IITB-Monash Research Academy

Indian Institute of Technology Bombay | MONASH University

An Indian-Australian research partnership

Project Title:	**Importin α and β from apicomplexan parasites: structure, function and screening for inhibitors**	
Project Number	**IMURA0929**	
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Research Clusters:

Highlight which of the Academy's CLUSTERS this project will address?
*(Please nominate JUST **one.** For more information, see www.iitbmonash.org)*

1	*Material Science/Engineering (including Nano, Metallurgy)*
2	*Energy, Green Chem, Chemistry, Catalysis, Reaction Eng*
3	*Math, CFD, Modelling, Manufacturing*
4	*CSE, IT, Optimisation, Data, Sensors, Systems, Signal Processing, Control*
5	*Earth Sciences and Civil Engineering (Geo, Water, Climate)*
6	*Bio, Stem Cells, Bio Chem, Pharma, Food*
7	*Semi-Conductors, Optics, Photonics, Networks, Telecomm, Power Eng*
8	*HSS, Design, Management*

Research 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*
8	Design

The research problem

Importins are transporters that carry cargo proteins into the nucleus of a eukaryotic cell. Importins alpha and beta are present in human cells and in the apicomplexan parasites, Toxoplasma gondii and Plasmodium falciparum. The functions of these two importins involve recognition, transport and release of cargo proteins into the nucleus, in an energy-dependent manner. Importin alpha binds to the cargo, while importin beta binds to importin alpha and also to proteins in the nuclear pore complex. Importin alpha exhibits "auto-inhibition", a phenomenon where the N-terminal Importin beta-binding domain (IBB domain) binds to the central region of the protein and prevents binding of the cargo. When importin beta is bound to importin alpha, at the IBB domain, this auto-inhibition is relieved and cargo can bind.

Apicomplexan importins show some unusual properties compared to their homologues. For example, importin alpha proteins from P. falciparum and T. gondii show either a lack of or reduced auto-inhibition. While amino acid residues that confer lack of auto-inhibition have been identified and experimentally validated for P. falciparum importin alpha, the structural basis of reduced auto-inhibition is not clear for the T. gondii protein. These features lead to questions about molecular and structural aspects of the proteins. First, does the importin beta protein bind to the IBB domain of these unusual importin alpha proteins? Given the lack of auto-inhibition, and therefore no absolute requirement for importin beta-binding to expose the cargo-binding domains, it is of interest to understand the interactions between the two importins. Second, what is the structure of these importin alpha proteins that makes them lack auto-inhibition? Different importin alpha proteins show varying levels of auto-inhibition and an understanding of the molecular basis of these differences has been greatly aided by solving the structure of the importin alpha proteins. Third, is it possible to do high-throughput screens to find small molecules that block the interaction between importin alpha and beta from apicomplexan parasites? These screens are underway for small molecules that block the interaction between apicomplexan importin alpha and the nuclear localization signal from certain cargo, and that kill parasites in culture. The long-term goal of such screens is to find lead compounds that might be take further for drug discovery against the diseases caused by P. falciparum and T. gondii: malaria and toxoplasmosis.

This project aims to address the three questions mentioned above and by doing so, aims to understand the biology of nuclear trafficking in apicomplexan parasites, leading to potential therapeutic interventions for the diseases caused by these human pathogens.

Project aims

1) Understanding the binding of importin alpha and beta from P. falciparum and T. gondii
2) Using the results from aim (1) to do high-throughput screens for small molecules that block the interactions
3) Performing structural biology studies of importin alpha and beta from P. falciparum and T. gondii

Expected outcomes

The project will certainly lead to new knowledge and therefore publications. Depending on the outcomes of the HTS screen, if we find small molecules that satisfy the preliminary requirements of lead compounds for drug discovery, there may be a likelihood of patents as well.

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

This project will address the goals of the theme of "Biotechnology" as it works towards to discovery of small molecule inhibitors of nuclear trafficking that may be of use for further development as therapeutic agents. As such, the pharmaceutical industry might be interested in the outcomes of the project.

Capabilities and Degrees Required

Minimum Eligibility for Admission:
1. First Class or 60% marks (55% for SC/ST) in M. Sc or equivalent degree in subjects related to Life Sciences/ Physics/ Chemistry OR B.Tech Biotechnology with:

- *a valid GATE score (eligible for Institute TAship/ RAship) OR*
- *a valid CSIR/ UGC/ DBT JRF (eligible for FA category) OR*
- *a valid ICMR JRF (not linked to ICMR project) (eligible for FA category) OR*

Two year of relevant post M.Sc research experience (eligible only for project positions) OR
UGC/CSIR (Lectureship) eligible only for project position.
2. First Class or 60% marks (55% for SC/ST) in M.Tech or equivalent degree in Biotechnology

Students who have a background in structural biology, biochemistry and experience in protein expression and purification are encouraged to apply.

Select up to **(4)** keywords from the Academy's approved keyword list **(available at http://www.iitbmonash.org/becoming-a-research-supervisor/)** relating to this project to make it easier for the students to apply.

Bioscience, Biomedical Engineering, Biochemistry,