<u>List of Research Projects Available for Prospective PhD Students at LKCMedicine</u>

The list of research projects is grouped by the following 9 Research Areas.

- 1. Neuroscience & Mental Health
- 2. Nutrition, Metabolism & Health
- 3. Population & Global Health
- 4. Respiratory & Infectious Diseases
- 5. Skin Disease & Wound Repair
- 6. Data Science & Artificial Intelligence
- 7. Cancer Discovery & Regenerative Medicine
- 8. Microbiome Medicine
- 9. Medical Education
- 10. Others

No	Project Title with Brief Description	Principal Investigator
	1. Neuroscience & Men	tal Health
1.1	Brain mechanisms for executive function and their vulnerability to ageing, stress, and psychosis	Asst Prof Tsukasa Kamigaki tsukasar@ntu.edu.sg
	The project aims to elucidate the brain-wide mechanisms underpinning executive functions and their deterioration due to ageing, stress, and psychosis using behaving mice as a model system. The student will address this problem utilizing cutting-edge neuroscience technologies, including in-vivo calcium imaging, optogenetics, and the development of behavioral paradigms. Additionally, the student will receive extensive training in coding and data analysis. References: Chong HR., Ranjbar-Slamloo Y., Ho MZH., Ouyang X., and Kamigaki T.(2023) Functional alterations of the prefrontal circuit underlying cognitive aging in mice. Nature Communications,14, 7254. Kamigaki T., and Dan Y. (2017). Delay Activity of Specific Prefrontal Interneuron Subtypes Modulates	Website https://dr.ntu.edu.sg/cris/rp/rp01272

Memory-Guided Behavior. *Nature Neuroscience*, 20, 854-863.

Understanding Mechanisms of Cellular Cholesterol Distribution: Implications for Brain Health

1.2

Neurodegeneration and age-associated decline in cognitive function are often associated with altered compositions of lipids (or "fats") in the brain. Lipids play very important roles in regulating brain function, and abnormal distribution of lipids in neurons results in numerous neurological disorders. Among various lipids, cholesterol serves as a major building block for cellular membranes and maintains healthy neurons. In this project, we will use various cutting-edge techniques, including advanced microscopy, stem cells, and animal models, including *C. elegans*, to identify key molecular machineries that are responsible for the distribution of cellular cholesterol. As cholesterol metabolism plays an important role in brain health and animal physiology, our research has the potential to reveal new therapeutic targets for guiding major drug discovery efforts toward treating devastating neurodegenerative disorders, such as Alzheimer's disease.

Selected References:

- (1) Naito T, Ercan B, Krshnan L, Triebl A, Koh DHZ, Wei FY, Tomizawa K, Torta FT, Wenk MR, and Saheki Y (2019). Movement of accessible plasma membrane cholesterol by the GRAMD1 lipid transfer protein complex. *eLife*. 8: e51401.
- (2) Ercan B*, Naito T*, Koh DHZ, Dharmawan D, and Saheki Y (2021). Molecular basis of accessible plasma membrane cholesterol recognition by the GRAM domain of GRAMD1b. *EMBO J*. 40: e106524. *Co-first authors.
- (3) Naito T and Saheki Y (2021). GRAMD1mediated accessible cholesterol sensing and transport. *BBA - Molecular and Cell Biology of Lipids*. 1866: 158957.
- (4) Naito T, Yang H, Koh DHZ, Mahajan D, Lu L, and Saheki Y (2023). Regulation of cellular

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- cholesterol distribution via non-vesicular lipid transport at ER-Golgi contact sites. *Nature Communications*. 14: 5867.
- (5) Koh DHZ, Naito T, Na M, Yeap YJ, Rozario P, Zhong FL, Lim KL, and Saheki Y (2023). Visualization of accessible cholesterol using a GRAM domain-based biosensor. *Nature Communications*. 14: 6773.

