may not have access to high tech equipment it is important that a falls screening tool can be carried out quickly and requires no specialist training or resources. Study participants were recruited from the MS clinics in the Neurology department of St. Vincent's University hospital. 100 people with MS were assessed using a timed mobility assessment, a falls screening questionnaire and falls diaries for a three month period.

Main Findings:

- 56% of the 100 people who took part in the study reported falling over a three-month period; more than half of those had two or more falls
- Most common cause of falls were poor balance (25%), weakness in the legs (22%) and fatigue (14%)
- Falls happened most often in the afternoon (37%), followed by evening (28%) and the majority of falls occurred inside the home (63%)
- After analysing all the different variables that we collected data on from the initial assessment, the model with the highest sensitivity which can correctly identify 88% of fallers includes the variables of a fall in the past three months, no visual problems, problems with bladder control and slower walking speed
- To conclude, if a person with MS answers yes to problems with bladder control, yes to a history of a fall, no to visual problems and has a slower Timed Up and Go (a timed mobility assessment involving standing, turning, walking three metres and returning to sit again) than nine seconds this model suggests they are at risk of falls and should be referred for specific falls prevention treatment including education, exercise and falls prevention strategies/coping skills



Better Balance Study

By Laura Comber – PhD candidate,
University of Limerick

Falls are now recognised as a considerable consequence of MS, with 56% of people with MS (pwMS) experiencing a fall in any three-month period and 37% experiencing multiple falls. A fall can have significant implications for the individual with injuries, activity restriction and having a fear about falling commonly experienced by pwMS after falls.

Falls prevention typically refers to programmes which aim to reduce or manage risk factors that are causing people to fall. There have been multiple risk factors for falls identified for pwMS and it is likely that a number of these factors interact to cause a person to have a fall. These risk factors can be related to physical factors like having balance problems, personal factors like being worried about falling, environment factors like an uneven floor surface or behavioural factors like doing activities that are beyond a person's ability. Falls prevention for pwMS is a very limited research area with few studies conducted to date. The MS research team at the University of Limerick, led by Professor Susan Coote, set out to develop a falls prevention programme for pwMS.

This development was led by PhD student, Laura Comber, and involved reviewing information from previous research studies, asking physiotherapists and occupational therapists about what they felt was important to include in the intervention through interviews and gaining insight from pwMS through a survey of interest levels in intervention content and logistics of running the intervention. The MS research team at UL then collaborated with experienced researchers of falls in MS from the USA and Canada to design an intervention which has been called 'Better Balance'.

'Better Balance' is specifically designed for pwMS who have had a recent fall and who use at most a walking stick or one crutch to walk ten metres. The programme begins with assessing pwMS falls rate through documenting whether or not they have a fall for two-months using falls diaries. Their balance, walking and feelings about falls are then assessed by a physiotherapist. The 12 week programme then begins and is multicomponent meaning that it involves both exercise and education. Exercises are designed and tailored for each and aim to challenge and train an individual's balance. These exercises are then delivered in group exercise classes and through home exercise programmes. Education classes are delivered in groups and include education regarding known risk factors for falls and encourage the use of group brainstorming and problem solving through coaching strategies in order to equip pwMS with management strategies to manage their falls and falls risk. Overall 'Better Balance' aims to reduce falls and falls risk while providing pwMS with falls management strategies to use in their daily lives. Upon completion of the programme, each individual then completes another two months of falls diaries and is again assessed by a physiotherapist to see if the programme has reduced their falls and/or their falls risk.

Now that 'Better Balance' has been developed, the MS research team at UL are conducting a feasibility study with a small group of pwMS in Limerick to see if the programme can be implemented as it has been designed. Once the group have completed the programme, they will participate in a focus group to identify what elements of the programme they thought worked well and what elements could be improved with suggestions for how this can be done. This feedback will enable the team to review the programme and make necessary changes before hopefully conducting a larger study in the future to investigate if 'Better Balance' can reduce falls for pwMS.



