Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

LAIDLAW SCHOLARS

LAIDLAW UNDERGRADUATE LEADERSHIP AND RESEARCH PROGRAMME

APPLICATION – 2023 COHORT

Name	*Meher Sabharwal*
Programme	*Biological and Biomedical sciences*
Year of Study	*2nd year*
Research Project Title	*Interdisciplinary approach to failure of brain energy as an explanation for delirium in older patients*
Proposed Supervisor(s)	*Dr Colm Cunningham, School of Biochemistry and Immunology, Trinity Biomedical Sciences Instititute and Trinity College Institute of Neuroscience*

Before completing this submission, you should review the Laidlaw Programme Application Guide sections and "Leadership-in-action experience proposal (Summer 2)"

Research Project Proposal (750-1000 words max.)

See *Self-defined research project proposal (Summer 1)* in the guidance for more information

Introduction

This research proposal aims to identify an interdisciplinary approach to the failure of brain energy usage as an explanation for delirium in older patients. Delirium is an acute neuropsychiatric syndrome in which patients become highly disoriented and show an inability to maintain or shift attention[1]. Its clinical effects can range from comatose to increased aggressiveness and agitation. Though widely neglected and poorly understood, delirium is extremely common, with an overall prevalence of delirium in hospital inpatients of approximately 20% in studies internationally. Delirium is more common in older populations and is particularly prevalent in severely ill patients. Thus, with increasing age and declining health of a patient, the risk of delirium increases progressively and as many as 59-88% of palliative care inpatients become delirious in the weeks approaching death. It has also recently been found to be a diagnostic tool for dementia, appearing to have important long-term impacts on the health and integrity of the aging brain. Despite these global widespread ramifications, however, delirium is still a grossly under researched and neglected topic.

With this application I propose to explore the underpinning role of disturbed brain energy metabolism, using data from both human and mouse models that have been

[1] Wilson et al. (2020). Delirium. Disease Primers, Nature Reviews. 6:90

developed to study this neuropsychiatric syndrome. In both cases, I will have access to datasets that have been collected from acute inflammatory trauma in individuals who developed delirium. In the case of humans, these are patients who have been hospitalized with a hip fracture, while in mice I will utilize data from mice that have had a mimic of acute systemic inflammation. I aim to explore the lack of cerebral glucose availability or its impaired uptake and how this is related to the sudden changes in cognitive status of the patient.
This project aims to build on work being done on delirium in the laboratory of Professor Colm Cunningham. We expect to contribute key information regarding this major disorder, which may eventually help in the prediction and improvement of outcomes among affected patients. Since the main questions to be addressed can be pursued from these existing datasets, very significant progress is achievable in 6 weeks.

Project Methodology & Timeline

This project, being of an interdisciplinary nature, comprises various components.

Literature review
A detailed literature review, in the initial 2 weeks will characterize the limited existing research on energy disruption in delirium and dementia. This will underpin subsequent questions to be addressed in the data analysis part of this project. The identified topics include:

1) Insulin resistance/defective insulin signalling: Causing impairment of brain's ability to use glucose. Disrupted insulin signalling can leave brain cells more prone to failure, contributing to cognitive dysfunction.

2) Impaired ability of the brain to take up glucose: Glucose is taken up by the brain via two essential transporters; GLUT1 and GLUT3. Impairment of these transporters may limit available brain glucose with consequences for the brain.

3) **Failure to make and provide alternative sources of energy**: During low glucose situations, the brain can use fat-derived molecules called ketone bodies to avert the energy crisis. The implementation of this alternative energy pathway and its association with cognitive impairment will be studied.

This literature review will be independently carried out and will allow me to accurately understand the reasons behind disrupted brain energy metabolism and will provide an excellent basis with which to continue into practical investigations of these molecules/pathways in human and mouse data.

Analysis of altered metabolism in human delirium and dementia.

Cerebrospinal fluid samples of hip fracture patients were collected in a recently completed collaborative study, in which up to half of the patient's experienced delirium. Samples were analysed, in Trinity Biomedical Sciences Institute by a method called NMR (nuclear magnetic resonance). Detailed examination of small number of detectable molecules related to glucose metabolism and ketone body metabolism has yet not been performed. Based on the results of my reading to date, an analysis of these molecules will provide valuable data that will clarify energy disruption in these patients, and I will undertake this analysis in close collaboration with Profs Colm Cunningham and Ken Hun Mok in TBSI.

Analysis of altered metabolism in mouse models of delirium and dementia.

Professor Colm Cunningham's laboratory developed the first animal models to study delirium during dementia. Using their ME7 model, supplemented with the inflammatory molecule LPS, they have shown delirium-like deficits and have collected the brains of these animals to perform an analysis of brain metabolism using a method called Mass-Spectrometry (MS). The analysis of the very many changes occurring in these animals remains incomplete and I will perform a focused examination of the brain glucose/energy metabolism in these MS data. I predict that I will uncover significant convergence between the human and mouse datasets examined in these proposed studies.

