

# From reducing relapse to restoring function

**Professor Patrizia Casaccia** leads a successful laboratory at the Icahn School of Medicine at Mount Sinai. In an engaging conversation, she reveals how she and her colleagues work together to understand the mechanisms underlying multiple sclerosis onset and progression, and use their knowledge to research innovative new treatments



## How did you come to set up the Casaccia Lab, and can you describe its aims for regenerative medicine?

The idea of creating a Center of Excellence for Neural Repair was in line with the translational effort and mandate of the Friedman Brain Institute at the Icahn School of Medicine at Mount Sinai. The goal of the Center is to develop interdisciplinary approaches to stop the progression of neurodegenerative and demyelinating diseases and most importantly to restore function.

## Could you briefly outline the mechanisms by which neurodegeneration occurs?

The actual mechanism of neurodegeneration (ie. damage to axons and loss of neurons) is still debated and its elucidation is critical for development of effective therapies. It was traditionally believed that damage was the direct consequence of 'loss of myelin', but we now know that this is not the only cause. Damaged axons can also be detected in areas that do not show signs of clear demyelination. Existing treatments have successfully reduced the number of relapses

by targeting the immune component of the disease, but the neurodegenerative aspect remains an open target.

This combined evidence suggested the existence of alternative mechanisms of axonal damage. We have recently identified at least two novel mechanisms and are working towards the development of new treatments. One of the lead candidates is being tested in animal models of MS and the first results are very encouraging. We hope to translate them into a therapy for patients with severely impaired motor function.

## How do epigenetic mechanisms influence the likelihood of someone developing MS?

Epigenetics refers to the modulation of genes by external factors. We think that genetics provides the susceptibility to develop the disease, but environment and lifestyle have the ability to tweak this propensity by changing the expression of certain genes. In other words, the manifestation of the disease is the result of a combination between genetic predisposition and environmental influences including sun exposure, smoking, possibly diet and lifestyle, viral infections and microbial populations.

An example of how the environment can affect gene expression is exposure to smoke. It is now well accepted that smoking modulates the methylation of bases in the DNA and changes the expression of certain genes. If the affected genes are expressed in the brain and serve a neuroprotective function, then the brain of a subject exposed to smoke will be more 'fragile' or 'less protected'. An example of how the expression of genes can be affected by the environment is the study of identical twins. Despite sharing the same DNA, it is often the case that only one twin of the pair is affected by MS; a phenomenon called 'discordance'. A first study revealed no apparent differences in DNA methylation in some immune cells, but it will be of great interest to study whether

discordant twins bear differences in DNA methylation in the brain.

## Could you describe some of your most groundbreaking findings?

All the cells in our bodies share the same genetic information, so each one must define its own identity by making sure that only genes involved in its specific function are expressed. My lab has been investigating how oligodendrocytes acquire their identity during development. We showed that the identity of these myelin-making cells requires the inactivation of genes that prevent myelin gene expression. We then demonstrated that the process of myelin repair in the adult brain recapitulates developmental events and is severely impaired with ageing. We are therefore exploring the idea that myelin regeneration in the adult brain could be achieved by finding ways of eliminating the expression of genes interfering with myelin synthesis.

## To form a unified theory of MS, knowledge of the complex processes involved must be integrated. How have you achieved this so far? In which direction do you foresee treatment options for people with MS developing?

Knowledge must absolutely be integrated and we need to keep our minds open to new strategies. To date, most studies have focused on the immunological components of MS. These efforts have paid off and we have been able to achieve good management of the relapse rate in patients. It is now time to address the neurodegenerative aspect and start thinking about developing new animal models to study disease progression. We need to identify treatment options for patients with the primary progressive form of the disease and integrate specific treatment with lifestyle changes. The goal is to stop progression and render MS a curable disease.

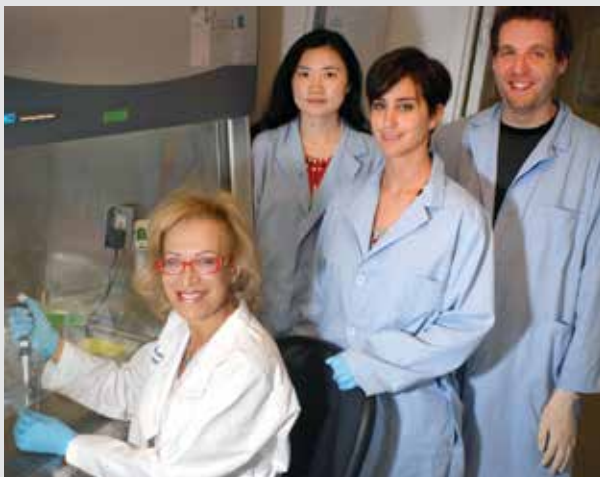
# Multiple sclerosis: an end in sight?