International Progressive MS Alliance update

The International Progressive MS Alliance (IPMSA) is an international collaboration of MS organisations, researchers, clinicians, pharmaceutical companies, trusts, foundations and people affected by progressive MS, working together to transform the landscape of progressive multiple sclerosis research. A number of MS Ireland Branches have made donations towards the work of the IPMSA in the last three years. Below is an update on the Alliance's current work. This is reproduced from the Alliance's '2017 Report of Progress' which is available to download in full here:

www.progressivemsalliance.org/wp-content/uploads/2018/04/Alliance_2017_report_of_progress.pdf

Collaborative Network Awards

The Alliance-funded Collaborative Network Awards are multi-year grants that are fueling international networks of researchers and institutions, working together to make crucial breakthroughs in understanding and treating progressive MS. The work of the Collaborative Networks began in 2017 and updates on these three projects are as follows:

DRUG DISCOVERY/TARGET DISCOVERY/VALIDATION

Project Title: Development of a drug discovery pipeline for progressive MS

Principal Investigator: Francisco Quintana, PhD, Brigham and Women's Hospital (U.S) in collaboration with eight investigators from the United States, Canada, Israel and Sanofi Genzyme.

The goal of Francisco Quintana, PhD's project is to identify drug candidates that may be effective therapies for progressive MS. The project's central idea is that targeting the innate immune system in the central nervous system will uncover effective therapeutic approaches for progressive MS. While the innate immune system normally functions to protect the body from infections, Dr. Quintana and others have found that innate immune cells in the central nervous system promote disease activity in MS and other diseases. To date, Dr. Quintana's Network team have been examining enzymes in a cell signaling pathway that are the target of the drug miglustat and are potentially druggable targets to block the destructive properties of some innate immune cells. The team is also evaluating miglustat in cells and considering a clinical trial to administer miglustat and examine the cerebrospinal fluid.

They have completed testing of 500 compounds that can penetrate the blood-brain barrier— and identified an

additional compound, which mediates signalling between different cells—for further investigation. Subsequently, they have commenced testing an additional 3,000 molecules.

Project Title: Bioinformatics and cell reprogramming to develop an in vitro platform to discover new drugs for progressive multiple sclerosis (BRAVEinMS).

Principal Investigator: Gianvito Martino, MD, Division of Neuroscience, San Raffaele Hospital Milan (Italy) in collaboration with 13 investigators from Italy, France, Germany, Europe, Canada and the United States.

The BRAVEinMS team are using bioinformatics and cell reprogramming to develop an in vitro platform (for example, in culture dishes) to discover new drugs for progressive multiple sclerosis and are working to identify molecules that may have a protective role in nerve cells or neurons and/or the capacity to promote myelin repair.

The BRAVEinMS team is focusing their efforts in three phases: **1)** identifying potential drugs or compounds, **2)** screening these compounds for their ability to protect nerve cells or promote myelin repair in laboratory tests, and **3)** evaluating candidate compounds in animal models of progressive MS. In the study's first phase, the researchers will leverage their world-class IT expertise to comb through large data sets of biological and chemical information. The short-term goals for this project are to have a definitive list of molecules that can be tested in mice using new procedures being developed by the Martino team. Then, the team will test neurons and oligodendrocytes derived from hiPSCs (human induced pluripotent stem cells). In 2018, the team expects to develop outcome measures to best evaluate the results of the assays. Martino's team believes that BRAVEinMS will pinpoint previously unidentified molecules with a high chance of therapeutic efficacy in progressive MS patients.

Over the past year, Drs. Quintana and Martino have formed strong collaborative linkages between teams and will be coordinating their drug discovery efforts as their projects move forward.

BIOMARKERS— BIOLOGICAL/IMAGING

Project Title: Identifying a biomarker of disability progression for use in clinical trials.

Principal Investigator: Douglas Arnold, MD, McGill University (Canada) in collaboration with 16 investigators from The Netherlands, United Kingdom, United States, and Switzerland.

