

An Indian-Australian research partnership

Project Title: **Design and Synthesis of Small Organic Molecules as Blockers of Neuronal Calcium Ion Channels Relevant to Neuropathic Pain**

Project Number **IMURA0619**

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Research Academy Themes:

Highlight which of the Academy's Theme(s) this project will address?

(Feel free to nominate more than one. For more information, see www.iitbmonash.org)

1. Advanced computational engineering, simulation and manufacture
2. Infrastructure Engineering
3. Clean Energy
4. Water
5. Nanotechnology
6. **Biotechnology and Stem Cell Research**
7. Humanities and Social Sciences

The research problem

Define the problem

Neuropathic pain is a pathology of the nervous system that is often highly debilitating and is thought to affect up to one-sixth of the world's population. There are numerous causes for the condition including nerve damage resulting from surgery, trauma, infection and disease. This type of pain can be unresponsive to existing therapies. A combination of opioids, antidepressants and anticonvulsants is often prescribed, but this usually only provides moderate pain relief and only in about 50% of cases, thus

effective treatments for neuropathic pain represent a significant unmet medical need. We are interested in developing small molecules that will help understand pain transmission and aid in finding new ways to treat neuropathic pain.

Project aims

Define the aims of the project

Neuronal voltage-gated N-type calcium channels (Ca_v2.2) and T-type calcium channels (Ca_v3.2) are strongly implicated in chronic and neuropathic pain. Previously studies have used highly constrained nature of ω -conotoxin GVIA [a peptide selective for Cav2.2 channels] to aid in the design of peptidomimetics. Recently libraries of compounds have been synthesised and tested for their ability to block Ca_v2.2 and Ca_v3.2 calcium channels.

This project will follow on from previous studies of a current IITB/Monash student. The aim of the project is to synthesise small-molecule drug-like compounds that bind selectively to N-type or T-type calcium channels and elicit pain-blocking effects in a range of in vitro and in vivo tests.

Relevant publications:

- Andersson, A.; Baell, J. B.; Duggan, P. J.; Graham, J. E.; Lewis, R. J.; Lumsden, N.G.; Tranberg, C. E.; Tuck, K. L.; Yang, A. *Bioorg. Med. Chem.* 2009, 17, 6659.
- Duggan, P. J.; Lewis, R. J.; Lok, Y. P.; Lumsden, N. G.; Tuck, K. L.; Yang, A. *Bioorg. Med. Chem Letts*, 2009, 19, 2763.
- Tranberg, C. E., Yang, A., Vetter, I., McArthur, J. R., Baell, J. B., Lewis, R. J., Tuck, K. L., and Duggan, P. J. *Mar. Drugs*, 2012, 10, 2349.
- Gleeson, E. C., Graham, J. E., Spiller, S., Vetter, I., Lewis, R. J., Duggan, P. J., and Tuck, K. L., *Mar. Drugs*, 2015, 13, 2030.

Expected outcomes

Highlight the expected outcomes of the project

- The synthesis of drug-like organic compounds that can be used as tools to probe the mode of action of pain types and neuronal pathways. Specifically we will rationally develop small molecules that will selectively block human N-type or T-type channels.
- Publications and patents.
- PhD graduate trained in synthetic organic chemistry and medicinal chemistry.

How will the project address the Goals of the above Themes?

Describe how the project will address the goals of one or more of the 6 Themes listed above.

Biomimicry is a sub-discipline of Biotechnology where the useful properties of a biological product are incorporated into a synthetic construct, while eliminating its less useful properties. In this project we will be building on our previous small-molecule drug-like compounds which mimic the Ca-channel blocking properties of conotoxin peptides developing compounds that overcome the bioavailability and toxicity issues associated with the natural peptides.

Capabilities and Degrees Required

List the ideal set of capabilities that a student should have for this project. Feel free to be as specific or as general as you like. These capabilities will be input into the online application form and students who opt for this project will be required to show that they can demonstrate these capabilities.

1. A Master of Science degree from a recognised University, majoring in chemistry.
2. Knowledge and the commitment to safe work practices in the laboratory
3. Demonstrated ability in the techniques of synthetic organic chemistry
4. Experience in chromatographic separation techniques, such as HPLC, column chromatography, and also in recrystallisation techniques
5. Experience in the use and interpretation of NMR and IR spectroscopy and mass spectrometry

6. Evidence of problem solving skills
7. Evidence of ability to co-operate and perform effectively as part of a research team
8. Demonstrated self-motivation and the ability to work independently on a given task
9. Proven ability to communicate effectively, both verbally and in writing
10. Industry experience in synthetic organic chemistry will be viewed favourably

Potential Collaborators

Please visit the IITB website www.iitb.ac.in OR Monash Website www.monash.edu to highlight some potential collaborators that would be best suited for the area of research you are intending to float.

Please provide a few key words relating to this project to make it easier for the students to apply.

Organic Synthesis, medicinal chemistry, drug discovery, pain