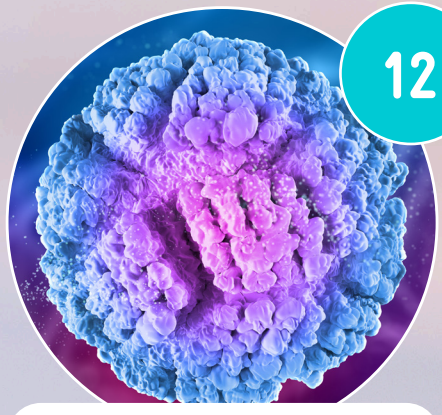
MS research

Issue 07

9 DATING WITH MS

10 A VISION FOR MS



12 NANOMODULATION

Friends

Welcome to **Issue 7** of MS Research.

This edition features some of the incredible research that has been happening across the country. 2020 has certainly presented everyone with unrivaled challenges. Through it all, the MS research community has been adaptable and innovative. An example of this adaptability can be found on **page 5** where we see how the COB-MS trial in Galway has been conducting research remotely.

On **page 6** the value of participating in PPI is discussed by Dr Rebecca Maguire. This piece is complimented by Lauren McCauley on **page 7** who shares her thoughts on taking part in PPI activities as a person living with MS.

Page 9 features a piece on Dating with MS – this outlines how MS can impact the dating life of a person living with the condition.

An abstract on Nanomodulation of Micrornas in Macrophages by PhD student Frances Nally can be found on **page 12**. This abstract was selected for a 12-minute presentation at MS Virtual 2020, hosted by ECTRIMS/ACTRIMS.

In this edition, we also feature two pieces by Dr Maria Gaughan in relation to the management of MS and the impact of COVID-19. The first, an overview of MS can be found on **page 3 & 4**. The second, which can be found on **page 11** discusses COVID-19 and MS.

We would like to quickly highlight the Researchers Profiles section on our website. This section houses profiles for MS researchers across the country. It can be found here - **https://www.ms-society.ie/researchers-profiles** If you would like to have your profile added, please email **aoifek@ms-society.ie** to request a profile template.

We hope you enjoy this issue.

Aoife Kirwan
Information, Advocacy and Research Officer

Professor Susan Coote
Chair of MS Ireland's Research Committee

CONTENTS

3 MS OVERVIEW
5 CHANGES TO THE COB-MS
6 INVOLVING PPI IN MS RESEARCH
7 PARTICIPATING IN PPI
7 DEAN MEDAL
8 PRIMARY PROGRESSIVE MS
9 DATING WITH MS
10 A VISION FOR MS
11 COVID-19 AND MS
12 NANOMODULATION OF MICRORNAS IN MACROPHAGES
13 COGNITION IN MULTIPLE SCLEROSIS

'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.

Multiple Sclerosis Ireland, 80 Northumberland Rd, Dublin 4.
www.ms-society.ie | **01 678 1600** info@ms-society.ie |
Info Line: **1850 233233**

EDITOR & EDITORIAL
Aoife Kirwan - **aoifek@ms-society.ie**

ADVERTISING
Sally Spearman Tel - **01 678 1600 – sallys@ms-society.ie**

Aoife Kirwan

Professor Susan Coote

MS Overview
Written by: Dr Maria Gaughan

Multiple Sclerosis is a neurological condition caused by inflammation affecting the brain and spinal cord. It is a demyelinating disease, which pathologically is characterised by damage to the myelin. The exact aetiology remains unclear although a combination of genetic and environmental factors such as EBV exposure, Vitamin D and smoking play a role. First-degree relatives of those with MS are slightly more likely to develop the condition.

MS is common in Ireland, about 10,000 people are affected and the incidence rate approaches 1 in 400.1

It is typically diagnosed in young people, and there is a marked female preponderance. The increased use of MRI imaging has likely led to diagnosis at an earlier stage of the condition than in the past. The clinical course typically begins with isolated relapses and almost complete recovery. Within this period, radiological lesions can accumulate without any clinical signs. Progressive difficulties in walking emerge in almost 80 - 90% of people with MS, although the time that this occurs following the onset of the illness can vary between 10 and 50 years.

Common initial presentations include optic neuritis; transverse myelitis; hemisensory symptoms; diplopia; vertigo.

Relapses can be quite subtle and difficult to identify, resulting at time in a delay in diagnosis. Intravenous steroids are frequently given to shorten the duration of the relapse, but evidence suggests they do not make a significant difference to the overall degree of recovery. In some centres, high dose oral prednisolone at a dose of 1g/day is now given in certain situations, avoiding admission or repeated hospital attendances.

As outlined above, the mainstay in MS management is early initiation of appropriate disease modifying therapy. This has changed significantly over the past 10 years, and our advice and management continues to evolve with changing evidence in the field.