Douglas Arnold, MD of McGill University is developing the next generation of tools for measuring disease progression in progressive MS by pioneering the development of magnetic resonance imaging (MRI) markers that signal disease progression and adapting these for use in early (phase II) clinical trials of progressive MS treatments. Dr. Arnold's research examines the underlying idea that brain

injury-associated disease progression in MS is detectable by MRI prior to its identification by physicians in a clinic visit. Using data from previously completed clinical trials, including existing data from more than 2,000 patients and 40,000 MRI scans, the group has been working on developing machine learning tools (also known as artificial intelligence) to automatically predict future disease activity from images acquired from Relapsing Remitting MS (RRMS) patients. Although they have been focusing on RRMS patients for now, the machine learning tools they are developing will be transferable to the context of progressive MS patient images. They have been asking whether new lesions seen on MRI might predict future disease activity or changes in EDSS scores. Their team has also been creating computer tools to share and control quality of the data they are generating. Finally, the team is in discussions to add more images (equaling more data) to their database which will help in developing even more robust algorithms.

Alliance Industry Forum

Industry's collaborative partnership with the Alliance is managed through the Industry Forum and is led by Co-Chairs, Prof. Giancarlo Comi, MD, Director of the Department of Neurology, Scientific Institute San Raffaele and Bruno Musch, MD, PhD, Medical Director US Medical Affairs Neurosciences, Genentech, Inc.

- The Industry Forum ensures pharmaceutical and biotechnology companies are engaged to help inform and accelerate progress.
- Leading MS pharmaceutical and biotech companies have been working together on a shared agenda to address progressive MS and have established focus areas in order to break down barriers, including a focus on translational pathophysiology of progressive MS and data sharing.
- Industry Forum members, regulatory authorities, the Scientific Steering Committee and the Collaborative Network Award investigators met in Washington, D.C. and London in 2017.
- Industry has engaged with key regulatory authorities, including the Food and Drug Administration, Health Canada and European Medicines Agency in a continuing dialogue in MS drug development.
- Industry leadership has contributed to the development of the Alliance's future research planning, served on Collaborative Network Award Oversight Committees, and coordinated on a shared agenda for regulatory engagement.
- Industry Forum collaborators include Biogen, EMD Serono; Genentech, a member of Roche; Sanofi Genzyme; MedDay Pharmaceuticals; Novartis AG; and Teva.
- Industry is critical in helping the Alliance fulfil its goals. Their extensive knowledge of drug discovery and development, including clinical trials, and their willingness to contribute resources and financial investment will also accelerate progress.

Engagement activities, publications and presentations

- 13 scientific publications and 20 meeting abstracts have been generated from Challenge Award research.
- The Collaborative Network teams led by Dr. Francisco Quintana, Dr. Doug Arnold and Dr. Gianvito Martino's published several papers, including the highly regarded scientific journal Nature.
- The work of the three Collaborative Networks was featured in a Hot Topics session at the 2017 meeting of the European Committee on Treatments in MS (ECTRIMS). This meeting is the world's largest MS research meeting and brings together close to 10,000 delegates.
- The Alliance hosted two webcasts from Harvard (Boston, MA) and ECTRIMS/ ACTRIMS (Paris, FR). These webinars featured Dr. Tim Coetzee; Scientific Steering Committee Members impacted by MS, Caroline Sincock and Jon Strum; and, Alliance Collaborative Network lead researchers Dr. Douglas Arnold, MD, McGill University (Canada); Dr. Gianvito Martino, San Raffaele Scientific Institute, Milan (Italy); and, Dr. Francisco Quintana (U.S.) from Harvard University/Brigham and Women's Hospital. These webinars covered the three network projects and how more than 40 leading researchers from 21 institutions in Canada, France, Germany, Israel, Italy, The Netherlands, Switzerland, United Kingdom, and United States are working together to reduce the time and cost of getting therapies ready for clinical trials.
- Members of the Scientific Steering Committee— including Ireland's own Alexis Donnelly and Caroline Sincock from the UK—assisted the European Medicines Agency on a number of engagements, putting across the perspective of people affected by progressive MS. Jon Strum launched the "RealTalk MS" podcast in 2017, covering an array of topics, including the Alliance and progressive MS.
- Prof. Alan J. Thompson, MD, Dean of the University College of London Faculty of Brain Sciences and Alliance Scientific Steering Committee Chair, was chosen by a committee of his peers to receive the American Academy of Neurology/ National MS Society's 2017 John Dystel Prize for Multiple Sclerosis Research. Professor Thompson was honored for pioneering research in ways to address symptoms and improve quality of life for people with MS, and as a leader and driver of the Alliance.
- Prof. Per Soelberg Sorensen, MD, DMSc, Head of MS Research Unit Curriculum Vitae (Denmark) and Alliance Scientific Steering Committee member, received the MS International Federation's Charcot Award for his leadership in MS research.
- Leaders in progressive MS research met in Rome in March 2017 under the auspices of the ECTRIMS and the Alliance. MS Journal released a special issue that featured papers stemmed from the meeting. The Alliance and ECTRIMS provided sponsorship funding to allow open access to these papers.

