



MS Society Research Directory

**MS Society Funded Research
into Causes and Cures
for MS**

Grantholder: Professor Richard Reynolds

Institution: Imperial College, Charing Cross Campus, London

Title: The Multiple Sclerosis Society UK Tissue Bank

Grant number 458

The provision of high quality post-mortem brain and spinal cord tissue from people with MS is vital to the future of MS research in the UK. The primary aims of the MS tissue bank are:

- To provide bona fide researchers with high quality post mortem material from people with MS that can be used for a wide range of scientific techniques.
- To store tissue in ways that will provide optimal material for a wide range of scientific techniques.
- To increase awareness of the importance of studying human brain tissue amongst people with MS and their carers.
- To optimise procedures for the recruitment of MS donors.
- To ensure that after death, the brain is rapidly harvested and transported to the brain bank for processing.
- To neuropathologically confirm the diagnosis of MS and to communicate this to the donor's, GP, and neurologist.
- To report the results of research performed on material obtained from the brain bank.



**Professor Richard Reynolds,
Scientific Director of The
Tissue Bank**



Donated tissue samples



**Dr. Abhi Vora,
Tissue Bank Manager**

Grantholder: Dr. Gavin Giovannoni

Institution: Institute of Neurology, Queen Square, London

Title: Axonal loss and repair of damaged tissue in MS: a study of biochemical markers linked with clinical, MRI and immunological findings

Grant number 483

MS causes repeated bouts of inflammation within the brain and spinal cord. This damages myelin (the fatty insulating material that protects the nerves) as well as nerve cells and axons (the fibres extending from nerve cells). If the damage is severe, the nerve cells and axons die and are replaced by scar tissue, resulting in loss of nerve function and permanent disability.

During these processes, specific proteins (biochemical markers) are released into the spinal fluid and blood, and some of these are passed out of the body in the urine. The study plans to measure these proteins frequently in more than 100 people with MS for a period of three to five years. In this way, the study hopes to monitor the nerve cell loss and scar tissue, and see if they are associated with various brain scan changes and the disease getting worse.

The main aim of this study is to establish a reliable way for neurologists to monitor these disabling disease processes. This will provide us with a way to measure the effectiveness of new treatments and will further our understanding of MS.



Dr. Gavin Giovannoni

Grantholder: Dr. John Greenwood

Institution: Institute of Ophthalmology, London

Title: Investigation of the mechanisms involved in the migration of brain endothelial cells into the brain: identification of potential therapeutic targets.

Grant number 485

MS is now recognised as an autoimmune disease, where the body's own immune system mistakenly attacks brain cells. Much emphasis has been placed on the white blood cells involved in this immune response. However in MS, the majority of cells that enter the brain from the bloodstream are in fact called macrophages (Greek for "big eaters"). These cells are also responsible for demyelination, the process by which myelin (the fatty insulating material that protects the nerves) is damaged.

This study will examine what causes macrophages to enter the brain. In particular it will look at the cells lining the blood vessels. These cells normally form a barrier and must change to allow the macrophages to cross over. The aims of this study are to:

- Identify the signalling molecules on the surface of the cells lining the blood vessels. These signals may be important in allowing macrophages to pass through.
- Identify the how these signalling molecules work.
- Identify potential targets for new drugs that could prevent macrophages from entering the brain.

Grantholder: Professor David Miller

Institution: Institute of Neurology, London

Title: An MRI study of the development and course of multiple sclerosis

Grant number 491

MRI scans have been important in studying MS lesions and inflammation. They have also had some success in predicting whether a person with one isolated symptom is likely to go to develop full-blown MS.

This long-term study aims to develop several new and improved MRI techniques which will be used to look at the processes underlying relapses, irreversible disability and disease progression. This will help us to:

- Explain different disease courses
- Provide a rationale for new treatments
- Provide the best ways to monitor new treatments
- Improve the accuracy of predicting the course of MS after diagnosis.



**MRI scanner at the
Institute of Neurology,
Queen Square, London**



**Multiple Sclerosis NMR Research
Unit, Institute of Neurology &
National Hospital for Neurology
and Neurosurgery, London, UK**

Grantholder: Professor David Male

Institution: Dept of Biological Sciences, Open University, Milton Keynes

Title: What signalling molecules are produced by adult brain cells and what do these molecules do?

