NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

Reg. No. 200604393R

Research Theme: Structural Biology and Drug Discovery in Infectious Disease

Research Project Title: Identifying novel compound targets through understanding the Mycobacterial stringent response to stress

Principal Investigator/Supervisor: Professor Dr Gerhard Grüber

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

Project Description

a) Background

Tuberculosis (TB) continues to be one of the most serious infectious diseases on Earth accounting for 1.7 million deaths in 2019. Approximately one quarter of the World's population is infected with the pathogen *Mycobacterium tuberculosis* (Mtb) in latent form. TB is of enhanced concern when combined with other diseases, such as HIV and covid-19. A further concern is the rapid spread of multi drug resistant tuberculosis, gradually rendering the standard drugs ineffective and requiring the development of new drugs to ensure that the disease remains treatable. The rational development of new agents, leading to potential anti TB-drugs, requires the identification and understanding of essential biochemical pathways within the TB bacterium so that they can be specifically targeted with new molecular entities. The stringent response is a conserved global stress response in bacteria that involves the production of the hyper-phosphorylated guanosine nucleotides ((p)ppGpp) provoked by nutrient starvation. In Mtb, (p)ppGpp-metabolism is controlled by the bifunctional enzyme (p)ppGpp synthetase/hydrolase, MtRel. This enzyme is an interesting and novel target for therapeutic intervention as disrupting its function would compromise the ability of Mtb to respond to stress.

b) Proposed work:

In order to perform structure-based design of drugs to target MtRel, structural and mechanistic insights into the parts responsible for MtRel's catalysis and regulation, as well as its interaction with other biological molecules like nucleotides, tRNA or the protein synthesis machine ribosome are required. Such information will open the door for a) a novel understanding of communication between the catalysing- and regulating parts of MtRel, b) identification of possible targets for new anti-TB compounds, c) the design and synthesis of novel molecules to inhibit the enzyme and to eradicate the pathogen.

c) Preferred skills:

Have fun with science, be open for new approaches and enjoy working together in a lovely team.
Find more about us under: http://labs.sbs.ntu.edu.sg/ggrueber/

Supervisor contact:

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

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SBS contact and how to apply:

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Please apply at the following:

http://admissions.ntu.edu.sg/graduate/R-Programs/R-WhenYouApply/Pages/R-ApplyOnline.aspx