For more information and updates on the work of the Alliance, visit www.progressivemsalliance.org

Alliance Collaborative Network Award Identifies Links Between Diet, Gut Bacteria and Immune Activity in a Mouse Model

SUMMARY

- Researchers were able to trace a set of interactions that help explain how diet and the gut bacteria influenced by diet may act on the immune system to limit inflammation and nerve damage in mice. The team also found preliminary evidence verifying that similar interactions influence human cells.
- The study, supported by the International Progressive MS Alliance and others, provides important clues for better understanding the gut-brain connection and could lead to new treatment approaches for MS.
- The international team, led by Dr. Francisco Quintana (Brigham and Women's Hospital, Harvard Medical School) published their findings in the journal *Nature* online on May 16, 2018.

DETAILS

Background: MS involves immune-system attacks and inflammation in the brain and spinal cord. The gut, including the small and large intestine, is the largest immune organ in mammals, including people. Each of us has millions of “commensal” bacteria living within our guts. Most of these bacteria are harmless as long as they remain in the inner wall of the intestine. They play a critical role in our normal physiology, and accumulating research suggests that they are critical in establishing and maintaining immune balance by the molecules they release. Differences have been detected between the gut bacteria from people with MS compared to people without MS.

The effects of diet on gut bacteria and on immune system activity is difficult to tease out, and there is much that is not yet understood. Dr. Francisco Quintana and an international team of collaborators set out to understand the links between immune activity in mice with the MS-like disease EAE, and dietary components that are processed by gut bacteria, and how those interactions impact the activity of cells within the brain and spinal cord. Dr. Quintana leads one of three Collaborative Networks supported by the International Progressive MS Alliance.

This study focused on possible interactions between gut bacteria and glial cells, which are the most abundant cells in the central nervous system (brain and spinal cord) and play major roles in both health and disease. Specifically, the study focused on the interactions of two types of glial cells: microglia and astrocytes.

The Study: In a series of laboratory studies, the researchers investigated activities that could influence whether microglia increase or decrease inflammation in the brain. They explored the role of a protein called AHR (aryl hydrocarbon receptor). Dr. Quintana's team found that eliminating AHR from microglia worsened the MS-like disease EAE in mice, and increased nerve damage. EAE inflammation was then reduced by adding the amino acid tryptophan in the diet. This reduction of inflammation was driven by the conversion of tryptophan by the gut bacteria into a substance that activates AHR. Activating AHR reduced the amount of pro-inflammatory molecules made by microglia and also suppressed molecules that regulate the contribution of astrocytes to brain inflammation.

The team also found preliminary evidence verifying that similar interactions influence human cells. They have plans for continuing this line of research to identify therapies or probiotics that can reduce inflammation to turn off or decrease disease activity.

Identifying components of this “gut-brain” connection and better understanding this complicated web of interactions with the immune system and nervous system provides important clues that could lead to new treatment approaches for MS and other neurodegenerative disorders like Alzheimer's disease and glioblastoma.

“It is encouraging to see these early, important insights in gut-brain connections from one of the three Collaborative Networks launched and funded by the International Progressive MS Alliance,” said Prof. Alan Thompson, Chair of the Alliance's Scientific Steering Committee and Dean of University College London Faculty of Brain Sciences. **“These findings are just the beginning of what we expect will be major progress toward understanding underlying mechanisms and finding new treatments for people living with progressive MS.”**

Reports from 3rd International Progressive MS Alliance conference



Picture credit: Lisa Melton, Australian MS Society

The 3rd Scientific Congress of the International Progressive MS Alliance took place in Toronto, Canada in May. A strong Irish delegation of researchers attended and they were kind enough to report back, giving their different takes and perspectives on the event.