Gut-brain neurobiology: microbiome control of neural circuits and behaviour

1.3

The trillions of bacteria living in our body encode over 46 million genes – suggesting tremendous functional capacity (by contrast, the human genome has less than a thousandth of that). Moreover, emerging evidence suggests that the gut microbiota profoundly influences host physiology and behaviour. In this project, we will investigate the fundamental biological basis of "gutfeelings", how microorganisms and chemicals in the gut signal to brain to modulate neural substrates that control physiology and behaviour. We employ a range of experimental techniques in mice to study the mammalian gut-brain axis including sequencing, metabolomics, in vivo neural imaging/recording, and genetically-guided functional interrogation.

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2. Nutrition, Metabolism & Health

2.1 Investigating the role of gut microbiome in cardiometabolic diseases

In recent years, it has become evident that the gut bacteria living in our intestine significantly impact health and disease. This influence extends beyond intestinal disorders like inflammatory bowel disease encompass a wide range of conditions including obesity, diabetes, and neurodegenerative diseases. Our laboratory has previously reported that certain gut bacteria contributes to the progression cardiovascular disease (PMID: 30397344, 37279756). This PhD project focuses on gut microbiota and lipid metabolism, employing state-of-the-art technologies such as anaerobic culture systems, mouse models, and next-generation sequencing to advance research in this field.

Cardio-immunology: Elucidating the immune landscape of transplanted human cardiovascular progenitors in myocardial infarcted hearts

Ischemic heart failure is a non-communicable disease that affects a large number of individuals globally. A potential treatment that may enhance heart function and functionally replace injured cardiac muscles in cellular therapy. However, there is a gap in knowledge in understanding the immune rejection of xenograft after transplantation into myocardial infarcted hearts. Having this knowledge will be essential to devise strategies to target immune responses for a successful regenerative medicine therapy.

This project aims to (1) transplant potentially hypoimmune human pluripotent stem cells (hPSCs) -derived cardiac progenitors into a MI mouse model and (2) map out the temporal immune landscape that led to graft rejection in a healthy and metabolic disease mouse model. The student will be working with cell and molecular techniques, differentiation and culture of hPSCs toward CVPs in preparation for transplanting into animals and downstream tissue processing. The

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https://www.linkedin.com/in/lynn-yap-39969879/ study will focus on xenograft survival/rejection, immunology in healthy and metabolic MI animal models.

Unveiling the Hidden Impact of Microplastics on Metabolic Health: A Critical Research Frontier

2.3

Despite the alarming prevalence of microplastics, particularly in Southeast Asia which tops global intake, the short-term and long-term health impacts of these ubiquitous pollutants remain shrouded in mystery. This gap in knowledge is especially critical when considering the effects of microplastics on the development and progression disorders—a of metabolic understudied area. With the world grappling with a metabolic syndrome pandemic and an urgent focus on metabolic health in the post-Covid era, unraveling how microplastics impact those with metabolic syndrome could be groundbreaking. The findings from such research promise to revolutionize our understanding and pave the way for transformative public health strategies. This work is highly interdisciplinary, integrating expertise from diverse fields comprehensively understand the major types of microplastics present in dietary sources and everyday products. By employing human-relevant animal models of metabolic disorder and gut health, researchers can closely examine how these microplastics influence disease progression. This approach not only bridges gaps between environmental and material science, toxicology, and metabolic health but also promises to deliver insights that are directly applicable to human health, enhancing the relevance and impact of the findings.

Candidate interested in this project should also apply for the Interdisciplinary Graduate Programme (IGP).