Grant number 509

This research looks at signalling molecules (called chemokines) found in the brains of people with MS. These chemokines control immunological and inflammatory reactions.

More than 70 different chemokines have been discovered and several of them have already been identified in MS brain tissue. However we do not know which of the chemokines act on the cells of the central nervous system (CNS). We need to know this, because a new class of anti-inflammatory therapeutic agents is becoming available (chemokine analogues) which may be of use in the treatment of MS.

The study will involve the use of adult human brain cells (glial) to find out how the cells of the CNS interact with the chemokines. When active chemokines are identified, inhibitors will be used to try to prevent the glial cells from responding to the chemokines.



**Dr. Geraldine Flynn,
Research Postdoctoral Fellow
(Prof Male)**

Grantholder: Professor Nicola Woodroofe

Institution: Division of Biomedical Science, Sheffield Hallam University

Title: What is the role of signalling molecules called chemokines in the development of MS?

Grant number 517

MS is now recognised as an autoimmune disease, where the body's own immune system mistakenly attacks cells of the central nervous system (CNS). Normally the immune cells remain in the bloodstream. This project will examine the signalling molecules (chemokines) that cause immune cells to enter the brain. Chemokines may be important in activating these cells, making them attack the myelin.

The study will identify the chemokines within the brains of people with and without MS. It will look for differences in the type and amount of different chemokines in different parts of the brain. It will be important to identify these signalling molecules since blocking their action with new drugs could provide the means to block the autoimmune response in MS.



Professor Nicola Woodroofe's Team

Grantholder: Professor Nicola Woodroofe

Institution: Division of Biomedical Science, Sheffield Hallam University

Title: What is the role of a regulatory molecule (called a matrix metalloproteinase) during inflammation in the brain?

Grant number 526

When MS brain tissue is examined under the microscope, two main features are seen: (1) immune cells that have entered the brain from the blood, and (2) loss of myelin. In MS, these events are due to the immune system malfunctioning, and causing damage instead of protection.

Previous research has shown that the major cell types involved in this abnormal immune response in the brain are white blood cells called T lymphocytes, and cells in the brain called microglia and astrocytes. The cells lining the blood vessels (endothelial cells) are also involved as they normally provide a barrier to cell movement in and out of the brain.

This study will examine the role of two key signalling molecules in the process of cell movement into and within the brain: chemokines (signalling molecules involved in immune and inflammatory responses) and matrix metalloproteinases (enzymes that alter the physical environment in the brain).

These will be studied by examining their effects on cultures of microglia, astrocytes and endothelial cells grown in a dish in the laboratory. The cells will be studied to see if they produce these different signalling molecules. The researchers will then look for factors that could stop the action of these molecules to see if these factors could provide a means of stopping immune cells from entering the brain.



Kevin Gill - MS Society funded PhD student (Prof Woodroofe)

Grantholder: Dr. Daniel M Altmann

Institution: Human Disease Immunogenetics Group, Imperial College, London

Title: How do T-cells (immune cells) react in genetically modified mice with MS?

Grant Number 528

Although MS is not a hereditary condition, there is some research evidence to suggest that there may be a genetic link. Research has shown that several genes are likely to influence whether a person is more susceptible to getting MS. These genes have been linked to the functioning of the immune system. They normally help the immune system distinguish between your own body and foreign bodies like viruses and bacteria.

These researchers have genetically modified mice so that they contain these human genes. They aim to use these mice to study the details of what happens when the immune system mistakenly attacks myelin. They will look at how the immune cells develop and identify the conditions under which MS-like symptoms can be observed in the mice. This will make it possible to look for specific interventions that can block the development of the disease. They will also examine whether transplanting myelin-producing cells can alleviate symptoms or prevent progression of the disease in these mice.