Alexis Donnelly (member of the Scientific Steering Committee for the Progressive MS Alliance) and Gemma Donnelly-Cox

In the third week of May, more than 200 people – including myself and my wife Gemma, travelled to Toronto, Canada to attend the Third Scientific Congress of the International Progressive MS Alliance.

Introducing the Congress

The title “Congress” implies a gathering of scientists and the meeting in Toronto certainly was that – but so much more! The main purpose of this third meeting was to raise the profile of and interest in MS rehabilitation and why it works. For those of us with significant accumulated damage from MS, initial therapies to attack the disease progression might not return all the functionality we have lost. For us, this meeting’s focus on excellence in MS rehabilitation is critical. From a more emotional perspective, the awareness that I and my needs as a quadriplegic man in my 50s are not forgotten in the search for a cure is motivating me even more to support the Alliance and urge others to support its incredible work.

The research participants were drawn from three communities: rehabilitation therapists (physiotherapists, occupational therapists, neuro-psychologists etc.), neurologists and basic laboratory scientists.

In addition to researchers, there were also people affected by MS, staff and volunteers from the Canadian and other MS Societies, and philanthropists who want to fund research into (and development of) effective therapies and treatments for progressive MS.

For me, a big thrill of this meeting was simply being surrounded by well-known researchers, mainly from Europe and North America, but from as far afield as Argentina, and Australia, who are pulling out all the stops in their research efforts to develop therapies that will be effective for those of us with progressive MS. Even though I am very familiar with the work of the Alliance from my role on the Alliance’s main Scientific Steering Committee and am also familiar with many of the scientific questions of interest, I was close to overwhelmed by this meeting. I left with the unmistakable impression that these three research communities had never engaged so deeply or so freely before on the questions of MS rehabilitation and pathology.

Visit to the Toronto Rehabilitation Institute

Before the Congress got underway, participants were invited to take part in a tour of the Toronto Rehabilitation Institute. One of us (Gemma) went on this tour. The Institute’s research is focused on what might seem very mundane, day to day scenarios, such as how to ensure that the soles of snow boots will not slip on icy footpaths, or what depth a stair tread should be to minimise the risk of walking when climbing up and down stairs.

Most of the patient care innovations under test at the Institute were simple, but they were subject to complex and thorough testing to ensure that they delivered the greatest value for patient care. For example, there was a grab pole system under test. This is a vertical pole extending from floor to ceiling located beside one’s bed and it makes getting out of bed much easier than the traditional suspended triangle above a hospital bed. It is easy to assemble in a home environment as well.

The Institute featured a simulated home environment, which was a test site for all kinds of futuristic aids. The features included voices from the ether asking if you need help, talking mirrors that prompt you if you forget what you’re doing while brushing your teeth or washing your face, through to fully fledged ‘carer robots’ that follow the occupant around, chatting with you to help you stay focused on what it is you are trying to do. While I was initially cautious of assistive technologies that replace people with robots, by the end of the visit I was convinced that they definitely have a role to play. Assistive robotic technologies can be targeted at the tasks that real people find most difficult and which human assistants find overly repetitive.

The optimal height for the placement of handrails is being tested at the institute using an enclosed robotic platform (rather like a flight simulator). A volunteer wearing a harness stands inside the platform close to the handrail. The platform is programmed to induce a fall and the forces on the handrail are measured. Preliminary results indicate that higher the handrail the better. Yet another group has developed a simple device to diagnose sleep apnea. Normally a very expensive sleep laboratory is required. This group’s device, consisting of a modified respiratory mask with an SD memory card to record parameters, may cost as little as \$50!

While the research underway at the Rehabilitation Institute spans memory loss and conditions other than MS, it was easy to see how the research conducted there could enable people with MS to have better quality lives and also live more independently.

More about the Congress

Putting one of these points straight into practice, the very next session was devoted to understanding the perspectives of people with progressive MS. These differ from those of people with relapsing remitting MS as the condition is now unrelenting and more severe. An MSIF project, iPRO, designed to capture these perspectives and outcomes was then presented. A panel session followed in which John Strum (a PaMS also from the scientific steering committee) and myself participated.

