IITB-Monash Research Academy

Indian Institute of Technology Bombay | MONASH University

An Indian-Australian research partnership

Project Title:	An Antiviral Drug Target and Screening Platform for Anti-COVID Therapeutics	
Project Number	**IMURA0941**	
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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

The recent SARS-CoV-2 pandemic has created a massive push to develop effective antiviral therapies against this and future pandemics. To this view, limited success of protein-directed antivirals coupled with selection for resistant viruses, highlights the urgent need for alternative strategies. In this regard, an exciting paradigm for broad-spectrum, pan-COV intervention relies on targeting a universal cellular component - the viral lipid membrane. Notably, due to the non-biogenic virostatic nature of viral membranes along with their intrinsically fluidic nature, lipid-centric approaches are much less likely to generate antiviral resistance. To date, biomembranes have been largely ignored as a therapeutic target and are an untapped platform for drug development. Our proposal seeks to validate the viral membrane as a novel drug target and a screening platform for antiviral drug action. A vital pre-requisite for membrane-directed drug design and screening is investigation of membrane composition, structural properties and molecular organization of SARS-CoV-2 membrane lipids, which remains unexplored. This will constitute the prime objective of the proposed project and significantly advance the collective understanding of CoV-lipid membranes in viral physiology and drug interactions. The ensuing insights would be leveraged by "screening assay development" for the discovery of viral membrane-centric anti-invectives focused on a) viral membrane disruption and b) inhibition of viral-host membrane fusion. This would furnish tangible guidelines to aid researchers worldwide for the design/(re)-discovery of membrane intercalating agents, currently unexplored in SARS-CoV-2 infections.

Project aims

With the purpose of contributing to the drug-screening platform and structural characterization of SARs-CoV2 pathogen, the **specific aims** of this collaborative project are:

(i) Deciphering the supramolecular organization and biophysical properties of its lipid components

1. Topographical organization of SARS-CoV2 biomembranes using Atomic Force Microscopy

2. Membrane fluidity and order analysis using fluorescence spectroscopy

3. Lipid dynamics using fluorescence microscopy (FRAP)

4. Lipid domain characterization using Laurdan microscopy

(ii) Investigating the viral membrane as an anti-viral target; Membrane assay development for screening of antiviral agents that target membrane properties to potentially impede membrane-mediated steps in SARs infection

1. SARs-CoV membrane-host membrane fusion assay development(using lipids from mammalian cells as host and viral lipids)

2. Drug-membrane interaction studies (Fluorescence, and partition coefficients)

3. Drug-membrane interaction studies using Atomic Force Microscopy, Dual Polarization Interferometry and Surface Plasmon Resonance

(iii) Investigate SARS-CoV-2 membrane remodeling in response to established antivirals

1. How does drug binding affect the morphology and mechanical properties of the membrane bilayer? (AFM, NMR, FL)
2. How does drug affect the viral membrane fusion (FL) using in vitro fusion assay?

Expected outcomes

In this project we will establish the relationship between SARs-CoV lipid composition and membrane structure in terms of bilayer fluidity, membrane order, lipid dynamics, supramolecular organization, structural characterization, and bilayer thickness/charge. These outcomes will furnish tangible membrane properties that can be pharmacologically targeted. The same will be rendered by development of protocols for quantitative monitoring of drug-membrane interactions and characterization of drug-induced changes in viral membrane properties. In totality, these results will provide evidence that viral membrane can be exploited as anti-viral target, sensitive to membrane-active drugs that modulate SARs-CoV-2 membrane structure to impact viral-host fusion or induce viral membrane disruption.

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

COVID-19 is a global pandemic with no treatment currently available. Limited success of protein-directed antivirals, coupled with selection for resistant viruses, highlights the urgent need for alternative therapeutic strategies. Our proposal seeks to validate the viral membrane as a novel drug target and a screening platform for antiviral drug action and directly address the global health care crisis due to infectious diseases.

Capabilities and Degrees Required

- *Masters in Chemistry (Physical or Organic), Physics, or Biophysics. MTECH in equivalent fields are also eligible.*
- *Knowledge of Physical Chemistry*
- *Basic knowledge of Mass spectroscopy (MALTI-TOF, LCMS, ESI-MS), chromatographic separation methods.*
- *Basic knowledge and hands-on-experience in microscopy and fluorescence spectroscopy.*
- *Having experience in handling bacterial and mammalian culture would be advantageous.*
- *Proficient in written and spoken English.*

Potential Collaborators

NA