Dr Danny Altmann with Research Team

Grantholder: Dr. David Baker

Institution: Institute of Neurology, London

Title: Control of relapsing disease in models of MS

Grant Number 541

MS is triggered when white blood cells from the immune system enter the brain (which should not happen in normal circumstances), and mistakenly attack myelin (the fatty insulating material that protects the nerves). It is not possible to completely block these cells, as they are vital for fighting infection in the rest of the body.

This project aims to track these immune cells in mice with a condition similar to MS to investigate new avenues towards the treatment of symptoms and prevention of further disease development. The cells will be followed through the progression of the disease and following therapy, to help understand what the cells do when a relapse occurs.

One approach to treatment is to try to selectively block the actions of these cells when they are in the brain. This project is therefore aiming to develop new tools to target molecules to the brain, where they could act locally to inhibit the disease-causing immune cells. The aim is to develop tools that can release drugs over a long period and in a controllable fashion.

Once the numbers of disease-causing cells have been reduced, the researchers will attempt to re-educate any remaining immune cells such that they no longer cause disease. The lessons from these experiments in mice may eventually lead to new treatments for people.

Grantholder: Dr. Lawrence Wrabetz

Institution: San Raffaele Scientific Institute, Milan

Title: How do signals between nerves and oligodendrocytes affect myelin repair?

Grant number 550

Disease progression of MS occurs when the damage to myelin overtakes the repair to myelin. Myelin, produced by cells called oligodendrocytes, is necessary for normal transmission of messages along nerve fibres (axons), as well as protection of the nerves. Axons send signals to oligodendrocytes, promoting the formation of myelin. We only partially understand what these signals are – if we understand this more we could help encourage the process of remyelination.

A protein called Myelin basic protein (MBP) is necessary for oligodendrocytes to make myelin. When axons signal to the oligodendrocytes, the oligodendrocytes make more MBP and hence more myelin.

This study will identify the signals from the axons that switch on the MBP gene, resulting in myelin production. The molecules that transmit these signals could prove to be very good targets for new drugs. They may help to identify new ways to encourage remyelination.



Dr. Lawrence Wrabetz

Grantholder: Professor Peter Kennedy

Institution: Neurology Dept, Southern General Hospital, Glasgow

Title: Senior MS Fellow in Scotland

Grant Number 559

The aim of this project is to develop an active laboratory research programme in the field of MS. This is a Research Professorship with 80% of the individual's time being devoted to MS related research, building up a productive research programme.

The researcher will:

- Develop the use of animal models of MS to determine mechanisms of demyelination and inflammation in the central nervous system
- Provide an interface between parameters in people from the MS clinic and scientific (immunological) mechanisms such as in the laboratory
- Collaborate with several research groups within the area of neuroscience

Grantholder: Professor Stephan D Logan

Institution: Faculty of Medicine & Medical Sciences, Aberdeen

Title: Senior MS Fellow in Scotland

Grant Number 560

The principal purpose of this research is to provide new insights into the cause of MS, and to use scientific approaches to identify new targets that could be used either as a basis for novel therapies, or to devise new ways to monitor various components of brain injury (inflammation) and repair.

Application of these novel approaches to monitor the brains and spinal cords of people with MS, will allow direct assessments of specific processes occurring at different stages of the disease, and to determine how they are influenced by treatment. This should provide much better ways to evaluate the natural history of the disease, and its response to treatment.

Grantholder: Dr. Laurence S. Harbige

Institution: School of Chemical & Life Sciences, University of Greenwich, London

Title: The role of fatty acids in relapsing remitting MS

Grant Number 631

Fatty acids are found in the membranes of all cells, and are important in the regulation of chemical signals such as cytokines. Cytokines play important roles in inflammatory and immune reactions and therefore may be important in MS. Examples of such cytokines include IL-1 and TNF which promote inflammation, and TGF- β which is a particularly important cytokine because it switches off damaging immune/inflammatory reactions.

The blood cells of people with MS have a disturbed fatty acid composition. Trials have shown some benefit for people with MS who supplemented their diet with linoleic acid (LA), an essential fatty acid playing a role in nourishing the nervous system. LA has also been shown to be partly protective in animal models of MS. We have found that certain fatty acids produced from LA have a greater biological effect than LA.

