# List of IC@N Research Projects and Supervisors

## School of Biological Sciences (SBS)

| Name of Supervisor | Research Project Description |
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| **Prof. Dr. Gerhard Grüber**<br>GGrueber@ntu.edu.sg | **Identifying of enzyme inhibitors against *Mycobacterium tuberculosis* derived from Marine Actinobacterial extracts/compounds**<br><br>With one-third of mankind latently infected, an incidence of nine million new cases of active tuberculosis disease (TB) and 1.5 million deaths per year, *Mycobacterium tuberculosis* (*Mtb*), remains the most important bacterial pathogen in the world[1]. Although the South-East Asia region is home to 26% of the world's population, it accounts for 41% of the global burden of TB incidence with about 2,000 cases occurring each year in Singapore alone. The increased prevalence of co-infections with HIV and the infection with multi-drug resistant (MDR-TB) as well as extensively drug-resistant tuberculosis (XDR-TB) and totally drug-resistant tuberculosis (TDR-TB) mycobacterial strains are contributing to the worsening impact of this disease worldwide.<br>Despite being obligate aerobes, mycobacteria have the ability to metabolize in the absence of oxygen (hypoxia), by exiting the cell cycle and entering a dormant state. Hypoxic non-replicating *Mtb* displays a reduced pool of Adenosine-triphosphate (ATP), making them exquisitely sensitive to any further ATP depletion and susceptible to drugs targeting the maintenance of ATP homeostasis. This observation suggests that drugs that inhibit oxidative phosphorylation within the respiratory chain complexes could shorten the time of therapy for drug-resistant tuberculosis.<br><br>The nearly awarded TopNet (*Targeting Oxidative Phosphorylation Network*) has identified a number of drug targets within the respiratory chain enzymes. In parallel, the Centre for Drug Discovery and Development, Sathyabama Institute of Science and Technology, Chennai, India has isolated a large number of compounds from Marine Actinobacteria. Such novel molecules form a unique platform to identify and characterize new inhibitors of the respiratory chain complexes of *Mtb* and to archive synergistic efficacy by multi-drug combination with compounds unravelled by TOPNet. Identified hits will be further characterized by enzymatic assays and biophysical approaches to understand their mechanism of action. |
| | **Anti-Mycobacterial activity of peptides derived from Lactic Acid Bacteria**<br><br>Tuberculosis is more prevalent in the world than at any time in human history. With one-third of mankind infected subclinically, an incidence of almost nine million new cases of active tuberculosis disease (TB) and 1.5 million deaths per year, *M. tuberculosis*, remains the most important bacterial pathogen in the world. The increased prevalence of |

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| | co-infections with HIV and the infection with multi-drug resistant as well as extensively drug-resistant mycobacterial strains is contributing to the worsening impact of this disease. Conventionally, tuberculosis can be treated with a cocktail of first-line antibiotics, but recently mycobacterial strains resistant to first- and/or second-line drugs have emerged, and pose a global health challenge. In recent years, significant information has been gained on the essentiality of respiratory chain components in dormant as well as in replicating bacteria. The identification of new candidate drugs targeting the ATP-producing machinery illustrates the therapeutic potential of blocking mycobacterial energy conversion.<br>The *Targeting Oxidative Phosphorylation Network* (TOPNet) has identified a number of drug targets within the respiratory chain enzymes. In parallel, the Centre for Drug Discovery and Development, Sathyabama Institute of Science and Technology, Chennai, India has isolated a large number of peptides with anti-mycobacterial activity derived from Lactic Acid Bacteria. Such novel peptides form a unique platform to identify and characterize new inhibitors of the respiratory chain complexes of *M. tuberculosis* and to archive synergistic efficacy by multi-drug combination with compounds unravelled by TOPNet. Identified hits will be further characterized by enzymatic assays and biophysical approaches to understand their mechanism of action. |
| **Assoc Prof Surajit Bhattacharyya**<br>Surajit@ntu.edu.sg | **Peptide macrocycles as potent inhibitors of amyloids**<br><br>Protein amyloids are dreadful consequences of many diseases including AD, T2D, AIDS etc. We are developing macrocyclic peptides that would inhibit amyloid formation. In this project, student will investigate mode of action of selected peptide macrocycles in inhibiting amyloids of various proteins. The work will be carried out using a range of biophysical and spectroscopic methods e.g. fluorescence, cell based assays, NMR, ITC.<br><br>Duration: More than 2 months. |
| **Nanyang Assistant Professor Li Yinghui**<br>liyh@ntu.edu.sg | **Epigenetic regulation of NF-κB in cancers**<br><br>The nuclear factor κB (NF-κB) family of transcription factors regulate the expression of a broad range of inducible genes critical for various biological processes such as inflammation and immune responses. Deregulation of the NF-κB pathway has been causally linked to many diseases including cancer. However, how it regulates gene expression programs during cancer progression through non-coding RNAs remains uncharacterized. The primary objective of this project is to elucidate how the altered expression of non-coding RNAs during aberrant NF-κB activation drive the malignant development of cancers. Non-coding RNAs and their target genes which are identified from our genomics studies will be validated and characterized for their functions in the pathogenesis of cancers using a variety of molecular biology techniques such as CRISPR interference, in-situ hybridization, FACS and chromatin immunoprecipitation. |

