RADY FACULTY OF HEALTH SCIENCES

2018 RADY INNOVATION FUND AWARDEES

Three U of M research projects funded through inaugural grants from the Rady Innovation Fund

DEVELOPING AN INNOVATIVE CONCEPTUAL FRAMEWORK OF COMMUNITY-BASED REHABILITATION TO INFORM RESTORATIVE CARE

RESEARCH TEAM:

- Dr. Kate Sibley, Canada Research Chair in integrated knowledge translation in rehabilitation sciences; assistant professor, community health sciences; associate director – knowledge translation, George & Fay Yee Centre for Healthcare Innovation
- Dr. Ruth Barclay, associate professor, department of physical therapy
- Dr. Amanda Condon, family physician, Winnipeg Regional Health Authority
- Dr. Juliette (Archie) Cooper, professor emeritus, department of occupational therapy
- Jeanette Edwards, chief, community, services and quality management, Shared Health Services Manitoba
- Dr. Lorna Guse, associate professor, College of Nursing
- Dr. Leanne LeClair, associate professor, department of occupational therapy
- Dr. Alan Katz, director, Manitoba Centre for Health Policy
- Dr. Jacquie Ripat, associate professor, department of occupational therapy

PROJECT DESCRIPTION:
There is an urgent need for innovative health service models to support Canadians to live at home in the community as they age and live with chronic disease. “Restorative care” aims to help patients attain and maintain the highest levels of function possible, presenting an exciting opportunity to transform community-based rehabilitation and home care.

However, there is a critical gap in understanding of rehabilitation services offered in community settings, and of their effectiveness. The goals of this project are to gain a comprehensive understanding of the current state of community-based rehabilitation and to develop a framework for community-based restorative care which can be used in the design of future innovative community rehabilitation policy, planning, care and research.

In this multi-pronged project, we will conduct an environmental scan to identify existing services; interview community rehabilitation patients, caregivers and service providers; and hold an interactive knowledge exchange forum with health system stakeholders. The conceptual framework resulting from this one-year study will have both immediate, local impact as well as national and long-term impact.

This project is poised to have an immediate impact on policy and planning for community-based restorative care approaches to rehabilitation service delivery due to the integral role of a key provincial health decision-maker as a principal knowledge user on the project team (Jeanette Edwards of Shared Health Services Manitoba) and the evidence-based and contractually-sensitive approach to learning about the current state of rehabilitation services. The project will also establish conditions for national and long-term impact by identifying conditions, parameters and feasibility data for scaling up to a planned CIHR project scheme submission.

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A NOVEL HIGH-FIDELITY MECHANISM FOR NEURONAL COMMUNICATION UNDERLIES EMOTIONAL MEMORY ENCODING

RESEARCH TEAM:

- Dr. James Nagy, physiology and pathophysiology
- Dr. Michael Jackson, pharmacology and therapeutics
- Dr. Gilbert Kirouac, oral biology (Dr. Gerald Niznick College of Dentistry)
- Dr. Tabrez Siddiqui, physiology and pathophysiology

PROJECT DESCRIPTION:
The aim of our project is to investigate an intriguing means of inter-neuronal communication in the brain that is very different from the well-known mode of chemical neurotransmission, namely direct electrical transmission mediated by electrical synapses formed by structures called gap junctions at contacts between neurons.

It has long been known that electrical synapses are prevalent in the nervous systems of lower vertebrates, but their widespread occurrence and functional relevance in the mammalian central nervous system has only recently been recognized. Our focus is on an even more novel type of synapse where the components of chemical and electrical synaptic transmission co-exist, giving rise to potentially a dual mode of neuronal communication involving both neurotransmitters and gap junctions, hence referred to as "mixed synapses."

We have earlier reported anatomical evidence for the occurrence of such mixed synapses in a number of brain and spinal cord regions, including at specific neuronal connections referred to as "mossy fiber terminals" in a major brain structure called the hippocampus that is required for, and crucially involved in, the formation and retrieval of memories.

The focus of our work using animal models will be to establish for the first time anywhere in the mammalian central nervous system that the electrical component of a mixed synapse is functionally operative, meaning that these synapses at mossy fiber terminals transmit not only chemically via neurotransmitters, but also electrically via gap junctions.

