

Pathways to Cures

Pathways to Cures Research Funding Initiative: Generating Knowledge and Tools to Promote Remyelination and Neuroprotection in Multiple Sclerosis

Focus: Restoring Function

Targeted Research Grant: University of Kansas researchers are studying the importance of the formation and breakdown of a specific type of cholesterol in promoting effective myelin repair.

Title: “Defining the role of cholesterol ester metabolism in remyelination”

Term: 10/1/24-9/30/27

Grant Amount: \$835,102

Investigator: Meredith Hartley, PhD

University of Kansas

Lawrence, Kansas

Meredith Hartley, PhD, is an Assistant Professor at the University of Kansas (Lawrence). She received her PhD in biological chemistry from the Massachusetts Institute of Technology (Cambridge). She completed a postdoctoral fellowship at Oregon Health and Science University (OHSU, Portland). Dr. Hartley received postdoctoral funding from an NIH Neuroendocrinology training grant and the National MS Society (OHSU), and the resulting manuscript earned her the “Postdoctoral Paper of the Year Award” at OHSU.

Background: Damage to the protective coating of nerve fibers – called myelin – is characteristic of MS. Strategies that promote repair of the myelin could help restore lost function. One component of myelin is cholesterol, and Dr. Hartley’s group thinks that an important process in effective myelin repair has to do with cholesterol esters, which are formed when the myelin’s cholesterol breaks down. Cholesterol ester formation is an important step in cleaning up damaged myelin. After cleanup, cholesterol esters can be “recycled” back into cholesterol, which is important for myelin repair. Many different proteins assist with cholesterol ester metabolism (the breakdown and recycling process), but their specific roles are not well known. Understanding how the proteins regulate cholesterol ester metabolism could provide insights into myelin repair.

The Study: Using a mouse model of myelin damage, Professor Hartley’s group will target different proteins involved in cholesterol ester metabolism by using drugs that reduce their activity or genetic changes that delete them altogether. They will then monitor how those changes affect myelin repair. They will also measure how the proteins are affected following treatment with drugs known to promote myelin repair.

Potential Impact: This study has the potential to identify new targets for effective myelin repair strategies. In the future, therapies could be developed against these targets and provide a novel way to restore lost function in people with MS.

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Targeted Research Grant: A Georgetown University research group is investigating how a novel drug supports myelin repair and neuroprotection in mice with MS-like disease.

Title: “Analysis of a novel oral amino acid transport inhibitor in remyelination and neuroprotection”

Term: 10/1/24-9/30/27

Grant Amount: \$941,061

Investigator: Jeffrey Huang, PhD

Georgetown University

Washington, DC

Dr. Jeffrey Huang is an Associate Professor in the Department of Biology at Georgetown University (Washington, DC). He received his PhD in neuroscience from the Mount Sinai School of Medicine (New York, NY) and did postdoctoral work at the Gurdon Institute and the University of Cambridge (Cambridge, UK). Dr. Huang is a recipient of the Roger D. Semerad Award for Research in the Neurosciences from the TurnFirst Foundation and the Distinguished Georgetown Investigator Award.

Background: Nerve fibers in the brain and spinal cord are normally covered and protected by myelin, but a characteristic of MS is myelin attack and breakdown. Myelin repair is possible, but excessive, chronic inflammation is a barrier to success. Microglia, a specific type of inflammatory cell, are abundant in areas of myelin breakdown and can contribute to the chronic inflammation. Previous research has shown that blocking activity of a specific protein in microglia involved in transport of amino acids (the building blocks of proteins) helps with myelin repair by making the microglia less pro-inflammatory and increasing the number of cells that make myelin. The team is investigating a novel drug that inhibits amino acid transport and can be taken orally.

The Study: Using mice that exhibit myelin breakdown and high inflammation similar to that observed in people with MS, Professor Huang and team will investigate the effectiveness of the novel drug by measuring levels of microglia inflammation, number of new myelin-producing cells, and myelin repair. They will also investigate biological changes (such as the genes and proteins involved) following drug treatment to help clarify how the drug exerts its protective effects.

Potential Impact: The results of this study could support testing of this novel drug in humans and ultimately lead to development of a new therapy for enhancing myelin repair and neuroprotection.

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Targeted Research Grant: A team at Johns Hopkins University is exploring factors that could enhance the natural capacity for repair in people with MS.

Title: “Regulation of OPC inflammatory and repair functions by lipid metabolic reprogramming”

Term: 10/1/24-9/30/27

Grant Amount: \$836,539

Investigator: Michael Kornberg, MD, PhD

Johns Hopkins University

Baltimore, MD

Michael Kornberg, MD, PhD, is Assistant Professor of Neurology and Associate Director, Neurology Residency Program at Johns Hopkins University. Dr. Kornberg received M.D. and Ph.D. degrees from the Johns Hopkins School of Medicine and stayed at Johns Hopkins for neurology residency and a clinical and research fellowship in neuroimmunology. Dr. Kornberg is a recipient of the Nupur Dinesh Thekdi Research Award and the Neurology Core Clerkship Resident Teaching Award from the Johns Hopkins University School of Medicine.

Background: In MS, an inflammatory immune response results in damage to the myelin that surrounds nerve fibers. An early form of myelin-making cells – oligodendrocyte precursors (OPCs) – are abundant in the brains of people with MS but fail to form new myelin. Recently, it was demonstrated that the immune response not only blocks OPCs from repairing myelin but causes them to become inflammatory cells themselves, contributing to injury rather than repair. Preliminary studies show that the way OPCs process lipids (fats) may inhibit their myelin repair capabilities. Lipids are a main component of myelin.