The advent of the 2017 McDonald criteria, has allowed an earlier diagnosis of Multiple Sclerosis - a single clinical event with imaging showing evidence of typical inflammatory lesions in more than one area usually associated with MS (periventricular, spinal cord, brainstem, pericallosal) and positive oligoclonal bands in the CSF, with exclusion of MS mimics will allow for a secure diagnosis. MS medication has become increasingly personalised as we consider both disease factors and patient factors in choosing the medication in conjunction with the patient. One of the challenges in MS management is that we are frequently recommending a medication to people who feel very well, on the basis that evidence has demonstrated that in a large cohort of pwMS this will reduce the chance of further relapses and delay the time to disease progression.

In choosing a medication with a patient, factors that are typically taken in to account include

- severity of initial relapse
- lesion load
  lesion location > brainstem and spinal cord lesions are more likely to have clinical manifestations
- potential complications of treatment

Patient factors that are considered include

- Patient age
- Comorbidities
- Pregnancy planning
- Current work or school commitments
- Plans to travel
- Side effect profile of medications
- Burden of monitoring
- Patient tolerance of risk

The current availability of a wider range of treatment options has allowed us to make treatment decisions that are effective and palatable to pwMS.

More recently treatment options have emerged for the previously neglected side of MS - progressive multiple sclerosis. Progressive MS often manifests as an increased difficulty in walking. It is typically irreversible, although progression can evolve slowly. Treatments are emerging on the market that aim to slow this progression. These include Siponimod and Ocrelizumab, although strict eligibility criteria remain. Activity is often defined as new radiological activity in a pwMS who is following a progressive course. The pivotal clinical trials of the medication suggest a slowing of progression of approximately 30% over a two-year clinical trial.3 The effect was more pronounced in pw disease activity on imaging.
A frustrating aspect of MS is that DMTs appear to have a less pronounced impact on the condition in patients who are older. Aging appears to also have an additive effect in progression. Overall despite advances, there are significant unmet needs in the population with

MS, particularly those who have a long history of the condition, and those who are at a more advanced stage of disability. Clinical trials are beginning to focus on this population, for example the O-HAND trial is designed to assess the impact of Ocrelizumab on hand function in people with primary progressive multiple sclerosis.

Key Points:

- MS is a relatively common neurological disorder
- Common presentations include optic neuritis, transverse myelitis, sensory symptoms, oculomotor abnormalities, gait disturbance.
- Clinical course is highly variable and difficult to predict at disease onset.
- Early initiation of DMT is now strongly recommended based on clinical trial and epidemiological data.
- Treatment of MS during pregnancy is now increasingly common, plans ideally could be discussed prior to pregnancy with the treating neurology team.
- Options for the management of progressive MS have emerged, but the treatment benefit remains modest.

Treatment options in MS - Table 1: Currently used DMTs in Multiple Sclerosis

Generic name	Trade Name	Administration	Monitoring	Complications/SEs
Interferon beta 1 a	Avonex	Weekly I/M	FBC, U/E, LFT 6 monthly (if stable)	Flu like symptoms, ITP, injection site rxns
Interferon beta 1 b	Betaferon	Alt days S/C	FBC, U/E, LFTs 6 monthly (if stable)	Flu like symptoms, ITP, injection site rxns, possibly depression
Inteferon beta 1a	Plegridy	S/C fortnightly	FBC, U/E, LFTs 6 monthly (if stable)	Flu like symptoms, ITP, injection site rxns, possibly depression
Glatiramer Acetate	Copaxone	Three times weekly s/c	FBC, U/E, LFTs 6 monthly (if stable)	Can be continued in pregnancy
Terflulomide	Aubagio	Once daily po	LFTs 2 weekly for 6 months, then every 2 months	Alopocia, headache.
Potentially teratogenic in pregnancy				
Dimethyl Fumarate	Tecfidera	Twice daily po	FBC and LFTs	Flushing, GI symptoms during first month
Fingolimod	Gilenya	Once daily po	Lymphocyte count 3 monthly	
(>0.2 10^9/L)	Cardiac monitoring on first dose,			
Cladribine	Mavenclad	PO treatment	2 and 6 monthly FBC, U&E.	Follow cancer screening guidelines
Lymphopenia, Herpes zoster				
Ocrelizumab	Ocrevus	IV infusion 6 monthly	6monthly bloods prior to next imfusion	
FBC, lymphocyte subsets,				
immunoglobulins	Infusion reactions			
Hypogammaglobulinemia				
Natalizumab	Tysabri	Monthly IV infusion	JC V Serology 6 monthly;	
MRI 4-6 monthly	PML – progressive multifocal leukoencephalopathy.			
Risk c. 1: 80 if JC+ and Natalizumab>6 years				
Alemtuzumab	Lemtrada	IV Infusion x 5/7 in Year 1; 3/7 Year 2	Monthly FBC, U&E, dipstick; 3 monthly TFTs for 48 months post Rx	Thyroid dysfunction, wide range of autoimmunity, ITP, Glomerulonephritis, Stroke

References:

1. O'Connell K, Tubridy N, Hutchinson M, McGuigan C. Incidence of multiple sclerosis in the Republic of Ireland: A prospective population-based study. Multiple Sclerosis and Related Disorders 2017;13:75-80.
2. Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. Brain 2006;129:584-594.
3. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary

Conducting Research Remotely: The Impact of COVID-19 on the COB-MS trial

Written by: Fionnuala Rogers- research assistant at NUI Galway with the COB-MS feasibility trial.