We were then treated to be very interesting presentations in the next session. The common theme was basic mechanisms - from spinal cord injury, from exercise and brain shrinkage. What can we learn for progressive MS? The exercise presentation appeared particularly relevant as we are learning more and more about the effect of exercise on the immune and central nervous systems.

Two sessions later focused on how some of these insights can be put into practice and some of the difficulties that may arise. What can we learn from stroke rehabilitation? How can exercise help? What are the implications for cognitive rehabilitation? How can we help functional recovery? What symptoms get in the way? (e.g. depression, cognition).



Pictured (L-R) starting at the back row: Gemma Donnelly-Cox; Klaus Hom, PMSA EC and CEO of the Danish MS Society; Professor Alan Thompson, PMSA SSC Chair and Dean of Brain Sciences, University College London; Karen Lee, PMSA SSC and VP of Research, MS Canada; Alexis Donnelly PMSA SSC; Corey Turner, Leadership Council MS Canada and CEO of Spicers Ltd. [PMSA = Progressive MS Alliance, EC Executive Committee, SSC = Scientific Steering Committee]

A very practical session followed on the implications for implementation and healthcare delivery. Marcia Finlayson (Queen's University, Kingston Ontario, Canada - who has made presentations for MS Ireland) spoke about fatigue management and gave lots of practical suggestions. I have made a mental note, following her advice, to think of these interventions as "smart energy management". Bernie Porter (National Hospital for Neurology and Neurosurgery, Queen's Square, London) described an initiative she has developed to deal with bladder management in MS. Bladders can cause so much avoidable trouble in MS; it was great to hear of so many simple things to avoid them - courier collection of urine samples, early recognition of symptoms, the importance of drinking fluids and starting antibiotics early. The

initiative has dramatically reduced hospital admissions from bladder infections in her area.

The concluding session of the Congress took a more strategic look at the global agenda to enhance wellbeing in progressive MS. This included the global rehabilitation research agenda (P. Heys, Hasselt University, Belgium) and using lifestyle factors, rehabilitation and symptom management strategies to influence the biological systems in our bodies to limit the effects of MS (P. Matthews, Imperial College, UK).

Progress from the Collaborative Network Awards

The imaging network - led by Professor Doug Arnold (McGill University, Montreal Canada) - continues the sometimes tedious task of collecting (and re-formatting if necessary) MRI images to train a powerful machine learning system (see page 18 for more information). I was treated to a personal demonstration by Professor Charles Guttman (Brigham and Women's Hospital, Boston - and partner in the network) of the image analyser being built. This analyser will compute many image features and then look for correlations between these features and more clinical data (e.g. performance on clinical tests such as walking ability, balance or response to drugs). The aim of this network is to identify an imaging biomarker responsive progression that can be used in a shorter clinical trial. Knowing the powerful multi-processor computers in Montreal and Boston that were being used in my personal demo (and all controlled from a laptop on my knee in Toronto), it felt a little like firing up the warp engines of an unfinished spacecraft for a demonstration run. It's early days for much remains to be done, but the demonstration worked perfectly. "Warp engines are online, Cap'n". Cool. Many thanks to Professor Arnold and his team!

One of the drug discovery collaborative networks - led by Professor Francisco Quintana (Harvard University, Boston USA) - chalked up a major success two weeks before the Congress. His team had a paper published in the prestigious science journal "Nature" - a pinnacle of success for a scientist (see page 19 for more information). While I was thanking (and congratulating) Francisco in person for his work, he introduced me to another scientist - a neurologist called Jorge. I was thrilled to meet any colleague of Francisco's. He was (also) from Argentina. Then I began to remember - he was the Jorge Correale who had written a paper in 2012 about people in Argentina with MS who also had intestinal worms. These people seemed to have a better time with their MS perhaps because of the worms. Having been remembered, it seemed as if it was now his turn to be thrilled... anyway animated discussion followed. During this I got the distinct impression Francisco and Jorge had been having lunch together to discuss commonalities between Francisco's bacterial work and Jorge's work on worms. This is an excellent example of the kind of collaboration encouraged by the Progressive MS Alliance. It may also have happened on the fringes of a major neurology conference, but the singular focus of Alliance Congress vastly increases this probability. I was privileged to have been a witness... perhaps it will be a story for the grandchildren...