The Study: Dr. Kornberg and colleagues are studying the extent to which such changes in lipid metabolism occur in tissue obtained from people with MS and models of MS-like disease. They also are testing whether therapies that target the process of lipid metabolism can restore the ability of OPCs to repair myelin in models of MS.

Potential Impact: These studies have the potential to identify new treatments to promote myelin repair, which is a critical unmet need for people living with MS. Restoring myelin through repair would lead to recovery of function while also preventing or delaying conversion to progressive MS.

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Targeted Research Grant: Researchers at the Alicante Neuroscience Institute in Spain are investigating how a specific protein in the brain interferes with myelin repair and if it could be an effective target for MS therapies.

Title: “Restoring plasticity of oligodendrocyte progenitors to foster remyelination in the aged and diseased brain”

Term: 10/1/24-9/30/27

Grant Amount: \$967,435

Investigator: Isabel Perez-Otaño, PhD

Instituto de Neurociencias de Alicante, Spanish National Research Council (CSIC)
San Juan de Alicante, Spain

Isabel Perez-Otaño, PhD, is Professor at the Instituto de Neurociencias de Alicante (Spain) where she leads the scientific program “Synapse Modulation of Neural Circuits and Behavior”. She earned a PhD in Neuropharmacology at the Cajal Institute (Madrid) and the University of Navarra (Pamplona, Spain), and completed postdoctoral fellowships at the Salk Institute (La Jolla, CA) and Duke University (Durham, NC). Prof. Perez-Otaño serves as an expert reviewer for: the National Research Agency of Spain, the Wellcome-Trust Fund in the United Kingdom, the Agence National de la Recherche in France and National Science Centers of other European countries. She has earned Young and Independent Investigator Awards from The Brain and Behavior Fund and an Early Investigator Excellence Award from the Spanish Ministry of Science and Innovation.

Background: Multiple sclerosis (MS) is caused by loss of the myelin sheaths that enwrap nerve fibers. Advances have been made in stopping the immune attack towards oligodendrocytes (the myelin-producing cells), but currently there are no therapies that prevent the progression of disability and restore function. Myelin repair is spontaneously activated following damage at early disease stages, but eventually fails. Oligodendrocyte precursor cells, OPCs, are present throughout the brain and spinal cord in people with MS and offer an opportunity for generating new oligodendrocytes and promoting myelin repair. Recent studies show they can be activated by the activity of nerve cells themselves.

The Study: Prof Pérez-Otaño’s team has discovered a molecule that might help to activate OPCs. They are deleting this molecule in mice to determine its specific effects on OPCs and identify pathways that make OPCs respond to nerve activity. They also are seeking to determine whether therapeutic strategies like gene therapy or pharmacological treatments can be used to combat myelin repair failure in aged mice. They also are studying whether combining gene therapy, pharmacological treatment and rehabilitation approaches can be used to boost myelin repair after injury.

Potential Impact: This project can provide novel strategies for boosting signals that can promote the existing capacity for repair in people with MS.

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Targeted Research Grant: Researchers at Case Western Reserve University are using cutting edge techniques to study brain cells that become toxic in MS, for clues to protecting the nervous system from damage.

Title: “Controlling pathological astrocytes for neuroprotection in progressive MS”

Term: 10/1/24-9/30/27

Grant Amount: \$999,998

Investigator: Paul Tesar, PhD

Case Western Reserve University
Cleveland, OH

Paul Tesar, PhD, is a Professor in the Department of Genetics and Genome Sciences at Case Western Reserve University School of Medicine and Director of the Institute for Glial Sciences. He earned his Ph.D. from the University of Oxford as a recipient of the NIH-Oxford Biomedical Research Scholarship. His lab has made numerous seminal contributions at the interface of stem cell biology and oligodendrocyte function. Dr. Tesar has received recognition for the work including the International Society for Stem Cell Research Outstanding Young Investigator Award and selection as a Robertson Investigator of the New York Stem Cell Foundation.

Background: In MS the immune system mistakenly attacks the myelin sheath, a protective layer surrounding nerve cells in the nervous system. The loss of this protective myelin combined with ongoing inflammation results in dysfunction and death of nerve cells, eventually leading to worsening disability in people with MS. Recent research has shown that in MS, particularly in the progressive stages, support cells in the brain called “astrocytes” can become toxic. These toxic astrocytes contribute significantly to nerve cell damage and disease progression, exacerbating disability. This team is looking to develop new medicines that specifically prevent the formation of toxic astrocytes.

The Study: Dr. Tesar along with Dr. Benjamin Clayton and colleagues are using a multi-faceted experimental approach. They have discovered a class of compounds that inhibit toxic astrocyte formation, and will administer these to a mouse model of progressive MS, assessing the impact on nerve cell survival and myelin repair. Second, they are using a cutting-edge genetic approach, deleting each gene in astrocytes one by one to determine which are required for toxicity. Third, they are using a three-dimensional model that closely resembles human brain tissue from people with MS. They will use this model to test therapeutics that suppress toxic astrocytes, providing a more accurate representation of how these treatments might perform in human tissue.

Potential Impact: Stopping these toxic astrocytes from forming may protect nerve cells, potentially halting or even reversing the disability progression that occurs in people with MS.