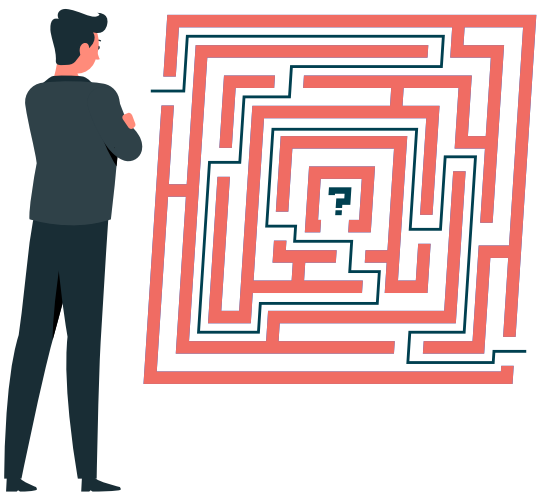
More than eight months have passed since we first entered lockdown. In that time, we have seen a plethora of changes in our society: with working from home; waving to loved ones through windows; and 2-metre distances being the new social “norms”. The ways in which we can safely conduct research with people, and particularly with those who may be vulnerable to infection, have also been transformed. The pros and cons of conducting such research remotely have become clear to our COB-MS research team at NUI Galway in recent months.

The Cognitive Occupation-Based programme for Multiple Sclerosis (COB-MS) project has been significantly adapted to reduce risks of contracting COVID-19. The project set out in November 2019 to test the feasibility of a new therapy, COB-MS, which focuses on helping people with multiple sclerosis who also experience cognitive difficulties, such as difficulties with memory, concentration and problem-solving through education and developing new skills. In a pre-pandemic world, interventions of eight sessions were to be run by qualified occupational therapists (OTs) in group and individual settings, with six of these sessions to be held in groups of 5-6 people in local community centres. Individual sessions were also to take place in participants’ homes. As well as this, home visits were to be carried out by a research assistant pre- and post-intervention, and at two follow-up timepoints. A year on, the project has changed considerably due to the unforeseen pandemic.

All intervention sessions and cognitive assessments are now taking place online, via the videoconference platform, “Zoom”. Along with this new virtual method of running the intervention and collecting data comes perks and obstacles for both researchers and participants alike. Although some participants are au fait with using Zoom, others need a helping hand in getting things set up, and in making sure the camera, microphone and sound are switched on. Time and resources can be saved due to the lack of travel - a bonus for both participant and researcher. But other factors such as the strength of internet connection, sound quality and video clarity can have a significant impact on the quality of interaction between participant and researcher.

Cognitive assessments rely on an individual’s ability to clearly hear and understand instructions, as well as the researcher’s ability to clearly interpret the participant’s responses. In testing verbal memory in face-to-face scenarios, the researcher simply reads a list of words to the participant, and the participant recites back as many words as they can remember. But, when carried out over Zoom, the validity of this test is reliant on the stability of internet connection and sound quality. Low bandwidth or sound feedback may interfere with the understanding of instructions or auditory processing of word lists. Screen-freezing can also impact assessments that require performances to be accurately timed. In visuospatial memory assessments, which require drawing shapes from memory, the size of screen may have an impact on a participant’s performance, particularly if there are visual deficits. Other technological factors such as security settings, e-mail alerts or error messages popping up can also cause distraction and influence performance.

One of the most notable challenges is building one-to-one relationships with participants based on trust without ever meeting in-person. The subtleties of body language can sometimes be lost over camera, and there is a risk of meetings sometimes feeling impersonal. Effective communication is key to overcome these potential barriers. We are incredibly grateful for the resilience and perseverance of the participants who, despite the obstacles, have gotten on board with this new way of communicating and will not allow the pandemic to stand in the way of progression and research.



The value of involving PPI in MS research: A case study of anxiety in MS

Written by: Dr Rebecca Maguire – Associate Professor, Department of Psychology, Maynooth University

Why do we conduct research in MS? Most researchers will acknowledge that the primary reason is to improve our understanding of the disease, which may, in turn, help contribute to the development of more effective treatments and supports for patients and their families. However, until quite recently, MS research was typically carried out "on" patients, with people with MS viewed as passive subjects in research studies. Thankfully, this mindset is now changing and researchers are placing more value on fostering PPI, or Public and Patient Involvement, in research. In Ireland, bodies such as IPPOSI are playing an important role in providing a platform for this patient involvement and funders often require PPI to be considered in the planning for future projects.