<u>Interdisciplinary Graduate Programme | Graduate College | NTU Singapore</u>

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2.4

Systematically Investigating Molecular Mechanisms Underlying Aging-Related Human Diseases through Multi-Omics Profiling

Aging is a complex biological process characterized by a gradual decline in physiological functions, which increases susceptibility to diseases and death. This process is influenced by a myriad of genetic, environmental, and lifestyle factors. To better understand aging and study the relationship between aging and aging-related diseases, our research group is focused on building predictive models using machine learning techniques. The model is to integrate multiomics datasets, focusing specifically on gut microbiome and metabolomics data. The comprehensive analysis of these multi-omic datasets aims to unveil crucial molecular indicators, intricate biological pathways, and influential regulatory circuits that play a role in the aging process and the pathogenesis of age-associated disorders. Such an understanding is likely to be helpful in the development of innovative therapeutic interventions to promote healthy aging and to address the onset and progression of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases.

2.5

Modulation of digestive enzyme activity as a safe approach to improve metabolism and health

This project aims to design new therapeutic targets, with structure-function lead optimisation of compounds that inhibit luminal carbohydrate enzymes. Guided by naturally occurring plant-based compounds, this project involves side-chain modifications to improve enzyme inhibition selectivity and specificity. From chemistry to biology, this project will continue with the characterization of luminal carbohydrate digestion modulation on the recipient host. Investigations will include an assessment of intestinal health, alterations in gut microbiome, impact on immunology and finally carbohydrate metabolism and homeostasis.

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2.6

Nutritional intervention and the impact on muscle health in elderly health

This project aims to molecularly dissect pathways that are altered under (i) intermittent fasting conditions and (ii) plant-based nutritional intake. These dietary interventions are increasingly being suggested as disease-modifiers, but the molecular mechanisms that support these claims are still not well-defined. With a focus on insulin sensitivity, immunology and metabolic organ homeostasis and health, the candidate will undertake a series of in vitro and in vivo experiments to understand the role of intracellular lipid regulation response to both dietary interventions. In collaboration with exercise physiologists from the National Institute of Education, candidate will also undertake a human study to validate translation and clinical relevance.

2.7

In-vivo functional genetic screen to identify novel modulators of Non-Alcoholic Fatty Liver Disease (NAFLD)

The project focuses on employing in-vivo mouse models that resemble and recapitulate human disease to study NAFLD disease progression. Our preliminary results have identified several shRNAs that confer a negative or positive effect on the regenerative capacity of the hepatocytes. Further approach will be focused on validation of these shRNAs, such as their cell migration and cell proliferation characteristics using various invitro assays, followed by selection of the top performing shRNAs for in-vivo validation. In addition, combined transcriptomic and proteomic approaches will be undertaken to unravel new insights with the aim of identifying targets for therapeutic intervention and treatment of the disease.

2.8

Identification of novel senolytic targets for improving liver regeneration

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The project focuses on conducting in vivo & in vitro functional genetic screens to identify targets to eliminate senescent cells. Senescent cells are known to drive inflammaging attenuating the regenerative capacity of the liver. Through a negative selection screen in senescent cells we can identify vulnerabilities of these cells. The goal is to identify novel senolytic targets for therapeutic purposes.

2.9 Identifying novel biomarkers in liquid biopsy derived exosomes

The project focuses on identifying novel blood-based biomarkers for liver disease. Mouse models of chronic liver disease will be used, exosomes will be isolated from the blood and the content will be analyzed by transcriptomic and proteomic approaches. The same approach will be applied for liver patient derived blood samples. The goal is to identify novel conserved biomarkers for liver disease.

Ageing of bone microenvironments

Our skeletons play a crucial role in regulating key physiological processes, including mineral homeostasis, energy metabolism, and blood cell production. The presence of multiple blood vessel (BV) subtypes and the distinct microenvironments they support contribute to the skeleton's multifaceted functions. Vascular aging is a key factor in the agerelated functional and physical changes observed in the skeleton. Understanding vascular niches and their agerelated alterations could help target specific functional niches for managing age-related bone and blood diseases.

