NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

Reg. No. 200604393R

Research Theme: **Molecular and Structural Virology**

Research Project Title: **The L protein from the Respiratory Syncytial Virus: Structures and functions**

Principal Investigator/Supervisor: **LESCAR Julien**

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

Project Description

a) Background

RNA viruses represent a large group of major human pathogens causing hundreds of thousands deaths annually and for which suitable vaccines and effective antiviral strategies are mostly lacking. In addition, RNA viruses constitute invaluable tools to decipher basic cell biology. A better understanding of RNA virus replication at the molecular level offers vast perspectives for the design of new vaccines and antiviral compounds. We use tools in reverse genetics, molecular and cell virology, recombinant protein expression, enzymology, structural biology (X-ray crystallography and electron cryo-microscopy) to identify and characterize virulence factors of selected viral components including RNA structures, enzymatic and protein domains with a view to identify drug targets and to engineer attenuated viral strains for vaccine development. We have initiated a project targeting the L protein of Respiratory Syncytial Virus, a negative strand (NS) virus and a major human pathogen. L proteins from NS viruses are large molecular machineries (up to ~2300 residues) evolutionary related to the RdRps of positive strand viruses. L proteins contain multiple enzymatic activities such as RNA synthesis and cap formation, required for genome replication and are therefore attractive drug targets.

b) Proposed work

Many infections of the lower respiratory tract accounting for over 2 million deaths per year are caused by an RNA viruses from the *Paramyxoviridae* family: Respiratory Syncytial Virus (RSV) a leading cause of viral pneumonia and bronchiolitis in infants with no vaccine in sight. Tragically, an early clinical trial using formalin-inactivated RSV actually enhanced disease in children, significantly increased hospitalization rates and led to two deaths. Developing effective and safe vaccines against RSV remains challenging because of antigenic variations and the fact that RSV causes severe diseases in infants. To date, ribavirin, a broad-spectrum non-specific nucleoside analogue, is the only approved small molecule drug, with limited use and an elusive mode of action. Another approved RSV drug is palivizumab, a monoclonal antibody used for RSV prophylaxis, which is very costly and has to be injected. Clearly, there is an urgent need for a better understanding of RSV replication at the molecular level to assist the design of small molecule drugs to treat severe infections caused by RSV. As for other NS viruses, high-resolution structures are required to understand the molecular basis of viral genome transcription and replication for RSV to enable structure-based drug discovery programs. We aim to determine 3D structures for functionally active, independently foldable domains of the L protein as well as for the entire L protein, using a combination of X-ray crystallography and electron microscopy. The project should suit a candidate interested in Virology with emphasis on molecular and structural virology.

Supervisor contact:

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