PATHWAYS TO CURES

January 2023

Society Launches New MS Research Projects to Drive Pathways to Cures

The National MS Society has just committed $7.8 million to launch important new research projects as part of our commitment to drive progress in Pathways to Cures for MS.

Fourteen of the new awards stemmed from a targeted request for applications focusing on understanding how pockets of inflammation in the brain drive MS progression. In addition, the Society committed funds to study long COVID and other infections in people with MS.

The Society aligns the global MS research community around the most promising areas outlined in the Pathways to Cures Roadmap. The new research awards described in the following pages align with the three Pathways: STOPPING MS, RESTORING function, and ENDING MS by prevention. Here are a few examples:

STOPPING MS:

• A team at the Cleveland Clinic is investigating whether activating an immune mechanism will turn off chronic inflammation linked to MS progression. (see p. 10)

RESTORING what's been lost:

• A team at the University of Pennsylvania is investigating features of brain cells called "astrocytes" that could be manipulated to enhance myelin repair. (see p. 11)

ENDING MS:

• University of Western Australia researchers are determining if components of the brain that are targeted by the immune system in MS are mistaken as components of the Epstein-Barr virus. (see p. 12)

NEW PROJECTS SUMMARIZED INSIDE:

Pathways to Cures:

Of Note:

Pathways to Cures: STOPPING MS

Stopping MS is defined as achieving a state of no new disease activity, no worsening of daily living or quality of life, and no change in disease manifestations or clinical activity in people living with either relapsing or progressive forms of MS. Two key objectives have been targeted for the next three years: to advance the STOP pathway: early detection before symptoms appear, and precision medicine for individualized treatment and lifestyle strategies to prevent further progression.

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Martina Absinta, MD, PhD
Università Vita-Salute San Raffaele
Milan, Italy
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $534,858
Title: "MRI-single cell transcriptomic investigation of chronic active inflammation of the spinal cord in patients with multiple sclerosis"
Summary: A team in Italy is investigating chronic inflammation in the spinal cord by analyzing genes from spinal cord cells, combined with MRI scan analysis, to find ways to target and stop inflammation in MS.

Background: Chronic inflammation in the nervous system in MS contributes to early disease progression. Whether chronic inflammation is present in the spinal cord as well as seen in the brain is not clear. MS lesions in the spinal cord contribute to physical disability experienced by many.

The Study: Dr. Absinta and team are investigating chronic inflammation in the spinal cord. They are studying how cells communicate with each other in this specific disease context. In the first part of the study, using advanced techniques called single cell transcriptomics, they are investigating the genes that are turned on or off in chronic inflammatory lesions in the spinal cord of people with MS (using autopsy tissue). They are then relating this information to images of these regions obtained with MRI.

Potential Impact: Results from this study may suggest new therapeutic targets aimed at decreasing chronic inflammation in the spinal cord and improving function in people with MS.

Laura Airas, MD, PhD
University of Turku
Turku, Finland
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $600,000
Title: "Exploring microglia and astrocyte-driven pathology in MS using multimodal MRI and PET imaging"
Summary: University of Turku (Finland) scientists are determining the best types of imaging for detecting and tracking chronic inflammation in the nervous system of people with MS.

Background: Current MS therapies do not completely stop the damage to the nervous system that leads to disease progression. Harmful, persistent pockets of inflammation may be the cause of this damage. This inflammation is difficult to detect using typical MRI scans.

The Study: Professor Airas and team are determining which type of imaging is best for visualizing chronic inflammation in MS. They are looking at PET (positron emission tomography) scanning as a possibility. They are also looking for biomarkers present in blood that may also provide information about an individual's disease activity. The team is analyzing images and blood samples from 128 people with MS and comparing them to people without MS.

Potential Impact: These assessments are being performed at the level of individual people, which may eventually allow selection of personalized treatments to decrease inflammation and prevent nervous system damage and disease progression.

Susan Gauthier, DO, MPH
Weill Cornell Medical College
New York, NY
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $656,698
Title: "Establishing the clinical relevance of chronic active MS lesions and quantification of their inflammatory trajectory for a new treatment target"
Summary: A team at Weill Cornell Medical College is using a type of MRI to understand the role of inflammation in chronic, long-term lesions in the brain of people with MS.

