UNIVERSITY OF MANITOBA

CANADA FOUNDATION FOR INNOVATION
Innovation Fund

15-2

Notice of Intent

1. Completed NOIs must be submitted by the Associate Dean (Research)/Research Liaison Officer of the "Lead" Unit to the Office of Research Services to: Birtukan.Gebretsadik@umanitoba.ca by May 15, 2018.

Proposed name of project: Multiscale Brain Connectivity Centre	**Estimated Total Project Costs:** $11.5 million
Designated Project Leader/Faculty/Dept: Chris Anderson/RFHS/Pharmacology CV: x	

List Principal Users/Faculty/Dept:

1.	Chase Figley/RFHS/Radiology	CV: x
2.	Michael Jackson/RFHS/Pharmacology	CV: x
3.	Tabrez Siddiqui/RFHS/Physiology	CV: x
4.	Yasser Iturria-Medina/McGill	CV: x
5.	Soheila Karimi/RFHS/Physiology	CV: x
6.	Ruth Ann Marrie/RFHS/Internal Medicine	CV: x

'Lead' Unit ADR/RLO:

Name: Peter Nickerson

Briefly describe (max 2 pages, 12 pt. font size, 2 cm margins):

- The proposed research and how it is world-class, innovative and demonstrates clear benefits to Canada.
- The infrastructure and how it will enhance the University's existing research capacity.
- The excellence of the team, including expertise and existing collaborations necessary to conduct the proposed research.
- Plans to secure matching funds and the potential funding sources for the operation and maintenance of the infrastructure.

The proposed research and how it is world-class, innovative and demonstrates clear benefits to Canada. Neuroscientists are proficient investigators of basic synaptic biology and functional brain readouts, but there is limited knowledge about how synaptic building blocks are integrated to form functional circuits. Understanding circuitry requires detailed cartography of synaptic diversity and cell-to-cell connectivity, from centimeter down to nanometer spatial resolutions, throughout brains comprised of billions of neurons, each with unique projection patterns to other cells. Meeting this requirement has long been limited by inadequate technological capabilities, but revolutionary advances in brain imaging and microscopy are yielding new potential to construct brain-wiring maps representing the entire brain connectome. These advances are enabling a new era of unprecedented power to consider the nature of 3D brain connectivity patterns responsible for complex animal and human behaviours, and disease. We will seize this opportunity by building on existing institutional strength and investments to establish an internationally-unique research center that applies a multiscale experimental and data science workflow to study nervous system circuitry and the effects of injury and disease on brain connectivity.

The vision unites complementary strengths of established and emerging research leaders, integrates over $65 million in previous infrastructure and personnel investments by the UM and HSC, and adds revolutionary technological capacity. The concept is innovative because it incorporates new technologies at the leading edge of discovery to study connectivity over a broad range of spatial resolution scales. It is transformational because these approaches will allow the team to consider 3D brain circuitry in critical research questions historically not considered that way.

One-in-three Canadians will be directly affected by a neurological or psychiatric disorder, and the yearly costs of acute care represent the highest portion of the overall financial burden of disease in Canada (14%, BrainCanada.ca). There is thus a clear and urgent need for interdisciplinary research designed to diagnose and treat brain-related disease. The overarching goal of this project is to enable elucidation of brain structure and function more fully than ever before, and use that information to develop new ways of diagnosing and treating neurological disease and mental health disorders.

The infrastructure and how it will enhance the University's existing research capacity. In order to fully comprehend the fundamental organization of the nervous system, researchers must merge their understandings of its construction at multiple spatial connectivity scales. The macroscale connectivity range is millimetres to centimetres, and is studied by mapping axon fibers from region to region in brain and spinal cord. Advanced diffusion-based MRI approaches will be used in humans and animal models, leveraging existing human 3T MR and small animal 7T PET/MR scanners. The cost of the animal PET/MR is included in the project costs **($1.5M)** but will be considered a partner contribution from the UM. Mesoscale connectivity includes long and short-range neural connections and local neuronal circuits. Structurally, this will be studied by using light sheet fluorescence microscopy (LSFM) **($0.91M)** in whole tissues that have been optically cleared. Functionally, users will activate genetically-encoded activity modulators in selected neuronal populations, and network activity will then be monitored using fluorescent activity indicators and two-photon laser scanning microscopy (TPLSM). Two existing systems will be upgraded for this purpose **($0.90M)**. Microscale connectivity is connections between individual neurons and synapses. A super-resolution fluorescence microscope (SRFM) **($1.84M)** will be acquired to allow co-localization of fluorescent signals with resolution higher than conventional light microscopy (~20 nm). This will be combined with serial physical sectioning using an automated ultramicrotome **($0.22M)** to enable super-resolution reconstructions in 3D (array tomography). A companion approach will permit overlay of optical array tomography signals on top of images depicting fine neural tissue ultrastructure with sub-nanometer resolution. A field emission scanning electron microscope (FE SEM), with STEM detector for TEM-like resolution, will be acquired **($0.96M)** for this purpose. Microscopes will have 5-year service contracts **($0.86M)**. Large amounts of data will be produced. A Storage Area Network **($0.54M)** and Picture Archive and Communication System **($0.02M)** will be purchased. Remote computer terminals will be required in Manitoba and Québec **($0.04M)**. There will be construction of space to amalgamate infrastructure and personnel. A 4180 sq ft research center will be built in the Kleysen Institute to house facilities for neuroimaging analysis, computational neuroscience, 3D microscopy, tissue processing and drug screening **($3.6M)**.