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| | Preferred research project duration: May-Nov 2019 (6 months) |
| **Nanyang Assistant Professor Guillaume Thibault**<br>thibault@ntu.edu.sg | **Characterising the anti-aging role of the unfolded protein response from high glucose diet**<br><br>Aging is one of the most critical risk factors for the development of metabolic syndromes. Both, T2D and insulin resistance have a strong association with endoplasmic reticulum (ER) stress. Upon ER stress, the unfolded protein response (UPR) is activated to limit cellular damage by adapting to stress conditions and to re-establish ER homeostasis. However, genes upregulated from the UPR tend to decrease while the incidence of developing metabolic syndromes increases with age. Although stress resistance correlates with increased longevity in a variety of model organisms, the link of the UPR, ER stress resistance and longevity remains poorly understood. Surprisingly, our preliminary data demonstrate that aged animals subjected to high glucose diet (HGD) live longer in a UPR-dependent manner which is contrary to young adult animals subjected to HGD. Based on these observations, we hypothesise that HGD activates the UPR in aged worms to overcome stress of aging and to restore ER homeostasis. Here, we aim to (1) dissect the role of the UPR in extending longevity of aged animals challenged with HGD, (2) characterize molecular mechanism leading to HGD-induced longevity, and (3) determine conserved HGD-induced longevity pathway in human. The powerful approach using nematodes to decipher molecular mechanisms underlying longevity and HGD offers an outstanding opportunity to identify new target genes and metabolites. Complementary studies in human cell lines will help to identify conserved pathways linked to age-dependent HGD-induced UPR. In future, findings can be used for the development of novel biomarkers for diagnostics and prognostics for future human intervention. The student will manipulate the worm C. elegans and carry out techniques such as fluorescence microscopy, RT-PCR, and lipid extraction and analysis.<br><br>The project will require more than 2 months to be completed. |
| **Prof James Tam**<br>jptam@ntu.edu.sg | **Discovery of Druggable Biologics from Medicinal Plants**<br><br>Peptide and protein biologics are therapeutics and prophylactics known for their desirability of high specificity and low toxicity. They display a wide range of biological activities such as antimicrobials, immunomodulation, neurotransmission and hormonal functions. The major aims of this project are: (1) Discovery of novel biologics from medicinal plants with particular focus on cyclotides, knottin, hevein and plant defensins. (2) Pharmacological profiling of novel biologics base on their traditional usages in folk medicine. The proposed study may provide leads compound for drug development and aid in quantitative profiling of active ingredients in commercial viable medicinal herbs. |

