NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

Reg. No. 200604393R

Research Theme: Structural Biology and Drug Discovery

PhD Research Project Title: **Structural variation and inhibition of key coronaviral ion channels in SARS-CoV-2**

Principal Investigator/Supervisor: Associate Professor Konstantin Pervushin

Co-supervisor/ Collaborator(s) (if any): **NA**

Project Description

The novel coronavirus (SARS-CoV-2) is the causative agent of atypical pneumonia disease COVID-19. Since the beginning of this global pandemia, 1.5 million cases have been reported and almost 100,000 deaths. The spread of the infection poses a major health challenge for the entire population, medical care facilities and the economy, but also is a severe warning on how future epidemics should be handled. A vaccine against SARS-CoV-2 or antiviral drugs with proven efficacy are not available. These would have helped decrease the epidemic peak, known as "flattening the curve", through reducing the rate of new infections. Indeed, slowing the infection rate helps decrease the risk of health services being overwhelmed, allowing for better treatment of current cases, and delaying additional cases until better working therapeutics or a vaccine become available.

The genomes of SARS-CoV-1 and 2, and also other coronaviruses, encode three confirmed ion channels, ORF3a, envelope E protein and ORF8 (ORF8a in SARS-CoV-1) which can be exploited in drug development. These channels are not only critical to virus survival, but also largely unexplored experimentally, and specifically from the structural point of view. The paucity of high-resolution structural data, or in some cases complete absence of experimentally confirmed structural models, hampers the progress in the therapeutic development targeting coronavirus encoded viroporins. Even if the inhibition of viroporins might not result in a curative medicine, reduction of viral load, tropism (type of cell in which infection is established) or virus attenuation might in combination with other therapeutic measures help to reduce the infection rate and thus favourably flatten the curve in the epidemic dynamics.

Although in many viruses the channel activity of viroporins have been shown to be virulence factors, the progress in the discovery of inhibitors for these ion channels has been slow, and only significant in the case of influenza A M2. Even in those cases, promising inhibitors still have toxicity issues, whereas others have triggered wide-spread resistance. Considering the existing large pool of known CoV viroporins and the even larger pool of unknown potential viroporin variants, we propose a systematic search for viroporin structures and inhibitors. Recent progress in solid-state NMR enables structure determination of viroporins in planar bilayers where lipid composition might be adjusted to the corresponding lipid composition of various cellular compartments. Thus, the solid-state NMR is our method of choice to achieve the goal of structural characterization of viroporins.

This search will be coupled to rigorous biophysical data of viroporin-drug interactions. In favourable cases, it may be possible to identify a resistance mutation landscape to these drugs even before they arise in the field. The project aims to identify consensus structural features in the viroporin proteins that enable simultaneous inhibition of all three key SARS-CoV-2 viroporins, since absence of one can be compensated by the other two. The identification of

mutations that abolish channel activity are essential for validating a viroporin as a viable drug target. In this proposal we will systematically explore, both computationally and experimentally, all available amino-acid sequence space of the three key SARS CoV-2 viroporins, ORF3a, envelope E protein and ORF8, develop their principal ion channel structural models by NMR and computations and estimate structural variation and identify and validate ion channel deactivating mutations. The high resolution experimental structural models as well as methods for channel activity characterization will provide a robust platform for discovery of much-needed direct-acting antivirals.

Supervisor contact:

If you have questions regarding this project, please email the Principal Investigator:

KPervushin@ntu.edu.sg

SBS contact and how to apply:

Associate Chair-Biological Sciences (Graduate Studies) : AC-SBS-GS@ntu.edu.sg

Please apply at the following:

Application portal:

https://venus.wis.ntu.edu.sg/GOAL/OnlineApplicationModule/frmOnlineApplication.ASPX