Background: In MS, lesions, or spots of damage or disease activity, seen in the brain on MRI scans may persist for a long time. These are called chronic lesions. A subgroup of these older lesions continue to show inflammation around their edges, which may lead to more myelin loss. These lesions are called chronic active lesions, and this study will focus on exploring the impact of chronic active lesions on disease progression.

The Study: Dr. Gauthier and team are assessing whether chronic active MS lesions contribute to clinical disability in people with MS. To do this, they are using

a type of MRI called quantitative susceptibility mapping (QSM) and are using imaging and clinical data previously collected from people with MS. QSM assesses the amount of iron present in the lesion, which indicates the presence of active immune cells. The team is asking if the development of more chronic active lesions over time leads to more accumulation of disability, and whether using stronger MS medications can decrease the chance of developing these lesions. They are also determining if QSM can be used as a tool to measure the effect of treatment on reducing the inflammation in these lesions.

Potential Impact: Incorporation of QSM into the assessment of people with MS may provide a more comprehensive understanding of chronic inflammation in older lesions and could be used to determine disease stability and response to therapy.

Jennifer Gommerman, PhD
University of Toronto
Toronto, Ontario, Canada
Co-Investigator: Alexandre Prat, MD, PhD
Université de Montréal, Quebec, Canada
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $300,000 plus $300,000 co-funding by the MS Society of Canada
Title: "Compartmentalized inflammation in MS – A Focus on Fibroblasts"
Summary: A team at the University of Toronto and l'Université de Montréal is working to understand cell interactions in the meninges (a protective cover of the brain) and to determine if blocking these interactions will stop MS.

Background: In MS, inflammation is present in the protective envelope of the brain, called the leptomeninges. This inflammation appears to be related to injury to adjacent gray matter, which is a part of the brain that contains the cell bodies of nerves. Immune cells present in the meninges interact with cells called fibroblasts, which make connective tissues. These interactions may be a source of gray matter injury.

The Study: Professor Gommerman and team are working to better understand the interactions between immune cells and fibroblasts in the leptomeninges by examining tissue samples from people with MS, as well as mice with an MS-like disease, and cells grown in a dish. They are looking at the characteristics of these interactions using sophisticated tools. They will also block important molecules they identify to see if doing so reduces inflammation.

Potential Impact: Results from this study may suggests ways to decrease the inflammation in the leptomeninges that injures gray matter in people with MS.

Tanja Kuhlmann, MD
University Hospital Münster
Münster, Germany
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $574,838
Title: "Histological, transcriptomic and functional characterization of a new lesion type associated with fast disease progression"
Summary: A team at the University Hospital Münster, Germany and the Netherlands Institute for Neuroscience in Amsterdam is investigating a type of lesion that is commonly present in the brains of people with rapidly progressing MS and therapies that may treat these lesions.

Background: In some people with MS, their disease progresses rapidly. In other people, their disease progresses more slowly. Rapid progression may be due to the presence of a type of damaged areas, or lesions, called broad rim lesions.

The Study: Prof. Kuhlmann and team are examining brain tissue from people who died following rapid or slow MS disease progression. They are investigating the inflammatory cells and their functions that are present in broad rim lesions compared to inflammatory cells present in other types of MS lesions from people with rapid and slow MS disease progression. They are also looking at whether the cells that make nerve-insulating myelin (oligodendrocytes) are especially injured in broad rim lesions. Finally, they are testing whether therapies that are being tested in people with MS affect the inflammatory cells in broad rim lesions.

Potential Impact: Results from this study may help researchers understand what therapies are more likely to work in people with rapid or slow disease progression.

Luca Peruzzotti-Jametti, MD, PhD
University of Cambridge
United Kingdom
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $599,422
Title: "METAbolic control of smoldering NEUROinflammation (META_NEURO)"
Summary: A team at the University of Cambridge is investigating miscommunication between cells in the brain that may occur during the course of progressive MS.

Background: Two types of cells in the brain, called microglia and astrocytes, normally communicate with one another. This communication appears to be disrupted in progressive MS, leading to persistent inflammation and failure of the body's normal capacity to repair some of the damage.