Simply put, PPI involves carrying out research "with" patients, acknowledging the valuable perspective that they have in shaping the development of studies and the interpretation of findings. Who better to guide research than the people we are researching in the first place?

The growth in PPI has particular personal relevance for me. While I have been conducting research into how people cope with chronic conditions for a number of years, I have only recently begun to expand my research portfolio into the area of MS. This is because I too am a patient. PPI has shown me the value of championing this lived experience: those of us living with MS have a unique set of experiences which are important to consider when shaping future research agendas. I consider myself extremely privileged to be able to now contribute to research into my own condition and I am eager to get more people with MS involved in this pursuit too.

Research in Progress – The Experience of Anxiety in MS

At the moment, one of my research postgraduate students Austin Fahy, is conducting a PPI-led project in the Department of Psychology at Maynooth University. In this study we are hoping to explore the key influencing factors on the experience of anxiety in MS. While research suggests that anxiety can be a common experience in MS, only a few studies have explored why this might be the case, and, more importantly, less is known about what may help alleviate anxiety in MS. We can learn a lot from reading about previous studies in this area, but in our own research we want to gain a more in-depth experience into the factors influencing anxiety in people with MS living in Ireland.

In order to help us in the design of our study, we were extremely lucky to discuss this topic with a wonderful group of MSers in September. This PPI panel, organised by Aoife Kirwan of MS Ireland, involved eight patient experts who had varying experiences with MS and anxiety. Over the course of an hour's discussion, we covered a range of issues. It was evident that there were a number of shared experiences, but also individual differences, in the panel's experience. Possible reasons for why people with MS may experience anxiety (e.g. perceived lack of control over symptoms), and the strategies that people may find useful in helping cope with anxiety (e.g. seeking out social support, engaging in mindfulness and exercise) were suggested. This information was incredibly useful to us as researchers, but, perhaps more importantly, hearing about the experiences of others was incredibly positive for those of us with MS. It was clear that many people with MS can have worries, but that, thankfully, there are many things that can help alleviate this.

Based on these PPI discussions, we have designed a larger scale study intending to capture the factors influencing anxiety in a wider group of people with MS. Currently, this study is undergoing ethical approval, but once approved, we hope to get a number of people with MS to take part. If you are interested, please feel free to get in touch!

We also hope that our PPI panel will be later able to assist us in the interpretation of the study findings. By doing this, we can be sure that research will be of relevant and value to people with MS, which should ultimately help inform the provision of supports for MS.

Email: **rebecca.maguire@mu.ie**

Twitter: **@RebeccaMaguire**

Acknowledgments: We are incredibly grateful for the time our PPI panel members took in sharing their experiences. **#patientsinvolved**

Participating in PPI

Written by: Lauren McCauley – person living with MS

There is a saying surrounding the empowerment of those with disabilities that goes 'Nothing for us, without us'.It is this simple motto that motivated me to volunteer for patient involvement in MS research. Over the past year, MS Ireland has presented me with several opportunities to get involved with current MS research both as a patient advisor and a participant.

Getting involved with research as a patient advisor ensures that the wishes of people with MS are incorporated into research study designs. This process involves consulting people with MS on the proposed research plans prior to the research taking place. This patient input helps ensure that the research objectives, and in turn, the research findings will be useful and relevant to the MS community. Furthermore, patient involvement helps guarantee that funding directed to towards MS research in utilized appropriately and to its fullest potential.

My experience of being both a patient advisor and a participant in various studies around MS has been overwhelmingly positive. It has been a privilege to learn more about and get involved in current MS research which is directly relevant and potentially beneficial to me. It is paramount that the wishes and opinions of people with MS are respected when designing and carrying out research which directly concerns them. Given this, it has been reassuring to see how accepting, and considerate researchers in the studies I have been involved in have acted towards their participants lived experiences.

On a personal note, as I also come from a research background in my professional life, I have found it incredibly valuable to get involved in MS research from the perspective of a participant and patient advisor. It is based on both my professional background as a researcher and my personal experience of being a participant that I would encourage anyone with MS to get involved and have a say in current MS research. In particular, as these projects are directly relevant to your life and could benefit the future of those living with MS. Further still, it is vital that a range of people with MS volunteer to get involved in research in order to ensure researchers have access patient advisors and participants which fairly represent all corners of the MS community.

Dean Medal

The Dean Medal award was established to enhance the understanding and knowledge of MS researchers by enabling them to travel to centres of excellence. In our last edition of the MS Research eZine we advertised the Dean Medal and invited applications.

MS Ireland wish to thank those who applied for the Dean Medal Travel Bursary last year. Due to the COVID-19 pandemic and travel restrictions, the Research Committee made the decision not to award the Dean Medal. We hope to reopen the Dean Medal for applications in 2021 when there is more clarity on travel restrictions. Please keep an eye on our website and social media channels for an announcement on this in the coming months.