In this study, we aim to identify and characterize bone vascular microenvironments and their functions. Leveraging cutting-edge techniques developed in our laboratory—including high-resolution 3D imaging, single-cell and spatial transcriptomics, metabolic analysis, and advanced mouse genetics—the candidate will have the opportunity to:

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3.0

- Characterize different types of microenvironments in bone.
- Understand how blood vessels support these niches.
- Identify strategies to replace or target aging blood vessel subtypes specifically.

3.1 Metabolic control of bone marrow microenvironments

The mammalian skeletal system undergoes continuous remodelling throughout life, intricately interacting with whole-body physiology. Metabolic changes significantly influence bone health by altering the cellular composition and functional dynamics of bone tissue. However, the cellular and molecular mechanisms underlying these dynamic changes remain poorly understood. In this study, we investigate the impact of metabolism on the mesenchymal composition of bone microenvironments. Specifically, the student will

- 1. Map and characterize the distribution patterns of mesenchymal cell subtypes in bone.
- 2. Explore how metabolic conditions such as diabetes, modulate mesenchymal cell composition
- 3. Identify metabolic targets to modulate mesenchymal cell differentiation and composition.

The student will employ advanced techniques, including confocal and intravital imaging, single-cell and spatial transcriptomics, metabolic profiling, and state-of-the-art mouse transgenics. Overall, this study aims to uncover the mechanisms driving bone pathology in metabolic diseases like diabetes, providing a foundation for targeted therapeutic strategies.

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3. Population & Global Health

3.1 Comprehensive Multi-omics Analysis of Human Aging Using the Large Language Module based Functional Module Annotation

Multi-omic methods provide great opportunities to systematically reveal the critical molecular alterations of aging from a multidimensional perspective, while matching and investigating the biological information and functions from multi could be a heavy subjective work. Large Language Models (LLMs) has shown high efficiency and accuracy in repetitive search and collection work, which will help us to extensively and quickly investigate potential research objects and validate them with published works to prove their roles and molecular mechanism. So in this project, we aim to build up a tool utilizing LLM, such as GPT4, to accelerate and improve the biological investigation in multi-omics data for aging research.

3.2 Climate and health – mapping the impacts towards positive action

This PhD is located within a wider multidisciplinary project NTU "Climate Transformation Program" that seeks to map and model impacts of climate change. World Health Organization (WHO) emphatically noted that the risks of the climate crisis to human health extend way beyond physical impact(s) to mental health and called for intervention(s), mitigation and adaptation. The evidence however on mental health impacts in Singapore and Southeast Asia is limited. The PHD project will integrate evidence synthesis and observational mixed methods approached to identify mental health risks and at risk populations.

Mapping and Optimising Public involvement in Biobanks

Biobanks play an important and emerging role in supporting basic and translational research. The PHD project will be nested in a population cohort study

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3.3

(HELIOS; https://www.healthforlife.sg), established and led by Lee Kong Chian School of Medicine that aims to identify environmental, lifestyle and genetic factors that cause heart disease, diabetes, cancer and other chronic diseases in Singapore. The work will seek (a) to sunthesise evidence on Patient Public Involvement in context of biobanks; (b) to develop implement and evaluate Patient Public Involvement initiatives and (c) to conduct mixed methods study related to return of results procedures. The work will involve scoping literature reviews, preparatory work for evaluation studies including public and community involvement and engagement activities, collection analysing qualitative and quantitative data, building relationships with relevant stakeholders.

3.4

Ageing of bone microenvironments

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• Identify strategies to replace or target aging blood vessel subtypes specifically.