We have set up an early clinical trial for people with relapsing remitting MS, to test the benefits of a natural oil containing some of these fatty acids. Blood samples will be taken to look at peoples' fatty acids and cytokines. This study may provide an understanding of biochemical processes underlying MS and help to identify ways to correct any fatty acid imbalances in people with MS.

Grantholder: Professor Peter Brophy

Institution: Dept of Preclinical Veterinary Science, University of Edinburgh

Title: The role of cell adhesion molecules in remyelination of the human central nervous system

Grant Number 669

Oligodendrocytes are the cells in the human brain and spinal cord (central nervous system; CNS) that are responsible for producing myelin (the fatty insulating material that protects the nerves). When myelin is destroyed, as in MS, the body must find a way to produce new myelin or we begin to lose functions. Although we know that some repair can occur, it is still something of a mystery as to why the ability of the CNS to remyelinate is limited. One of the major challenges in MS research is to try to understand why this is so and to try to overcome these limitations so that repair of nerves can be promoted.

Oligodendrocytes myelinate nerves by extending processes which encircle the nerves many times to form a multi-layered sheath. The first step in myelination (and remyelination) is for these processes to make contact with the nerve, a step which we know to involve very specific interactions between the oligodendrocyte and the nerve. However, at the present time we have a very limited understanding as to what molecules on the surface of the oligodendrocyte and the axon allow this interaction. We have recently identified one of these molecules, called neurofascin, which is expressed on oligodendrocytes surfaces.

In this project we are aiming to identify all the molecules involved in this process of interaction. The expression of such molecules will then be analysed in MS tissue. This research may likely to shed new light on the function of such cell adhesion molecules both in health and disease.



Professor Peter Brophy

Grantholder: Professor Nicola Woodroffe

Institution: Division of Biomedical Science, Sheffield Hallam University

Title: What is the role of an enzyme called ADAM 17 in the development of MS?

Grant number 672

This study will look at whether a molecule called ADAM 17 is part of the mechanism that leads to damage in MS. ADAM 17 is an enzyme which causes chemical change in other molecules affecting how they function. ADAM 17 alters some of the molecules that are already known to be involved in MS.

This study will look at the pattern of ADAM 17 activity in the brains of people with and without MS and also at how the enzyme works in the brain and spinal cord of animals with a condition similar to MS. In this way it will assess whether ADAM 17 plays a role in inflammation and myelin damage. The researchers will also look at what happens when you inhibit the action of ADAM 17 and whether this might be a useful approach for therapy in MS.



Dr Julie Simpson - MS Society funded research assistant (Prof Woodroffe)

Grantholder: Dr Sandra Amor

**Institution: Dept of Neurodegenerative Disorders, Imperial College,
London**

**Title: The role of galectin-1 in experimental inflammatory and
demyelinating neurological diseases.**

Grant number 701

The clinical signs and symptoms of MS are thought to be due to damage to the myelin (the fatty insulating material that protects the nerves and axons) in the brain that are essential for the nerves to function properly. Damage to the myelin in MS may be due to an attack by cells of the immune system called T cells. While it is still not sure why and exactly how T cells damage the myelin, it is possible that by stopping the T cells from getting into the brain or by killing those T cells responsible, the progression of MS can be slowed down or halted.

Recently scientists have been studying a naturally occurring protein called galectin-1 (GAL-1), which has shown to kill T cells. GAL-1 is also important for movement of T cells through tissues and has been found to induce destruction of T cells while allowing other cells to survive. Furthermore GAL-1 has been shown to help the repair of axons and so eventually be very useful to stop the inflammation and promote repair of axons and thus treat diseases such as MS.

This project will study two MS-like diseases in mice in which myelin damage due to T cells is seen in the brain. We will first measure the levels of GAL-1 in the brains of these mice and see if production is related to the severity and course of disease. We also have the unique opportunity to use specially bred mice that do not have GAL-1. The study will determine if the MS-like diseases are worse in these mice and examine the immune response to determine the difference between these and normal mice. GAL-1 protein will be given to mice during disease to examine if GAL-1 protein can kill the T cells and stop them going into the brain and therefore stop the neurological disease occurring or progressing.