Needs of people with primary progressive multiple sclerosis (NIPS) – a cross-cultural study

Written by: Joan Mc Hugh, Final Year Occupational Therapy Student at NUI Galway.

Primary progressive multiple sclerosis (PPMS) accounts for approximately 10-15% of MS patients, representing an estimated 350,000 patients worldwide (Rice, 2013). The mean age of onset is usually 10 years later than relapsing remitting MS (RRMS) with no differences across gender. Rehabilitation and symptom management could play a possible role in PPMS, but studies in this area are lacking. There is, however, some evidence of the effectiveness of some interventions that address lifestyle management through mindfulness training and aerobic exercise in progressive MS (Venasse, 2018). In the United States in 2010 a needs assessment project in PPMS was carried out (Holland et al., 2010). The findings identified key that needed to be addressed including treatment strategies and support services available to manage PPMS.

We need to know more about the specific needs of people with primary progressive MS so we can deliver treatment that is targeted and appropriate. We, at NUI Galway, are part of a European project that is focused on identifying the needs, treatment options and supports required by people with PPMS in order to stay active and delay progression of MS. This study is part of a larger European project to assess the needs of people with Primary Progressive MS in Europe. The same procedure will take place across several different countries (e.g. Italy, Germany, Spain, Ireland, Czech Republic, Netherlands and UK,) to provide a picture of needs at a European level.

We will gather data for the project through interviews with people living with primary progressive MS and health care professionals. I, Joan Mc Hugh (occupational therapy student at NUI Galway) plan to interview approximately three people living with PPMS, and two healthcare professionals, as part of the study.

If you are interested in being interviewed as part of the study (anytime between January and March 2021) please get in touch. We are looking for people with primary progressive MS who are aged 18-65 years and were diagnosed in the last 10 years.

The interviews will last approximately 30-40 minutes and can be completed over the phone or online. Written consent will be obtained from all participants prior to commencing the study. Ethical approval from the study has been obtained from the HSE.

The results from the study serve as a basis for the larger European study to identify the unmet needs and patient information gaps in PPMS, with the hope that this data will work to set-up an intervention development agenda.

Email: Joan Mc Hugh **j.mchugh17@nuigalway.ie** or supervisor Dr Sinéad Hynes **sinead.hynes@nuigalway.ie**

References:

- Holland, N.J., Schneider, D.M., Rapp, R. and Kalb, R.C., 2010. Meeting the needs of people with primary progressive multiple sclerosis, their families, and the health-care community. International journal of MS care, 13(2), pp.65-74.
- Rice, C.M., Cottrell, D., Wilkins, A. and Scolding, N.J., 2013. Primary progressive multiple sclerosis: progress and challenges. Journal of Neurology, Neurosurgery & Psychiatry, 84(10), pp.1100-1106.
- Venasse, M., Edwards, T. and Pilutti, L.A., 2018. Exploring wellness interventions in progressive multiple sclerosis: an evidence-based review. Current treatment options in neurology, 20(5), p.13.

Dating with Multiple Sclerosis- research summary

Researcher: Kinza Tabassum, final year occupational therapy student NUI Galway.

Early adulthood, a time in which many people are diagnosed with multiple sclerosis, is considered to be an important time for the development of romantic relationships, however the impact of multiple sclerosis on dating and relationships has not been studied. The aim of this study was to understand how living with multiple sclerosis may affect developing romantic relationships and activities associated with dating.

Six females and two males aged between 23-51years took part in this study. Information was gathered through two online focus group discussions which were conducted through Zoom. Dating with multiple sclerosis involves decision making around when and how to tell the partner about the diagnosis. Telling the person about the diagnosis early on is seen as a way of "weeding out" partners who would be unsuitable or partners who would not be accepting of the condition. Some prefer to get to know the person and decide whether they can see a future with them before sharing this private aspect of their life. However, others believe that disclosing the diagnosis may complicate dating or reduce the chances of someone wanting to date them. As a result, they may prefer not to tell the person about the diagnosis and keep it a secret for as long as possible.

People considered the lack of knowledge by others about multiple sclerosis and found that the condition is often falsely associated with images of severe disability. These misconceptions often have to be addressed with the partner during dating however constantly explaining and educating people about the condition can become exhausting and tiring for people. People were glad that they were not in a relationship at the time of receiving their diagnosis because it meant that did not have to rely on another person for emotional support or have the extra burden of reassuring their partner and dealing with their emotional response to the diagnosis.

The symptoms of MS such as pain and fatigue can interfere with physical intimacy and dating activities. Therefore, planning in advance of the date is often required to consider the practical aspects of the date such as parking, suitability of the building or place, the activity and strategies which may be used to adapt e.g. taking breaks during a long walk, drinking coffee to counteract the fatigue. However, last minute changes to plans are sometimes required due to the fluctuating nature of the condition. The fluctuating nature of the condition can have an impact on the couple as they continually adjust to the day-do-day changes. People emphasised that it is important to tell the partner about the MS diagnosis early in a relationship, because not everyone will be able to adapt to or deal with the unpredictability of the condition.