Intended Outcomes

The expected impacts of the project are manifold, but collectively will shed significant light on an emerging hypothesis that may be transformative in our understanding of delirium.

1) Providing a succinct analysis of the medical/scientific literature with respect to energy metabolism disturbance in delirium
2) Detailing changes in energy metabolism in the brain fluid of patients experiencing delirium after inflammatory trauma (hip fracture).
3) Detailing analogous changes in energy metabolism in the brain tissue of mice treated with inflammatory stimulation to mimic delirium.
4) Searching for convergence between these 2 datasets

At a minimum, this proposal will have the very tangible outcome of increasing knowledge about an extremely prevalent but historically neglected condition and improving our understanding of this may ultimately cave benefits for at risk groups.

Planning for pre-approval requirements (if relevant e.g. ethics approval, Garda vetting)

All ethical approval for both mouse and human work have already been secured.

Planning for expected additional project costs (if relevant e.g. lab expenses, subscriptions, software, project-related travel)

All necesarry software and licenses are in place. If travel expenses are permitted, costs covering a flight and accomodation for two days in Liverpool are required.

Are there any other relevant details to your proposal e.g., interdisciplinary collaborations, potential for international travel, or links to existing projects or organisations?
As a part of the analysis of the mouse brain samples, I will undertake training/initial analysis with Prof Rick Dunn in the University of Liverpool. This training can be completed online or offline with the university. This will facilitate the analysis of the mouse brain samples and the statistical interpretations of the data.

Leadership-in-Action experience proposal (500 words max.) See *Leadership in Action Proposal (Summer 2)* in the guidance for more information		
LiA Category Insert **x** as appropriate	Category A: Central Laidlaw Foundation Project	**x**
	Category B: Leadership Placement	
	Category C: In-field application of research	

Leadership, to me, encompasses a wide range of aspects that go beyond the realm of academic and intellectual applications. Emotional intelligence, cultural conformity and empathetic awareness are features that go a long way, especially in a socially collaborative setting. An invaluable quality of one in a leadership position is the ability to encourage diversity and a sense of comfort amongst peers. Being an international student myself, I've experienced, first-hand, the unfamiliarity of novel environments, and subsequently, the importance of building vital connections and having understanding peers, to help adapt to them.
I've been fortunate enough in the past to experience being in leadership positions, which have certainly contributed to my insights on the matter. In high school, I was the captain of my house, placing me in charge of many students academically and with co-curriculars. I have also been quite involved in mentorship and volunteering programs within Trinity, particularly acting as an S2S mentor for the academic year 2022-23, guiding freshman students as they navigate college. This has surely been an enriching experience for me, allowing me to enhance my communication skills, team building abilities and emotional relationships with my mentees. I am also currently serving as a volunteer with Trinity, working closely with underprivileged children, helping them with their school syllabus.

As a part of my immersive leadership in action experience, I'm inclined to select the Central Laidlaw foundation project (A) to further my exposure in roles of leadership, working closely on projects contributing to a positive societal impact. My current proposed research topic for Summer 1 focuses on delirium (a neuropsychiatric disorder) and its impacts on selective risk groups in the population. As a part of this project, we aim to improve knowledge on this highly prevalent but severely neglected problem, and with that, hopefully contribute to the improved diagnosis of affected patients. While I am aware that the LiA experience in Summer 2 would not be a continuation of this research, I am truly very passionate about public health and its far-reaching benefits. Therefore, the 'Think Pacific Health Promotion Project' particularly, is a project I'd be thrilled to be a part of. My involvement with volunteering in the past, coupled with experience in navigating unfamiliar and challenging territories make me highly motivated to be a part of something that extends beyond the boundaries of college and academia. I would be excited to work closely with other scholars and local volunteers, trying to achieve our goals surrounding health development and it's awareness all while being deeply immersed in the culture of Fiji!

I'm a thoughtful, passionate, goal oriented person and believe I would thrive in an enthralling environment around such accomplished people and thought-provoking projects. I am also a keen learner and truly believe that I have a lot to gain from a programme like this. Very importantly, I believe that this is a wonderful opportunity for self-development and personal growth, and imagine to leave 18 months later, more resilient, determined, independent, and on the path to being a capable and dependable leader.

Are there any other relevant details to your proposal e.g., interdisciplinary collaborations, potential for international travel, or links to existing projects or organisations, plans to apply to a Study Abroad / Erasmus opportunity?
As mentioned previously, as a part of the research programme in Summer 1, I will undertake training/initial analysis with Prof Rick Dunn in the University of Liverpool. This training can be completed online or offline with the university and will facilitate the analysis of the mouse brain samples used for the project and the statistical interpretations of the data.