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| **Assoc Prof Richard J Sugrue**<br>RJSugrue@ntu.edu.sg | **Identification of signalling networks involved in respiratory syncytial virus morphogenesis**<br><br>Respiratory syncytial virus (RSV) is the most important cause of lower respiratory tract infection in young children and neonates. The clinical scenario is worsened by the lack of an effective vaccine, and the limited availability of specific antivirus drugs. A greater understanding of the biology of the virus should provide a greater understanding of the process of infectious virus particle assembly, which in turn should aid in the development of novel antirust strategies against RSV. During RSV infection the virus matures on the cell surface in the form of filamentous particles referred to as virus filaments. The involvement of lipid-raft microdomains and GTPase signalling pathways in the process of virus particle assembly has been demonstrated, and an important role for F-actin in RSV morphogenesis has also been suggested. Although the role that F-actin plays during virus morphogenesis has not been defined, virus infection is associated with changes in the cortical F-actin network structure that are essential for virus morphogenesis and virus transmission. Signalling pathways involved in regulation of F-actin structure such as rhoA and rac1 have also been implicated in RSV filament formation. However, these pathways are constitutively activated in many cell types used to examine RSV morphogenesis, and hence can't directly account for the virus induced change in actin structure that is required for virus maturation. This suggests the involvement of other down-stream signalling molecules in this process. The aim of this project will be to further define the role that down-stream signalling molecules play in virus morphogenesis, and will employ standard biochemical analysis and high-resolution imaging of virus-infected cells. |
| **Assoc Prof Mu Yuguang**<br>YGMu@ntu.edu.sg | **Computer Simulations in Biology and Materials Sciences**<br><br>1. Peptide/protein self assembly , it is an amazing research field, many disease related amyloid and other function amyloids are under study in my group.<br>2. Drug-protein interaction, molecular dynamics simulations and molecular docking will be applied to help find candidate small molecules to bind to functional proteins. More importantly experimental collaborators are eager to test your predictions. |
| | **In Silico Approach To Design a Drug for Osteoarthritis**<br><br>Osteoarthritis (OA) is a major disabling disease and is ranked as a major cause of chronic pain in adults. The pathology of the illness is characterized by a loss of articular cartilage leading to narrowing of joint space, increased joint friction, potential structural remodelling, persistent pain, and functional impairment. The pro-inflammatory cytokine interleukin 1ß (Human IL-1ß) has several chemical and |

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| | bioactive characteristics allowing this catabolic protein to be involved in initiation and progression of OA .<br>For specific inhibition of IL-1 production or activity, various treatment strategies could be used. One such strategy employed in our present study was, inhibiting the action of IL-1 by screening herbal compounds.<br><br>In the present study,10 herbal compounds were selected. The compounds chosen were of herbal sources (Ginger- *Zingiber officinale*) and their 2D, 3D structures, chemical and physical properties were retrieved and analyzed according to Lipinskis rule of five to determine the likeliness of the drug to be oral .Toxicity prediction was done by using online tool Osiris.**QSAR** analysis was performed. Docking was performed by using offline molecular modelling software, **Autodock 4.2.6.** By comparing the docking studies of the compounds, and analyzing their binding energies, the compound with least binding energy was selected as the most suitable as the drug. |
| **Nanyang Assistant Professor Miao Yansong**<br>yansongm@ntu.edu.sg | **Defence mechanisms of plant for pathogen infection**<br><br>Eukaryotic species have similar striking mechanisms for defence in response to bacterial pathogen infection. Innate immune response of plant is a complicated system involving several key intracellular events, including sensing and transport of pathogenic signals via the endocytosis process mediated by actin filament assembly in a spatiotemporal manner. Plants are constantly exposed to different types of pathogenic microbes. In response to pathogen infection, the plant has an innate immune system for defence by recognizing pathogen-associated molecular patterns from pathogen surface. Several major signalling transduction pathways will be activated and triggers ROS generation and cellular structure changes such as actin cytoskeleton. This project will use model plant Arabidopsis to study pathogen infection by performing biochemical assays and cell biology imaging. |
| **Asst Professor Shashi Bhushan**<br>Sbhushan@Ntu.Edu.Sg | **Structural Analysis Of Potential Mycobacterial Biosynthetic Enzymes For Drug Development**<br><br>Multi Drug Resistance Is A Serious Problem In Tuberculosis Where Bacteria Is Getting Resistance To Used Drugs. New Lines Of Drugs Are Therefore Always Required To Keep The Disease Under Control. We Have Identified A Number Of Potential Target To Determine Their Structure For Developing New Drugs. These Targets Will Be Expressed And Purified For Structure Determination With Single Particle Cryo-EM. |