Supervisors: Ms Jackie Fox and Dr Sinéad Hynes

A Vision for MS

Written by: Gemma McIlwaine

A feasibility study: The Belfast Eye and Multiple Sclerosis (BEAMS) study is underway with researchers from the Wellcome-Wolfson Institute for Experimental Medicine (WWIEM) and The Centre for Public Health (CPH), Queen's University, Belfast (QUB). This is an explorative and feasibility study for the use of new and conventional retinal imaging modalities for patients with MS. MS is a central nervous disease that doesn't discriminate from the retina (the back of the eye). Testing the eyesight of patients with MS and taking pictures through different retinal cameras has become a promising research field. Figure 1 shows an image from one of the new retinal cameras of the back of the eye. Correlations and similarities in progression of symptoms and changes in the eye have become evident in some studies, however the small numbers of participants in these studies and the lack of comparison between new and standard eye cameras has created conflicting results. It has been seen in some studies that progression of a disease course of MS (progression of neurodegeneration) including signs of increased disablement have correlated with changes in the eye; specifically changes in the thickness of different layers of nerve cells in the retina measured by a conventional OCT camera.

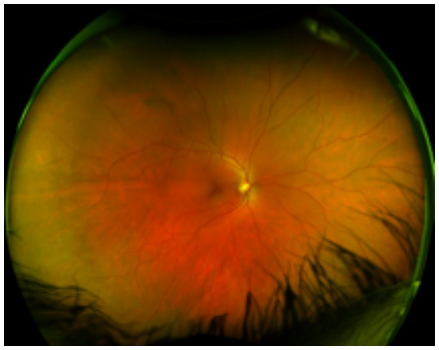


Figure 1: An example image of the back of the eye (retina) with eyelashes protruding the bottom border. The bright white/yellow spot near the middle is the optic disc with blood vessels spanning out to the periphery.

Preliminary analysis of some of the images already taken is being conducted due to Covid-19 halting the recruitment and participation in the study. One of the new eye cameras using adaptive optics (AO) software allows us to see extremely small detail providing images with the identification of single nerve cells in the retina. These particular cells are called 'cone cells' which are a type of photoreceptor cell that react to light. Figure 2 is an image taken from an AO camera with the cone cells being the round light and dark spots in the image. We can also see the shadows of some blood vessels that appear as thick black lines.

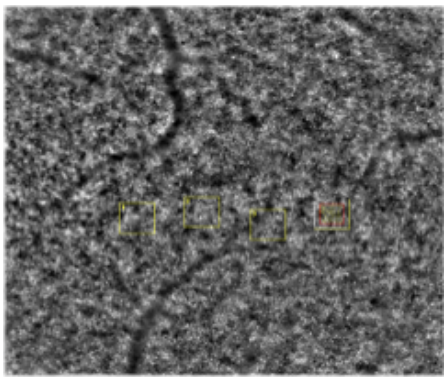


Figure 2: An image of cone cells from the back of the eye using a novel camera with adaptive optics software. The small (dark and light) circular structures are the cone cells and the longitudinal black areas are shadows of blood vessels that supply the retina.

When we compared the density of these cone cells in various areas of the retina we found a decreased density in patients with MS compared the healthy participants which has never been documented before. Figure 3 shows a graph of the density of these cone cells in both patients with MS (blue) and healthy controls (blue) along a central meridian of the eye. However, due to this being a preliminary study using only a small number of participants that were recruited before lockdown (16 patients with MS and 4 healthy volunteers) we cannot conclude anything yet, but it is an exciting start to the study.

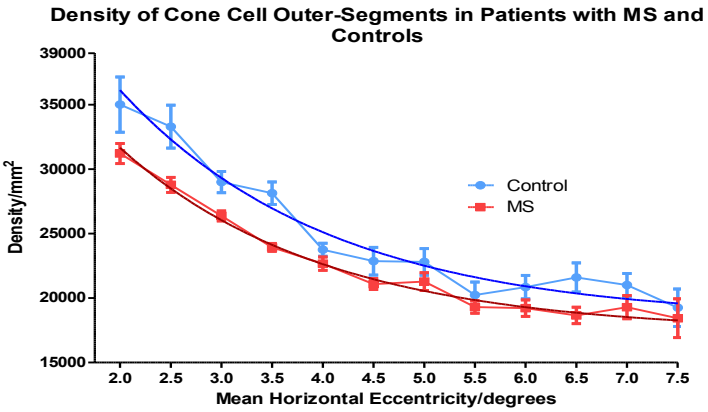


Figure 3: A graph showing the density of cone photoreceptor cells in patients with MS vs controls/healthy volunteers. Control R2 = 0.6669; MS R2 = 0.6578; Two-tailed, non-parametric Wilcoxon matched-pairs signed rank test p=0.0005; Control N= 4; MS N=16

COVID-19 and MS

Written by: Dr Maria Gaughan

As the implications of SARS-Co-V-2 gradually dawned in Europe, rapid changes occurred in MS management across Europe. The degree to which pwMS, the majority of whom are on immunosuppressive or immunomodulatory medications would be impacted was initially unclear. Internationally, experts in the field attempted to categorise the risk of DMTs based on mechanism of action of the medication and pathophysiological models of COVID-19. PwMS were advised to work from home, minimise social contacts and cocoon depending on the medication that they were taking.