3.5

Metabolic control of bone marrow microenvironments

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3.6

Understanding the tumor microenvironment: High-resolution 3D and multiplex imaging approach for deciphering cancer progression

Endothelial cells are pivotal architects of blood and lymphatic vessel integrity, forming the inner lining that regulates inflammation, immune cell trafficking, and organ-specific vascular functions. Perivascular and mesenchymal stromal cells dynamically shape vascular microenvironments, playing essential roles in tissue homeostasis and disease. In cancer, the tumor

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microenvironment (TME) drives disease progression by orchestrating a complex interplay among cancer cells, vascular networks, and stromal components. This dynamic milieu enhances metastatic potential and contributes to therapeutic resistance. Central to this process is epithelial-mesenchymal transition (EMT), which equips cancer cells with invasive properties. Critically, stromal and vascular cells are key enablers of EMT and therapy resistance, making them highly attractive targets for innovative therapeutic strategies.

Despite their significance, the complexity, heterogeneity, and spatial interactions of tumor stroma and vasculature remain poorly understood across different stages of cancer progression. This knowledge gap limits the development of precision therapies. To address this challenge, we propose leveraging cuttingedge high-resolution light-sheet microscopy and multiplex imaging to define, at an unprecedented level, the spatial interactions between vascular, stromal, and cancer cells throughout disease progression. Our approach focuses on three malignancies with distinct clinical and biological challenges: head and neck cancers, glioblastoma, and breast tumors. This study aims to illuminate the spatial interactions within the TME, providing a foundation not only for the development of targeted interventions to disrupt the stromal-vascular axis in cancer progression but also for precise diagnostic and prognostic strategies throughout the course of the disease.

4. Respiratory & Infectious Diseases

4.1 Exploring RNA Viral Vectors for mRNA Therapy Applications

This project aims to investigate the molecular mechanisms of RNA viral vectors and their implications in developing next-generation mRNA therapies for infectious diseases, cancer, and other chronic conditions. Leveraging the unique properties of RNA

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viral vectors, such as high transfection efficiency and low immunogenicity, we propose to systematically characterize the vector-host interactions at the molecular level. This will involve the use of cutting-edge biotechnological tools, including CRISPR-Cas9 genome editing and next-generation sequencing, to optimize vector design and functionality. By elucidating the molecular basis of RNA viral vector-mediated mRNA delivery, this research intends to pave the way for highly effective and targeted therapies. The outcomes are expected to have profound impacts on the treatment strategies for a wide range of diseases, enhancing the therapeutic efficacy while minimizing adverse effects.

4.2 Molecular Basis of the Flavivirus Replication Process

Dengue is a critical public health issue with severe forms affecting hundreds of thousands annually. Without a vaccine offering lasting protection against all DENV serotypes, treatment relies on symptomatic care and antivirals. The replication of the virus involves a complex known as the replication complex (RC), which is central to viral replication and a prime target for drug development. Despite advances in understanding individual components of the RC, its full architecture and interactions remain elusive. his project aims to protein-protein uncover kev and protein-RNA interactions within the DENV RC using methods from biochemistry, biophysics, structural biology, biology, and virology. Approaches include reconstituting the RC with selected proteins and isolating it from infected cells to study its composition and functionality.

Effects of host and environment in shaping the lipid coat of Gram negative bacterium

Gram negative bacterium (GNB) is well protected from its environment by its dual membrane. This barrier is one of the key factors for bacterial resistance to the **Assoc Prof Luo Dahai**

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4.3

actions of antimicrobials. In this study, we seek to understand how the environment and the host shapes the lipids of GNB, and the phenotypic effects, including virulence and antimicrobial resistance. The works will facilitate discovery of therapeutic strategies for fighting infections.

4.4 Understanding lipid variations in carbapenem-resistant *Klebsiella pneumoniae*

Carbapenem-resistant *K. pneumoniae* (CRKP) is a global and local health threat. Whole genome sequencing of clinical isolates have greatly facilitated the discovery of antimicrobial resistance mechanisms, and transmission. However, there remained a discordance between the genetics of the bacterium and its phenotypes. This project will explore the underlying basis of lipid variations clinical CRKP, and the impact on antimicrobial resistance in *K. pneumoniae*.