Further, in the context of hippocampal functions in cognition and behavior, we aim to demonstrate by manipulations of mixed synapses in the hippocampus that electrical transmission at these synapses has a functional impact on learning and memory performance in animals. Given the known reliable nature of direct electrical transmission at electrical synapses at other sites where these have been examined, we propose that the additional presence of electrical synapses at mossy fiber terminals provides a means for ensuring absolute transmission fidelity. In this manner, we envision that these synapses can function as a strategic element in hippocampal synaptic circuitry to guarantee efficient storage and recall of memories.

The hippocampus is especially critical for learning and memory, in particular the process of engraining moment-to-moment experience for long-term storage in other brain areas. How information within the hippocampus is transmitted, processed and retained has been hotly debated and intensively studied for the past half-century.

Intensive efforts have been directed toward uncovering neuronal pathways as well as cellular mechanisms that govern structural and functional remodeling of synapses, which is generally considered to be required during the process of learning. We anticipate that our identification of a novel contribution of electrical transmission at hippocampal mossy fiber mixed synapses will establish new principles surrounding brain circuits that control memory formation, which we expect will receive immediate attention and have long-term impact in the neuroscience community.

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TREATMENT-INDUCED PSEUDO-PROGRESSION IN BRAIN TUMOR: THE ROLE OF AQUAPORINS AND LIQUID BIOMARKERS

RESEARCH TEAM:

- Dr. Thomas Klonisch, human anatomy and cell science
- Dr. Marco Essig, radiology
- Dr. Marshall Pitz, neuro-oncology
- Dr. Jason Beiko, neurosurgery
- Dr. Donald Miller, pharmacology and therapeutics
- Dr. Sabine Hombach-Klonisch, human anatomy and cell science

PROJECT DESCRIPTION:
Response assessment of glioblastoma, the most frequent and aggressive brain tumor, has developed into a significant area of interest in the neuro-oncology community in recent years. This is a result of the limitations of current diagnostic tools. Conventional MRI is extremely useful, but changes on MRI do not always correlate with disease response.

In particular, pseudo-phenomena have been well described in neuro-oncology and now form a significant part of the standardized response criteria, termed the Response Assessment in Neuro-Oncology (RANO) criteria. Pseudo-progression refers to new areas of enhancement or edema that arise not from tumor progression, but from what is assumed to be chemoradiotherapy-related edema and/or inflammation, likely because of increased blood vessel permeability.

Recognized as early as 1979, pseudo-progression poses a clinical challenge because the imaging appearance is indistinguishable from true disease progression. Before the use of temozolomide-based chemoradiation, only approximately 1% of patients treated with focal fractional radiation alone would develop treatment-related imaging changes. However, with the current chemoradiation regimen, pseudo-progression has been reported in up to 50% of patients, typically noted at the first follow-up MRI obtained within two to three months after chemoradiation.

Failure to recognize pseudo-progression in patients can lead to premature termination of an effective therapy, unnecessary surgical intervention, or additional chemotherapeutic agents. Because pseudo-progression resolves spontaneously, this resolution might be misinterpreted as evidence that the new treatment is effective, thus skewing the results of clinical trials. On the other hand, successful recognition of pseudo-progression has been associated with improved prognosis, possibly because of the increased likelihood of methyl-guanine methyl transferase (MGMT) promoter methylation in this population.

This team of leaders in advanced clinical imaging, clinical management of brain tumor patients and experts in brain tumor and blood-brain barrier research will test a novel concept of pseudo-phenomena in brain tumors. We hypothesize that chemoradiation treatment alters the expression of water channel proteins in GB cells, which contributes to brain edema and neuroinflammation and promotes pseudo-progression in GB patients.

These changes in the brain can be distinguished from real tumor progression by combining advanced MRI and spectroscopy imaging. Furthermore, we will test whether a blood sample is sufficient to detect specific changes in the activation stage of circulating immune cells that reflect the neuroinflammation component of pseudo-progression.

Our focus on treatment-induced pseudo-progression in brain tumors has been identified as an under-researched, high-priority clinical problem by the Terry Fox Research Institute (TFRI). The research funded by the Rady Innovation Fund is essential for investigating new mechanistic concepts that better explain brain edema formation/resolution in the context of the brain tumor microenvironment.