Clinic appointments were cancelled and switched to virtual appointments. Medications considered to have a higher risk of immunosuppression, such as Ocrelizumab and Cladribine were postponed. Patients due to commence these medications were rapidly worked up for an alternative. The goal at all times was to ensure effective control of multiple sclerosis while minimising patient risk. Global registries were hurriedly established and have provided good data, although methodological issues remain.

Large French and Italian registries have provided interesting insights.1 PwMS are not at greater risk of catching COVID-19 than the general population. 2Indeed, due to the abundance of caution taken by pwMS, infection rates are likely lower than the general population. The majority of medications taken by pwMS do not significantly increase the risk of severe infection resulting in hospitalisation, ventilation, ICU admission or death. There is a suggestion that caution should be exercised with Ocrelizumab and Rituximab, with studies suggesting slightly increased risk of more severe infection, but not of death. 3 The factors that increase risk of severe COVID-19 in MS appear to be age, disability and co-morbidities.

Current practices in Covid have evolved to ensure that patients have, as far as is possible, access to neurology OPD with virtual OPD if this remains a preference. All services, both within the public and private systems, are attempting to deal with the backlog that arose during March and April. Timely access to disease modifying treatments has remained a priority for the majority of patients.

If a person with MS develops COVID-19 we would advise them to contact their MS team. They may require laboratory investigations to ensure they are not currently immune suppressed. They may require temporary suspension of their current treatment, although more commonly treatment is continued. As with other infections, they may experience a transient worsening of their MS symptoms, although these should improve with resolution of infection. We are attempting to collect data at a national level on pwMS who experience COVID-19 infection, in order to gain further insight into the degree of impact this may have.

Key points:

- Age, disability and co-morbidities are strongly correlated with more severe COVID clinical course.
- MS itself does not increase risk of severe COVID infection, however as above, disability does.
- Certain MS treatments such as Ocrelizumab and Rituximab may possibly increase risk of more severe COVID-19 infection.
- Prolonged cocooning can potentially result in deconditioning and isolation in pwMS - closure of day services, difficulty in accessing physiotherapy services, less ‘incidental’ mobility on a day to day basis. PwMS are encouraged to link in with online exercise classes such as those provided on the mstrust.org.uk website. We also encourage regular walks/exercise and social contact with safe practices, such as mask wearing and frequent hand washing.

References:

1. Sormani MP, Italian Study Group on C-iims, Italian Study Grp C. An Italian programme for COVID-19 infection in multiple sclerosis. Lancet neurology 2020;19:481-482.
2. Moss BP, Mahajan KR, Bermel RA, et al. Multiple sclerosis management during the COVID-19 pandemic. Multiple sclerosis 2020;26:1163-1171.
3. Louapre C, Collongues N, Stankoff B, et al. Clinical Characteristics and Outcomes in With Coronavirus Disease 2019 and Multiple Sclerosis. JAMA neurology 2020;77:1079-1088.

Nanomodulation Of Microrna s In Macrophages

Written by: Frances Nally

Frances Nally

Background: Multiple Sclerosis (MS) is characterised by central nervous system infiltration of peripheral immune cells, the largest fraction of which are macrophages. The macrophage role in MS is multifaceted, in a pro-inflammatory or 'M1' state instructing demyelination and axonal loss, while the anti-inflammatory 'M2' state holds a key role in tissue repair and regeneration. Previously, we have identified that IL-10 inhibition of miR-155 is a prominent mechanism utilised by macrophages to maintain an M2 state. Moreover, using a miR-155 floxed x LysMCre model, where miR-155 is specifically deleted from myeloid cells, there was reduced disease onset and less lesion burden in the experimental autoimmune encephalomyelitis (EAE) animal model. Thus, we hypothesise miR-155 inhibition may favourably modulate the macrophage population to an 'M2' or pro-repair phenotype, reducing inflammation, alleviating disease progression, mimicking an IL-10 mediated effect.

Objectives: To investigate the therapeutic potential of a miR-155 anti-miRNA oligonucleotide (AMO) packaged in nanoparticle-based carriers to enhance uptake into macrophages.