Finally

This is the second PMSA Scientific Congress which I have attended (the first was in San Francisco in 2016).

I left that Congress with the sense that the world's leading researchers were now focused on the wicked problem of progressive MS. We are still facing the wicked problem, but we now have a well-targeted and well-designed global strategy in place and I left Toronto with a very real sense that we are making progress.

I (Alexis) would like to close this report with my wife's words. She managed to elevate the one-liner to new heights of brevity, efficacy and truth. At one session, she said in response to the question

"What does the Alliance mean to you?"

HOPE

Bláthín Casey, PhD in area of Physical Activity and MS.

For me, an early career MS rehabilitation researcher, the Progressive MS Alliance Meeting 2018 was nothing but inspiring. The theme of the event was 'Making a difference through rehabilitation and symptom management'. I have pulled out some of the quotations that stood out to me during the two day meeting:

"We must make sure our research, services and advocacy are aligned so that people with MS can live their best lives".

**Cynthia Zagieboylo, President and CEO,
National Multiple Sclerosis Society (USA)**

The above words were reflected during the meeting, where the Progressive MS Alliance sought to bring researchers, healthcare professionals, advocacy groups and people with progressive MS together. Panel discussions during the two days ensured to include the voice of all those involved. The openness of these discussions and overall agreement by attendees highlighted that everyone is on the same page. I am hopeful that our priorities as researchers, patients and clinicians are aligned.

"We need to learn about and focus on what matters to people living with progressive MS."

**Prof Marcia Finlayson, OT and researcher at
Queens University, Kingston, Canada.**

Starting a line of enquiry about what people with progressive MS want from rehabilitation programs was a strong theme from the conference. Whilst there were conversations about how we could learn from the world of stroke and those with relapsing-remitting MS, I could not help but hear the voices of researchers and patients say we needed to talk to those with progressive MS directly. To add to that, we need to know what matters. What should we be measuring and monitoring after our rehabilitation programs. Should be aiming to promote maintenance? Or should we aim higher? The next quote may answer that question.

"What we believe, we can achieve"

**Prof Peter Feys, rehabilitation researcher,
University of Hasselt, Belgium.**

Alongside Professor Rob Motl who stated "Exercise is a powerful medicine for people with progressive MS", Professor Feys believes the same. There was a sense during the two day meeting that we should be aiming high for what we expect to see from future rehab interventions. The Alliance have showed support in this belief by the funding of rehabilitation trials, with a particular focus on cognitive rehabilitation which also has promising effects for improving/managing symptoms in progressive MS.

To conclude, this meeting provided evidence that progressive MS research is alive and well. However, I do want to finish with the words of our very own, Alexis Donnelly, member of the Progressive MS Alliance Scientific Steering Committee and living with progressive MS:

"We need to continue being the unreasonable and demand more for people with progressive MS clinically and in research"

Professor Susan Coote, University of Limerick and Chairperson of MS Ireland's Research Committee

Over two hundred rehabilitation researchers gathered in Toronto for a really excellent two day meeting that aimed to advance our understanding of the specific rehabilitation issues and their treatments for people with progressive MS. It was a true "gathering of the minds" with the leading international researchers invited - a real "who's who" in the MS rehab world. The meeting was truly enhanced by the people with MS from the steering committee who gave the occasional reality check. Our own Alexis Donnelly, and his wife Gemma, did Ireland proud and both spoke eloquently and emotively about the realities of living with progressive MS. A number of early career researchers from Europe were facilitated to attend by ECTRIMS and we can be assured that the future of MS research is in good hands.

Personally it was a privilege to have been invited. I left the meeting re-invigorated and reassured that our work is of international standard and that it is making an impact internationally. The reality about the poor access to rehabilitation services in Ireland also hit home and I write this as the Neurological Alliance of Ireland is presenting to the Oireachtas about the insufficient access to services, this is a local issue that we must address. I learned about MRI imaging, TMS (brain stimulation) and other areas I wouldn't normally chose to listen to and recognise their importance in unpicking the "why" rehabilitation works question.

