



## Hopewell M.I.N.D. Prize 2022 Finalists

[Dr Minh Dang Nguyen](#)

**Title of Project:** *“Gut Microbiome-Dependent regulation of the Brain Lymphatic System for the Treatment of Neurodegenerative Disorders”*

**Dr. Nguyen** is a tenured Associate Professor in the Department of Clinical Neurosciences since 2016. In Calgary, he has developed an externally funded, independent research program in the area of neurodegeneration. He was a AIHS Scholar Awardee (2006-2017), a CIHR New Investigator (2006-2011) and held both a Career Development Award from the Human Frontier Science Program Organization (2005-2010) and the Brenda Strafford Chair in Aging and Alzheimer’s Research at the University of Calgary (2006-2011).

Funded by CIHR and the Krembil Foundation, his lab is currently investigating the role played by genetic factors in cerebrovascular dysfunction in Alzheimer’s disease. In 2019, Dr. Nguyen reconnected to amyotrophic lateral sclerosis (ALS) research via a pilot project funded by the ALS Society of Canada looking at the impact of bacterial products on motoneuron degeneration. Together with HBI members Gerald Pfeffer and Keith Sharkey, he has now established an international consortium of basic and clinical scientists from Germany, Israel, South Korea and Turkey working on the gut microbiome in ALS.

In 2021, Dr. Nguyen accepted the position of co-Director of the Graduate Program of Neuroscience. This position allows him to bridge his interest in education and well-being of students to his administrative responsibilities.

(Lab website - <https://www.cytoskeletonexus.com/>)

### **Summary of Proposed Innovation:**

Accumulation of misfolded proteins is a central feature of neurodegenerative disorders including amyotrophic lateral sclerosis, Alzheimer, Parkinson and Frontal-Temporal Dementia. The gut microbiome, the ensemble of microorganisms (bacteria, viruses, protozoa, fungi and archaea) that reside in the gut, plays a critical role in the initiation and progression of these proteinopathies.

A common feature of neurodegenerative diseases is impairment and stagnation in the brain’s lymphatic system, the protective network of vessels that drain fluids within and clears waste from the brain parenchyma. Is there a link between alterations in the composition of bacteria in the gut (microbial dysbiosis) and lymphatic impairment in neurodegenerative diseases?

There is increasing evidence that microbial dysbiosis alters the function of the lymphatic system systemically, and therefore we postulate that microbial dysbiosis alters the regulation of the lymphatic (deep inside the brain) and



## Hopewell M.I.N.D. Prize 2022 Finalists

meningeal lymphatic (at the surface of the brain) drainage systems. Moreover, both microbial and brain lymphatic changes may also represent a unique etiological diagnostic indicator of neurodegeneration. The precise contribution of compositional changes of the gut microbiome, and subsequent effects of bacteria-derived products and their relation to brain lymphatic changes in neurodegeneration remain totally unknown.

Here we propose the formation of a multi-disciplinary HBI-led team with the overarching goal of harnessing the composition of the gut microbiome to enhance the activity of the brain's glymphatic and meningeal lymphatic systems and, ultimately, to reduce the burden of deleterious molecules in the brain.

We hypothesize that the brain lymphatic network becomes dysfunctional in neurodegenerative disorders featuring gut microbiome dysbiosis and re-establishing a normal gut flora enhances the functionality of the lymphatic system, thereby improving the clearance of toxic molecules in the brain and slowing neurodegeneration. To test this hypothesis, we will:

- 1) Characterize the brain lymphatic system in animal models of ALS with gut dysbiosis using 2-photon microscopy, confocal imaging and biochemical approaches.
- 2) Monitor brain drainage function in ALS mouse models and ALS patients using MRI.
- 3) Implement therapeutic interventions based on modifying the gut microbiome and assess the function of the brain's lymphatic system using clinically relevant samples and animal modeling.

Patients with neurodegenerative disorders are in urgent need of biomarkers for diagnosis and treatment. Via our comprehensive analyses of microbiota and brain lymphatic system, our research has the potential to capture these novel markers and identify the persons at risk. As the microbiome is a modifiable treatment target, our findings may allow tailored treatments that could prevent brain lymphatic dysfunction and battle neurodegenerative diseases.