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5. Skin Disease & Wound Repair

5.1 Decoding Neutrophil Heterogeneity: Transforming Chronic Wound Management

The intricate process of wound healing, involving phases from hemostasis to tissue remodeling, is welldocumented. However, it remains elusive in the context of chronic wounds stuck in perpetual inflammation. Neutrophils, key players in the initial inflammatory phase, must undergo timely apoptosis and clearance to progress healing, yet the detailed mechanisms, especially in chronic wounds, are not fully understood. This gap hinders effective treatment, impacting patient outcomes. Emerging research reveals that neutrophils are not a homogenous population but exhibit significant heterogeneity, influenced by their environment, leading to various subpopulations with unique Understanding this neutrophil heterogeneity is crucial for addressing chronic inflammation. Additionally, endoplasmic reticulum stress, which regulates immune responses, adds another layer of complexity, affecting

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neutrophil behavior. Yet, its impact on neutrophil heterogeneity remains unexplored. Unraveling this complexity could change treatment strategies, targeting specific neutrophil subsets to enhance healing and improve patient outcomes. These findings promise to transform our understanding and management of chronic wounds.

Candidate interested in this project should also apply for the Nanyang President's Graduate Scholarship.

The role of microtrauma in human hair regrowth and regeneration

5.2

Androgenetic alopecia (or male pattern baldness) affects more than half of men by the time they reach middle age, whereby hair follicles miniaturise over time. We currently do not understand the mechanism of the human hair cycle, or how to reverse miniaturization. The popularity of treatments like microneedling suggest that subclinical wounding (ie. Microtrauma) has a role in stem follicle cells their allowing hair and microenvironment to regenerate. Our team is focused understanding the basic mechanisms microtrauma on human skin and hair follicles, and translating these findings into exciting new treatments for hair loss.

Post-Translational Modifications of the Integrin 5.3 LFA-1 in the Regulation of T-Cell Motility

Leukocyte function-associated antigen-1 (LFA-1) is an integrin expressed on T-cells and plays a crucial role in T-cell signaling, adhesion, and motility. Protein post-translational modifications are known to influence integrin functions. However, LFA-1 post-translational modifications and their functional roles are not clearly understood. This project aims to determine the impact of glycosylation and sulfation on LFA-1 activation, clustering, and signaling, investigate how these post-translation modifications affect T-cell motility. The outcomes of this research will provide deep insights into

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the molecular mechanisms that underpin T-cell immunology, which could lead to developing novel and safe strategies to fine tune T-cell function.

5.4 Understanding the Role of DDX3 in Lymphoma Drug Resistance

Despite the use of multi-agent chemotherapy for non-Hodgkin lymphoma, treatment outcomes remain poor due to the development of chemoresistance and high relapse rates. We have recently reported that loss-of-function mutations in the X-linked RNA helicase DDX3X are associated with chemoresistance and poor prognosis in non-Hodgkin lymphoma subtypes. This project aims to further investigate DDX3X involvement in Epstein-Barr virus (EBV)-associated Natural killer/T-cell lymphoma (NKTCL), which is an Asian-prevalent aggressive subtype. The outcomes will advance our understanding of non-Hodgkin lymphoma disease mechanism and drug resistance that would have profound impact on treatment strategies.

Design of microneedle for efficient cutaneous delivery

The outer keratinized stratified epidermal layers pose a significant barrier for the entry of biomolecules. To breach this barrier, microneedles, which comprise of an array of micron-sized needles have been used. Owing to their minimal invasiveness and relatively pain-free nature, microneedles are attractive medical devices for cutaneous drug delivery. Nevertheless, some of the challenges associated with them include inconsistent penetration and poor delivery efficiencies. Herein, we aim to leverage on the versatility and speed of freeform prototyping via 3D printing to design and fabricate customizable microneedles. We will explore the use of various materials, designs and print parameters to optimize the efficacy in the performance of these devices with the goal of in-human clinical application.