Funded by the National Institute for Neurological Disorders and Stroke and National Multiple Sclerosis Society, work at the **Center of Excellence for Neural Repair** at the Friedman Brain Institute of Icahn School of Medicine at Mount Sinai is transforming our understanding of multiple sclerosis and how to prevent and treat it

**MULTIPLE SCLEROSIS (MS)** is increasingly recognised as a neurodegenerative demyelinating disorder with myelin and neuronal pathology. Whilst the majority of patients experiences symptoms that resolve over time (relapsing-remitting), a small percentage is affected by permanently debilitating symptoms (primary progressive). Eventually, both forms of the disease will share a phase characterised by worsening of the symptoms and identified as 'progressive MS'.

MS was originally described as an autoimmune disorder resulting from an immune attack on myelin – the shield for the nerve fibres that transmit messages between the brain and body – however, it is now clear that neurons and axons are also damaged. Because the central nervous system is involved in mediating how we think, speak, feel and move, patients can develop a wide range of physical symptoms such as fatigue, muscle spasms, dizziness and visual problems, as well as impacts on memory and emotions.

Scientists have been investigating the causes of MS for decades, but have not been able to decipher the mechanism leading to disease progression. Professor Patrizia Casaccia heads the Center of Excellence for Neural Repair at the Friedman Brain Institute at the Icahn School of Medicine at Mount Sinai in New York, USA. Her goal is to understand disease progression and how lifestyle, diet and environmental components can be integrated within an holistic and personalised approach for MS treatment.



Casaccia (left) with postdoctoral fellows: Jia Liu, Mar Gacias and Jeffery Haines.

## COLLABORATION AND TRANSLATION

The Center of Excellence for Neural Repair was founded with the mission to integrate various technologies across multiple disciplines in the pursuit of building new knowledge on MS, including the investigation of gene-environment interaction. It includes a comprehensive patient care centre and a strong research community aimed at finding new strategies for stopping the progression of the disease and restoring function. Casaccia's laboratory is focused on understanding the process of neurodegeneration in MS and developing strategies to stop it, while promoting mechanisms of myelin repair, by translating lessons learned from developmental studies.

At every stage of the research process, Casaccia has MS patients in mind. She thus operates an open-lab policy which is designed to break down the conventional barriers between scientists and the public: "I believe that patients should have access to research labs and understand what we are studying and why it takes time to achieve solid research findings," she explains.

All of the lab's research relies on interdisciplinary collaboration and developing strong relationships with other research centres in order to better pool expertise and resources between different scientists. As such, the Casaccia Lab has links with investigators from US institutions such as the University of California, Los Angeles; University of Colorado in Boulder; University of California, San Francisco; Massachusetts General Hospital in Boston; Johns Hopkins in Baltimore; University of Virginia; and the Cleveland Clinic, as well as with centres across Europe (University of Cambridge in the UK, Max Planck Institute in Germany, University of Valencia in Spain) and even Australia and Singapore. Casaccia describes the wide range of disciplines that her lab brings together: "We have been collaborating with biostatisticians and bioinformaticians to analyse terabytes of data from our experiments; with neuropathologists to define changes in human tissues; with electrophysiologists to define functional outputs; and

with chemical engineers for drug development". Without these collaborations, turning new knowledge about MS and its causes into effective treatments would be a much more laborious task.

## GENETIC AND ENVIRONMENTAL FACTORS

Her vanguard approach to research has earned Casaccia numerous accolades. For instance, she was recently awarded the prestigious Javits Investigator Award for Outstanding Contribution to Neuroscience.

In collaboration with her colleagues, Casaccia has significantly improved our understanding of myelin production and the role of the underlying molecular mechanisms regulating myelin repair in MS. One particularly important project proved that as we age the cells that produce myelin become increasingly defective, reducing the body's ability to reproduce any damaged myelin and prevent the onset of MS.