The Study: Dr. Peruzzotti-Jametti and team are investigating the idea that this miscommunication occurs due to a molecule called succinate and its docking site, or receptor, called SUCNR1. Using brain tissues from people who had

progressive MS, the team is examining which cells express succinate and SUCNR1. They are also studying microglia and astrocytes growing in lab dishes to look at how SUCNR1 works in these cells. Finally, in mice with an MS-like disease, they are blocking SUCNR1 to see if doing so stops the disease.

Potential Impact: Results from this study may ultimately lead to treatments that improve the quality of life in people with progressive MS by targeting an aspect of the disease that leads to disability.

David Pitt, MD
Yale University
New Haven, CT
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $660,000
Title: "Astrocyte network disruption in perilesional white matter is mediated by adenosine A2A receptors and contributes to multiple sclerosis progression"
Summary: Yale University scientists are investigating a docking protein on brain support cells called astrocytes and whether it plays a role in MS progression.

Background: Astrocytes are a type of supporting cell in the brain and spinal cord. They form a network of cells that is important for normal brain function. Dr. Pitt and team are investigating the idea that this network of astrocytes is disrupted in secondary progressive MS, and that this disruption causes cell damage and inflammation.

The Study: In previous work, Dr. Pitt's team has shown in the dish that proteins on the surface of astrocytes, called adenosine 2A receptors, can disrupt astrocyte connectivity. They have also shown that these receptors are highly expressed in areas surrounding MS brain lesions, especially in people with secondary progressive MS. They are now expanding on these observations by looking for this disruption in brain tissue samples from people who had MS compared to people without MS. The team is also looking at mice with an MS-like disease in which adenosine 2A receptors have been deleted and are asking if their disease is less severe. Finally, they will treat mice with an MS-like disease with an FDA-approved therapy for Parkinson's disease that blocks adenosine 2A receptors and will examine if this therapy is beneficial.

Potential Impact: If this study indicates that blocking adenosine 2A receptors has a benefit in mice with an MS-like disease, there is already an FDA-approved therapy that could be repurposed and tested in people with progressive MS.

Long COVID in People with MS

Amber Salter, PhD, MPH
University of Texas Southwestern Medical Center, Dallas, TX
Collaborators: Ruth Ann Marrie, MD, PhD (University of Manitoba)
Gary Cutter, PhD (University of Alabama)
Robert J. Fox, MD (Cleveland Clinic)
Award: Strategic Initiative
Term: 10/1/22-9/30/23; **Funding:** $165,592
Title: "Understanding Post-COVID-19 Syndrome in Individuals with Multiple Sclerosis using the NARCOMS Registry"
Summary: Researchers are investigating the impacts of long COVID and other infections in people with MS to improve care.

Background: The COVID-19 pandemic has affected millions of people, including those living with MS. Infections of all kinds can increase a person's risk for MS relapse, and also for "pseudo relapses," which involve temporary worsening of MS-related symptoms due to non-MS factors such as infection. Telling the difference between MS relapses and pseudo relapses is important because actual relapses may call for changes in disease-modifying therapy. Some people experience lingering, potentially debilitating effects after the acute COVID infection has subsided – this is called long COVID. Common symptoms include fatigue, loss of sense or taste, brain fog, cough, chest pain, shortness of breath, and muscle aches. Some of these symptoms overlap with symptoms of MS.

The Study: To improve care, it is important to figure out which symptoms, relapses, pseudo relapses and disease progression are the result of MS and which relate to long COVID. To do this, this team is tapping the NARCOMS registry to compare groups of people with MS over time. One group tested positive for COVID-19, one group tested negative but had some other infection, and one group did not have a positive test or infection. Comparing these groups will help the researchers tease out long COVID symptoms and relapses from MS-related disease activity.

Potential Impact: This project will enhance the general understanding of the consequences of infection in people with MS, and whether the effects of COVID-19 infection differ from those of other infections.