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5.5

5.6

Biofabrication of physiologically relevant skin constructs

Human skin tissues are widely used for many biological and pharmacological applications. However, current strategies to generate such in vitro constructs are tedious, labour intensive and suffers from lack of reproducibility. To overcome this issue, such constructs can be generated by using additive manufacturing. Otherwise known as bioprinting, the semi-automated platform enables the deposition of multiple materials and cells with spatial precision, allowing improved structural and compositional complexity that can further recapitulate native skin. In this project, we aim to develop bioinks for the reconstruction of physiologically relevant skin tissues and investigate the influence of biomaterial properties on the cell behaviour and tissue maturation.

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6. Data Science

6.1

Deep learning for Robust Analysis of Medical Scans

The doctoral project aims to develop a deep learning system for automated analysis of medical imaging scans such as X-rays, CT, and MR scans. The system will utilise deep learning models trained on large datasets of scans for different medical tasks. Students can conduct research on medical deep learning projects which includes:

- Object detection in medical scans
- Computer vision for medicine and population health
- Medical segmentation, diffusion. reconstruction, and classification
- Deep learning for the analysis of multimodal medical dataset
- Large language models for the analysis of medical imaging dataset
- Large foundation models for medicine

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6.2

Systematically Investigating Molecular Mechanisms Underlying Aging-Related Human Diseases through Multi-Omics Profiling

Aging is a complex biological process characterized by a gradual decline in physiological functions, which increases susceptibility to diseases and death. This process is influenced by a myriad of genetic, environmental, and lifestyle factors. To better understand aging and study the relationship between aging and aging-related diseases, our research group is focused on building predictive models using machine learning techniques. The model is to integrate multiomics datasets, focusing specifically on gut microbiome and metabolomics data. The comprehensive analysis of these multi-omic datasets aims to unveil crucial molecular indicators, intricate biological pathways, and influential regulatory circuits that play a role in the aging process and the pathogenesis of age-associated disorders. Such an understanding is likely to be helpful in the development of innovative therapeutic interventions to promote healthy aging and to address the onset and progression of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases.

6.3

Comprehensive Multi-omics Analysis of Human Aging Using the Large Language Module based Functional Module Annotation

Multi-omic methods provide great opportunities to systematically reveal the critical molecular alterations of aging from a multidimensional perspective, while matching and investigating the biological information and functions from multi could be a heavy subjective work. Large Language Models (LLMs) has shown high efficiency and accuracy in repetitive search and collection work, which will help us to extensively and quickly investigate potential research objects and validate them with published works to prove their roles and molecular mechanism. So in this project, we aim to

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	build up a tool utilizing LLM, such as GPT4, to accelerate and improve the biological investigation in multi-omics data for aging research.	
	7. Cancer Discovery & Regen	erative Medicine
7.1	Cardio-immunology: Elucidating the immune landscape of transplanted human cardiovascular progenitors in myocardial infarcted hearts	Asst Prof Lynn Yap lynn.yap@ntu.edu.sg Website
	Ischemic heart failure is a non-communicable disease that affects a large number of individuals globally. A potential treatment that may enhance heart function and functionally replace injured cardiac muscles in cellular therapy. However, there is a gap in knowledge in understanding the immune rejection of xenograft after transplantation into myocardial infarcted hearts. Having this knowledge will be essential to devise strategies to target immune responses for a successful regenerative medicine therapy.	https://dr.ntu.edu.sg/cris/rp/rp02163 https://www.linkedin.com/in/lynn-yap- 39969879/
7.2	The role of microtrauma in human hair regrowth and regeneration	Co-Supervisor:
	Androgenetic alopecia (or male pattern baldness) affects more than half of men by the time they reach middle age,	Asst Prof Etienne Wang

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Generating immune-privileged kidney organoids from gene-edited human pluripotent

7.3

stem cells

Autologous induced pluripotent stem cell (iPSC) derived cells and tissues represent a valuable resource for realizing disease modelling and replacement. However, it is time-consuming and costly to generate fully characterised GMP grade iPSCs from every patient who requires organ replacement therapy. In this project, we will harness gene editing to generate human iPSCs the progenies of which can evade T cells, NK cells, and complement system of immune competent rodent host.