This finding has opened up a number of new avenues for preventative treatments which use this knowledge to counteract the process. The impetus to translate better understanding of the mechanisms behind MS into more effective treatments for the condition underpins all of Casaccia's work, and the Javits Award will enable her and her team to continue to build on their breakthroughs in the field.

## BEYOND MS

One especially interesting outcome of Casaccia's collaborations was a discovery that contributed to a growing awareness that myelin depletion is a factor in a range of other neurological disorders. The team found that social behaviour and stress can affect myelin levels by altering oligodendrocytes – the cells which create the protective layer of myelin around axons.

The researchers were able to show that experiences of stress and social isolation can trigger changes in the nuclei of these cells leading to lower levels of myelin in the parts of the brain that regulate complex behaviours. Casaccia explains the significance of this breakthrough: "These findings are important for depression and may also shed some light on the comorbidity between MS and depression". Combined with the knowledge that certain lifestyle factors are likely to influence not only an individual's chances of developing MS but also the course of the disease

## INTELLIGENCE

### TRANSLATING SCIENTIFIC KNOWLEDGE INTO NEW APPROACHES FOR TREATMENT OF MULTIPLE SCLEROSIS

#### OBJECTIVES

- To understand the molecular mechanism of environment-gene interaction
- To study the progressive forms of multiple sclerosis (MS)
- To define the steps leading to the acquisition of oligodendrocyte identity
- To understand how myelin forms during development
- To develop new therapies to preserve axonal function and improve recovery

#### KEY LAB MEMBERS

Qi Wu, Senior Associate Researcher • Gregory Moy, Research Assistant • Jeffery Haines, Postdoctoral Fellow • Jia Liu, Postdoctoral Fellow • Laura Magri, Postdoctoral Fellow • Mar Gacias-Monserrat, Postdoctoral Fellow • Oscar Gomez-Vidaurre, Postdoctoral Fellow • Marylens Hernandez, PhD student • Jimmy Huynh, MD PhD student • Jialiang Liang, PhD student • Kadidia T Adula, PREP scholar • Patricia Mae Santos, Master's student

#### FUNDING

National Institute for Neurological Disorders and Stroke • National Multiple Sclerosis Society • Friedman Brain Institution Seed Funds

#### CONTACT

**Professor Patrizia Casaccia**  
Principal Investigator

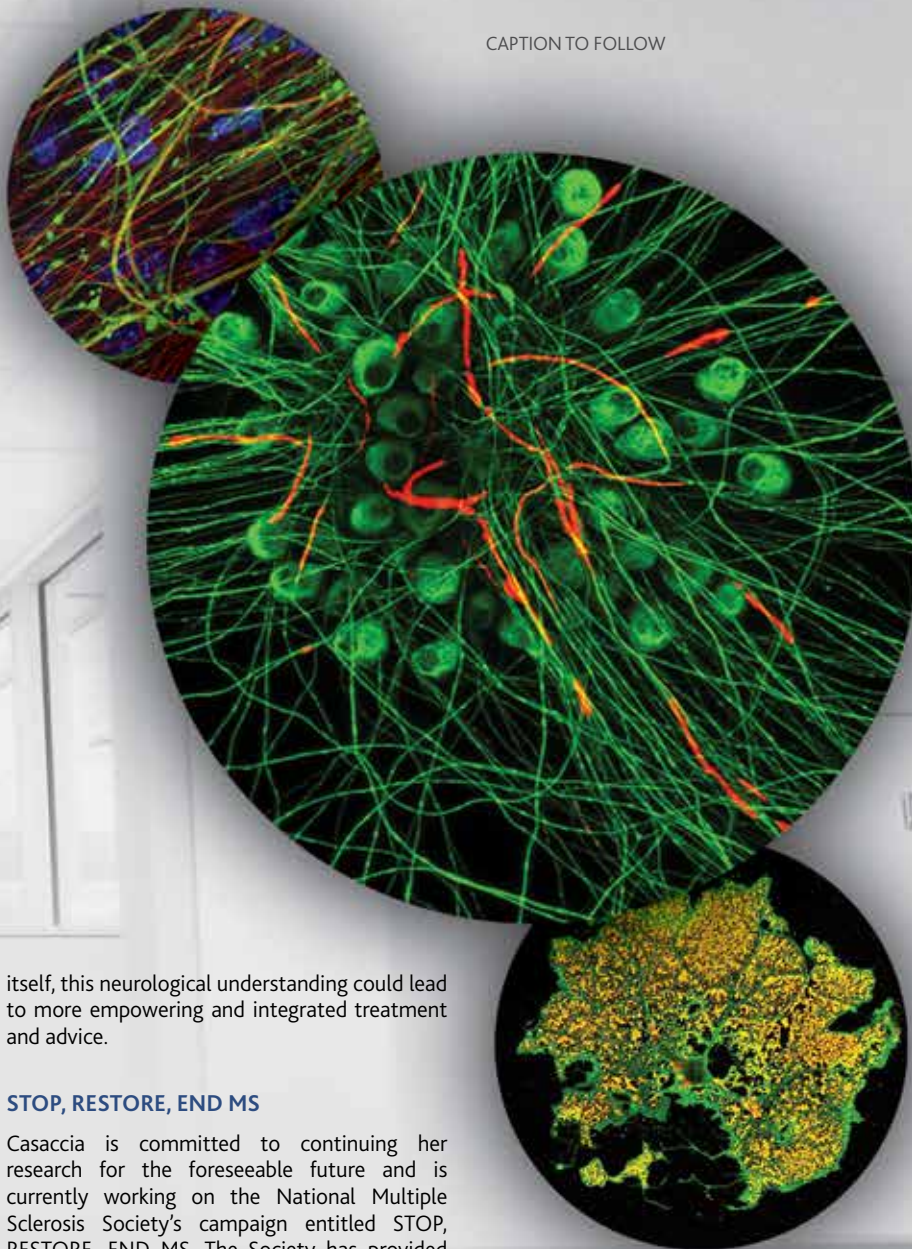
Department of Neuroscience and Department of Genomics and Multiscale Biology  
Icahn School of Medicine at Mount Sinai  
1425 Madison Avenue (Icahn Building)  
Room 10-70F  
New York, NY 10128  
USA