Lucas Schirmer, MD
University of Heidelberg
Heidelberg, Germany
Co-investigators: Kate Fitzgerald, ScD, and Peter Calabresi, MD
Johns Hopkins University
Baltimore, MD
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $358,939 (Schirmer) plus $192,556 (Fitzgerald)
Title: "Multiscale cell type mapping of gray and white matter pathology in multiple sclerosis"
Summary: Collaborators in Germany and the U.S. are identifying differences in genes turned on or off among various cell types and regions in the brains of people with MS for insight into why some areas are more vulnerable to inflammation than others.

Background: MS can affect different areas of the brain and spinal cord. Cells in different areas may respond to inflammation in different ways and likely have different sets of genes turned on and off. This team is focusing on cells that have been implicated in chronic inflammation in the brain.

The Study: Dr. Schirmer and collaborators are using brain tissue from people who had MS and from people without neurological disease. Using advanced techniques, they are characterizing individual cell types in the optic nerve that leads to the eyes, and two areas of the brain. They are identifying genes that are specifically turned on in particular regions and cell types, and that show differences in people with MS compared to people without neurological diseases. The team will also look at the genetic risk factors of individuals and how they might relate to what they are seeing in the brain. The team will end up with molecular atlases that may help explain how inflammation smolders in different parts of the brain.

Potential Impact: This study may suggest ways more personalized approaches to treating MS when specific areas of the central nervous system are affected.

Olaf Stuve, MD, PhD
University of Texas Southwestern Medical Center
Dallas, TX
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $659,363
Title: "Deciphering choroid plexus volume changes in multiple sclerosis"
Summary: University of Texas Southwestern Medical Center scientists are studying a structure in the brain called the choroid plexus to determine if it is an indicator of MS disease stage and a site of entry into the brain for particular subsets of inflammatory cells.

Background: In MS, inflammatory cells move from the blood into the brain. Some of these inflammatory cells may pass into the brain through a structure in the brain called the choroid plexus.

The Study: Prof. Stuve and team are investigating the idea that the choroid plexus looks enlarged on MRI scans in people with early relapsing MS and that this enlargement is an indication of inflammatory cells entering the brain. To test these ideas, they are comparing previously obtained MRI scans from people with active, relapsing MS with scans from people who have not had an MS relapse or MS lesions in many years. They are also examining mice with an MS-like disease to look for particular subsets of inflammatory cells that enter the brain through the choroid plexus.

Potential Impact: Changes in the choroid plexus may be an indicator of the stage of MS, and understanding which inflammatory cells enter the brain that way may suggest cell-specific therapies for MS.

Bruce Trapp, PhD
Cleveland Clinic Foundation
Cleveland, OH
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $660,000
Title: "Comprehensive analysis of compartmentalized inflammation in multiple sclerosis brain"
Summary: A team at the Cleveland Clinic is investigating how brain cells called microglia may have different activities depending on where they are located, which may be related to lesion expansion and disability progression in MS.

Background: In progressive MS, persistent inflammation is present in distinct areas, or compartments. Microglia, a type of supporting cell residing in the brain, are present in these compartments and monitor the small environment in which they are located. There are different types of microglia, and their functions can be beneficial or harmful.

The Study: Prof. Trapp and team are investigating the role of microglia in lesion expansion and disability progression in MS by testing the idea that microglia are different depending on the compartment in which they are located. Using autopsy samples from people who had MS, they are looking at differences in gene activity in microglia located in different types of lesions. They are also looking for differences in microglia located in gray matter (areas of the brain where nerve cell

bodies reside) lesions compared to white matter (areas of the brain largely composed of nerve fibers covered by myelin) lesions.

Potential Impact: Results from this study may suggest ways to modulate microglia to stop inflammation, depending on where they are located and in what type of lesion.

Jessica Williams, PhD
Cleveland Clinic and Case Western Reserve University
Cleveland, OH
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $660,000
Title: "The role of astrocyte PD-L1 in dampening compartmentalized chronic inflammation"
Summary: A team at the Cleveland Clinic is investigating whether activating an immune mechanism will turn off chronic inflammation in MS.

Background: During MS, immune cells enter the brain and spinal cord and release molecules that can act to both ramp up inflammation or tamp it down. These are called immune checkpoints, and inflammation is reduced when immune checkpoint molecules are activated.