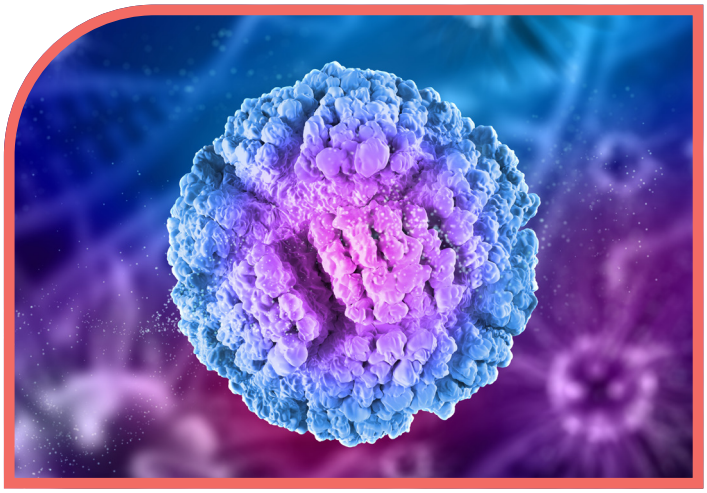
Methods: 4 AMOs were investigated for their ability to inhibit mir-155 in Raw 264.7 and bone marrow derived macrophages (BMDM). The downstream effect of macrophage pro-inflammatory function in response to mir-155 inhibition was examined by measuring a range of macrophage polarisation parameters, including pro-inflammatory cytokine and nitric oxide (NO) production, expression of M2 markers Arginase-1 and CD206, two markers intricately tied with metabolism in the context of polarisation. PLGA and novel star shaped polypeptides were also assessed for in vitro macrophage delivery.

Results: A locked nucleic acid (LNA) modified AMO showed the most promising results for mir-155 inhibition in both Raw 264.7 and BMDM. In further studies we show changes in expression of mir-155 target genes that mimic an IL-10 mediated phenotype, while mir-155 independent increases in M2 marker Arginase-1 suggest a more M2 like phenotype. Additionally, star shaped polypeptides demonstrate the capacity for AMO delivery to BMDM.

Conclusions: mir-155 inhibition can be achieved through delivery of an AMO, and mimics crucial aspects of an IL-10 mediated macrophage phenotype. Star polypeptides represent a promising avenue towards macrophage specific uptake and future in vivo delivery in MS animal models.

Frances Nally[1], Victoria Lyons[2,3], Chiara De Santi1, Sally Ann Cryan[1], Natalie Payne[2] and Claire E McCoy[1]

1. School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland
2. Australian Regenerative Medicine Institute, Monash University, Melbourne, Australia
3. Hudson Institute of Medical Research, Monash University, Melbourne, Australia



A Multidisciplinary Study of Cognition in Multiple Sclerosis

Written by: Orla Strahan

Researchers at Trinity College Dublin are carrying out a study exploring cognitive changes in individuals with Multiple Sclerosis (MS). This research study (titled: "A Multidisciplinary Study of Cognition in Multiple Sclerosis") is being led by Prof. Orla Hardiman, Principal Investigator and Consultant Neurologist, and Prof. Niall Pender, Principal Clinical Neuropsychologist. It is funded by Merck Pharmaceuticals and Science Foundation Ireland.

Changes in cognition (thinking and memory) are common in people with MS and can interfere with daily functioning and quality of life. However, these changes remain poorly understood. There is also a need for better and more reliable measurements of cognition in people with MS. Because of this, it is difficult to design treatments that can improve cognitive performance in those affected. Therefore, our aim is to improve our understanding of the cognitive changes in MS to better understand the needs of patients.

What's involved?

We are inviting individuals 18 years or older with a diagnosis of MS to take part in this study. If you are interested in getting involved, you're participation will involve completing an online survey, which takes approximately 20-30 minutes to complete. The online survey will involve:

- Filling in a short questionnaire about changes to your cognition;
- Filling in a short questionnaire about your mood;
- If possible, asking a family member/friend/ someone who knows you well to fill in a short questionnaire on their opinion of your cognition.

If interested, you may also be invited to complete additional cognitive tests that will assess your thinking in greater detail. These tests will take approximately 2 hours to complete, and at the moment are completed through a virtual appointment using a secure video-link. This will allow you to complete the tests from the comfort of your home.

As part of this study, you may also be invited to take part in EEG recording sessions, which will measure the electrical activity of your brain through a cap which is placed on your head. Each recording lasts approximately 2.5 hours and will be carried out at St. James's Hospital, Dublin. In order to gain a better understanding of MS as its changes over time, we would like to complete these recordings on three different occasions.

Control Participants

We are also seeking healthy individuals who do not have a diagnosis of MS. As this research focuses on the effects of MS on cognition over time, we need to recruit healthy participants to measure thinking over time in people without MS. In scientific research, these people are known as 'Control' participants. Please find the contact details below for anyone interested in participating a Control.

If you are interested in participating, or have any questions at all about the study, please don't hesitate to contact me on the details provided below. We hope our research can benefit people with MS and the community as a whole!

Contact:
Dr. Orla Strahan
Researcher at the Academic Unit of Neurology, Trinity College Dublin/Beaumont Hospital Dublin
Email: **strahano@tcd.ie**