The project aligns with two priorities of the UM Strategic Research Plan: fundamental research and integrative research in health and well-being. It consolidates and modernizes several previous CFI acquisitions and integrates with existing research platforms. There will be heavy use of the small animal imaging core, and this project will modernize the ultrastructural imaging core by placing new EM equipment in it. Team members will also rely on WRHA human MR research facilities, the Brain Canada neuroimaging platform (established by Dr. Anderson), the HSC cyclotron for PET probe synthesis, and the Centre for Proteomics and Systems Biology for screening of the synaptic proteome.

The excellence of the team, including expertise and existing collaborations necessary to conduct the proposed research. Principal users are unified by a common objective to investigate fundamental nervous system connectivity and how connectivity is altered in disease. Users will contribute complementary expertise, providing complete coverage across all connectivity scales. Together, they contribute the components required to establish a unique, multiscale workflow platform, and the computational and analytical innovation to integrate multimodal data sets.

This IF project will be a resubmission of a previous version that went to MAC review. Last time, the submission was laden with CRC's and senior investigators but the MAC clearly did not believe this group would work together to complete the work proposed. This time, the team will lean more towards emerging research leaders who have strong track-records, evidence of team cohesion and exceptional promise in the component areas required to make a feasible connectivity team.

There are 2 research chair holders, 4 mid-career scientists, and 3 early-career emerging leaders. The MAC was supportive of **Anderson's** leadership track-record and he will remain in that position. **Figley** is an emerging leader who gives the team strength in MRI studies of structural and functional macroscale connectivity. **Marrie** is a clinician-scientist with a world-class research track-record and an endowed research chair. She and Figley work together to identify aberrant connectivity patterns in MS patients. She will be instrumental in advancing knowledge to clinical practice and policy makers. **Karimi** is an established leader in spinal cord connectivity and re-connection strategies. She will provide leadership in mesoscale connectivity, and repair. **Jackson** is a productive mid-career research leader who will play a critical team role in microscale and mesoscale functional connectivity at the molecular, cellular and network levels by performing intricate electrophysiology and live cell imaging experiments. His contributions will be applied widely across a broad array of connectivity projects enabled by the proposal. **Siddiqui** is an emerging leader in microscale connectivity focused on understanding the molecular cues that guide development and function of synapses. He will play an integral role in microscale connectivity approaches, anchoring team research to understand how synaptic diversity contributes to functional nervous system connectivity. **Iturria-Medina** is an early career investigator at the Ludmer Centre for Neuroinformatics and Mental Health. He is a data science pioneer who integrates multi-modal neuroscience data with computer sciences, creating mathematical models of multifactorial causal analysis. He will lead the analytical strategy by applying these methods to data generated by other team members. This will facilitate determination of how different biological factors interact directly and inform one another, from microscale to the macroscopic scale. An inadequate unifying analytical strategy was identified as the major weakness by the MAC in the last submission. Inclusion of Iturria-Medina addresses this critique in an innovative and transformational way.

There are established collaborations among team members. Figley/Marrie and Siddiqui/Jackson hold grants and have published together, and Anderson has active collaborations with Siddiqui and Jackson. There are further team connections that will be described if the total number of principal users is more in the full application. If more are permitted, a certain addition will be Dr. **Fernyhough** who is a leader in mesoscale connectivity. His work has led to commercialization of novel topical drugs causing regeneration of peripheral nerve connections in diabetic neuropathy and a startup company leading phase 2 clinical trials. He will be the team driving force behind the project's drug screening platform. Other team members are likely to be Drs. **Kirouac** (mesoscale circuitry) and **Nagy** (microscale electrical connectivity). These individuals are extensively networked together with other team members.

Plans to secure matching funds and the potential funding sources for the operation and maintenance of the infrastructure. Project costs are $11.5M, including freight and tax. Contributors are CFI (40%, $4.57M), Research Manitoba (40%, $4.57M) and other partners (20%, $2.29M). Confirmed in-kind vendor contributions are 10% ($1.14M). The remaining $1.14M will be cash paid by the UM to purchase the animal PET/MR. The purchase was made after March 1, 2017, which is the anticipated cut-off date for eligible contributions. The animal PET/MR is in the UM imaging facility and O&M costs are covered by institutional support and user fees. Other platforms will be in the Kleysen Institute. For these, O&M revenues will include UM contributions from the Infrastructure Operating Fund, Health Sciences Centre contributions (e.g. utilities, facilities maintenance, information services) and platform user fees.