The Study: Dr. Williams and team are investigating whether an immune checkpoint molecule called PD-1 and its binding partner PD-L1 can be activated in MS-like disease in mice to resolve inflammation. The team is determining what immune system molecules (called cytokines) can induce PD-L1. They are testing whether an experimental compound that can activate PD-1 improves MS in mice, and what cell types are involved in this response. They are also examining brain tissues from people with MS to determine what cell types would be targeted by PD-1 activation to better understand the potential of this approach to resolving MS-associated inflammation.

Potential Impact: Activating PD-1 is a strategy currently in Phase I clinical trials for rheumatoid arthritis, alopecia, and transplant rejection. This will advance its testing in people with MS if this project and other work indicates this is a viable strategy.

Pathways to Cures: RESTORING FUNCTION

Multiple sclerosis can result in many different symptoms, including vision loss, pain, fatigue, sensory loss, impaired coordination, mobility, and cognitive changes. Translation of knowledge from basic mechanisms to functional impact is needed to optimize treatment, manage symptoms, and ultimately restore function for people living with both relapsing and progressive forms of MS. Two key objectives have been targeted for the next three years to advance the RESTORE pathway: remyelination and restoration of function.

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Jennifer Orthmann-Murphy, MD, PhD
University of Pennsylvania
Philadelphia, Pennsylvania
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $625,528
Title: "Defining cortical reactive astrocyte heterogeneity and contribution to remyelination"
Summary: A team at the University of Pennsylvania is investigating features of brain cells called "astrocytes" that could be manipulated to enhance myelin repair.

Background: Immune attacks on the brain and spinal cord during MS cause damage to nerve-insulating myelin, and loss of the cells that make myelin, the oligodendrocytes. The nerve cells can also be damaged. We do not yet understand what factors interfere with complete replacement of myelin and oligodendrocytes in the cortex, the outermost layer of the brain. Astrocytes are another specialized type of brain cell that spend their time interacting with oligodendrocytes and myelin to help the brain function. Astrocytes 'react' to myelin loss (or demyelination) by changing their function in a variety of ways that we are only starting to understand. This team is exploring whether some types of astrocytes support the formation of new myelin and oligodendrocytes (remyelination) and other types of astrocytes block remyelination.

The Study: Dr. Orthmann-Murphy and team are investigating the interactions between oligodendrocytes and astrocytes in lab mice. They are looking at how astrocytes change after myelin loss and determining if some astrocytes support oligodendrocytes and myelin repair and if other types block repair.

Potential Impact: Results from this study may help identify ways to manipulate astrocytes with treatments to improve myelin repair and restore function in people with MS.

Pathways to Cures: ENDING MS

Ending MS is defined as no new cases of MS. Two key objectives have been targeted for the next three years to advance the END pathway: primary prevention and secondary prevention. Primary prevention involves limiting exposures to MS risk factors in the general population. Secondary prevention focuses on individuals at high risk for MS and developing and deploying interventions in the period prior to preclinical/clinical stages of disease to reduce or eliminate the risk for developing MS.

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Allan Kermode, MD
University of Western Australia
Perth, Australia
Award: Request for Applications
Term: 10/1/22-9/30/25
Funding: $577,992
Title: "White matter lesion single nuclei transcriptomics and epitope discovery to identify immune targets in multiple sclerosis"
Summary: University of Western Australia researchers are determining if components of the brain that are mistakenly targeted by the immune system in MS are similar to components of the Epstein-Barr virus.

Background: In MS, the immune system attacks the brain and spinal cord, possibly by mistakenly recognizing a component as "foreign" that is in fact its own "self"tissues. The Epstein-Barr virus, which most people have been exposed to, is a trigger for MS in conjunction with other risk factors. One possibility is that the immune system thinks a normal component of the brain looks like the Epstein-Barr virus, triggering attacks on normal brain tissues.

The Study: Dr. Kermode and team are looking at immune cells in the brain from autopsy samples from people with MS and blood from people diagnosed with clinically isolated syndrome (often a pre-MS condition). The team is identifying what these immune cells are targeting through sophisticated lab techniques. These studies may help identify the cause of MS.

Potential Impact: Understanding the cause of MS may lead to development of ways to end MS by prevention. It should also aid the development of safer and more effective treatments for people already living with MS.