T +1 212 659 5988  
E patrizia.casaccia@mssm.edu

[www.neuroscience.mssm.edu/casaccia/](http://www.neuroscience.mssm.edu/casaccia/)

**PROFESSOR PATRIZIA CASACCIA** received an MD from the Catholic University of Rome and a PhD in Cell Biology from SUNY-HSCB, Brooklyn. In 1999, she became Assistant and then Associate Professor at UMDNJ Robert Wood Johnson Medical School. In 2008, Casaccia moved to New York, where she has since held the position of Professor of Neuroscience, Neurology and Genetics and Genomics. She is now Chief of the Center of Excellence in Neural Repair from Demyelinating Disorders at the Friedman Brain Institute of the Icahn School of Medicine at Mount Sinai, New York.

CAPTION TO FOLLOW



itself, this neurological understanding could lead to more empowering and integrated treatment and advice.

#### STOP, RESTORE, END MS

Casaccia is committed to continuing her research for the foreseeable future and is currently working on the National Multiple Sclerosis Society's campaign entitled STOP, RESTORE, END MS. The Society has provided her lab with funding to work in partnership with biotech company Karyopharm to accelerate the development of exciting new therapies targeting the neurodegenerative phase of the disease, based on Casaccia's success in animal models. They are also exploring ways to restore lost function by testing compounds that target newly identified molecular mechanisms of remyelination failure in older brains.

The ultimate goal is, of course, to put an end to the disease once and for all. To accomplish this, Casaccia is working closely with the Corinne Goldsmith Center for Multiple Sclerosis within the Mount Sinai School of Medicine. Together, the researchers are exploring potential new ways of predicting disease progression or therapy responsiveness. "We believe that the future of medicine will involve personalised treatments and holistic approaches tailored to each individual," she enthuses. The studies will include analysis of stools, blood and cerebrospinal fluids from each patient. As every individual suffers from MS in different ways

according to how their nervous system has been impaired, this personalised approach in the future promises to be far more effective than a one-size-fits-all solution.

Through her research, Casaccia has provided new hope to prevent, treat and cure MS. Her contributions to the field so far mean that there now exists a far more detailed understanding of the molecular mechanisms that underpin the development of the condition and how it is related to epigenetic and environmental factors. Casaccia's innovative approach means that all breakthroughs in understanding are channelled directly into the development of new treatments and preventative measures. Given the progress that she and her lab have made so far, and the respect she commands from the wider research community, it is hard not to share Casaccia's enthusiasm and optimism that the coming years will bring significant advances in the battle against this complicated and cruel disease.