A short five days after that I travelled to Amsterdam for the Rehabilitation in MS (European Network for Research and Best Practice) conference. We continued conversations started in Toronto and had a very positive exercise meeting. My biggest take home message from these two conferences was that from a rehabilitation and exercise point of view we have to think about "dose" – how much exercise, working how hard, how often. We can learn from our colleagues in stroke rehabilitation that it takes a lot more than once a week or 10 minutes per day to make a true difference to brain re-wiring (neuro plasticity) and hence to function. The other key factor is how we "package" exercise. For people with progressive MS many symptoms interfere, so treating strength or balance in isolation is likely not the way forward. "Multiple component" treatments where a range of symptoms such as fatigue, memory and thinking and strength are addressed by a programme will probably make the biggest impact.

On the first day of the conference Alexis quoted Shaw: "The reasonable man adapts himself to the world: the unreasonable one persists in trying to adapt the world to himself. Therefore all progress depends on the unreasonable man" and the theme of unreasonableness continued throughout the conference. The conference gives hope that together researchers can "be unreasonable" and find rehabilitation solutions to reduce and better manage the many symptoms of progressive MS.

Dr Sinéad Hynes, Lecturer in Occupational Therapy. National University of Ireland Galway

The 3rd Scientific Congress of the International Progressive MS Alliance took place in Toronto in May and was the first of these meetings that I have attended. As an occupational therapist it was inspiring to see an entire meeting dedicated to rehabilitation and symptom management. The Congress had four overall objectives (summarised below) which were achieved well:

1. Understand the perspectives of people living with MS.
2. Explore state-of-the art rehabilitation and symptom management research in MS and other neurological conditions.
3. Discuss priorities for research that can have the greatest impact on progressive MS.
4. Develop ways in which effective research can be quickly implemented into clinical practice.

The research that was discussed had a strong clinical focus. There was an effort made to relate the presented material to the patient. Not only that, but there was a forward-looking focus with priorities for the future being discussed by the congress delegates.

'Pre-habilitation' was a key term that I took from the congress – that is that interventions and management of MS needs to be happening before people are experiencing symptoms and not after. There is emerging research indicating that in order to be most effective early intervention is essential in symptom management. The talk that stuck with me most was by Dr Finlayson who presented on fatigue management and the importance of partnering with the patient. She spoke of the need to ensure that people can manage their own symptoms and do it in a way that work for them and their own lifestyle. The two patient panels that were part of the congress really drove that message home too - work closely with people who live with MS and their families, listen to what is needed and the best results are more likely.

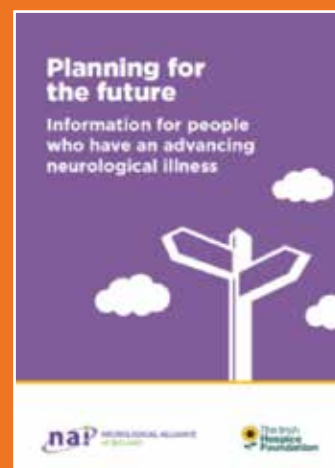
I am very grateful to have had the opportunity to attend this congress and hope to again in the future. There are many developments on the horizon in terms of rehabilitation and symptom management.

Planning for the Future with a Neurological Illness:

The joint Neurological Alliance of Ireland (NAI) and Irish Hospice Foundation (IHF) report, *The Palliative Care Needs of People with Advancing Neurological Disease in Ireland*, published in 2014, identified a clear need for information for individuals and their families to understand their experience of living with a neurological illness and signpost them to services available.

To address this, a working group was formed in 2016 and was compiled of people working in neurological illness organisations as well as a person with a neurological illness. The group explored the topic of palliative care in the context of living with a neurological illness. A draft booklet was prepared by the group and a national consultation took place, after which the final booklet was published. The booklet contains information on subjects to include advance healthcare directives, planning legal affairs, talking to others and palliative care. A list of organisations who can also provide assistance is also included.

The booklet, titled "Planning for the future Information for people who have an advancing neurological illness" was launched on March 6th during Brain Awareness week by Orla Hardiman Professor of Neurology, Trinity College Dublin. The booklet is available to download from www.hospicefoundation.ie and www.nai.ie



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