7.4 In-vivo functional genetic screen to identify novel modulators of Non-Alcoholic Fatty Liver Disease (NAFLD)

The project focuses on employing in-vivo mouse models that resemble and recapitulate human disease to study NAFLD disease progression. Our preliminary results have identified several shRNAs that confer a negative or positive effect on the regenerative capacity of the hepatocytes. Further approach will be focused on validation of these shRNAs, such as their cell migration and cell proliferation characteristics using various invitro assays, followed by selection of the top performing shRNAs for in-vivo validation. In addition, combined transcriptomic and proteomic approaches will be undertaken to unravel new insights with the aim of identifying targets for therapeutic intervention and treatment of the disease.

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7.5 Identification of novel senolytic targets for improving liver regeneration

The project focuses on conducting in vivo & in vitro functional genetic screens to identify targets to eliminate senescent cells. Senescent cells are known to drive inflammaging attenuating the regenerative capacity of the liver. Through a negative selection screen in senescent cells we can identify vulnerabilities of these cells. The goal is to identify novel senolytic targets for therapeutic purposes.

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7.6 Identifying novel biomarkers in liquid biopsy derived exosomes

The project focuses on identifying novel blood-based biomarkers for liver disease. Mouse models of chronic liver disease will be used, exosomes will be isolated from the blood and the content will be analyzed by transcriptomic and proteomic approaches. The same approach will be applied for liver patient derived blood samples. The goal is to identify novel conserved biomarkers for liver disease.

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7.7 Countering Cancer's Therapeutic Resistance Using CRISPR Screen

Therapeutic resistance is one of the major causes of treatment failure and poor prognosis in cancer. With the advent of CRISPR screen technology, we are now able to identify the novel genetic weaknesses of cancers that already developed resistance to conventional treatments such as chemo-/radio-therapy and targeted therapy. My lab's mission is to spot the 'Achilles' heels' of these obstinate cancers via state-of-art in vitro and in vivo CRISPR screen and to develop new therapeutic strategies targeting such vulnerabilities.

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7.8 Ageing of bone microenvironments

Our skeletons play a crucial role in regulating key physiological processes, including mineral homeostasis, energy metabolism, and blood cell production. The presence of multiple blood vessel (BV) subtypes and the distinct microenvironments they support contribute to the skeleton's multifaceted functions. Vascular aging is a key factor in the agerelated functional and physical changes observed in the skeleton. Understanding vascular niches and their agerelated alterations could help target specific functional niches for managing age-related bone and blood diseases.

In this study, we aim to identify and characterize bone vascular microenvironments and their functions. Leveraging cutting-edge techniques developed in our laboratory—including high-resolution 3D imaging, single-cell and spatial transcriptomics, metabolic analysis, and advanced mouse genetics—the candidate will have the opportunity to:

- Characterize different types of microenvironments in bone.
- Understand how blood vessels support these niches.
- Identify strategies to replace or target aging blood vessel subtypes specifically.

7.9

Metabolic control of bone marrow microenvironments

The mammalian skeletal system undergoes continuous remodelling throughout life, intricately interacting with whole-body physiology. Metabolic changes significantly influence bone health by altering the cellular composition and functional dynamics of bone tissue. However, the cellular and molecular mechanisms underlying these dynamic changes remain poorly understood. In this study, we investigate the impact of metabolism on the mesenchymal composition of bone microenvironments. Specifically, the student will

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- 1. Map and characterize the distribution patterns of mesenchymal cell subtypes in bone.
- 2. Explore how metabolic conditions such as diabetes, modulate mesenchymal cell composition
- 3. Identify metabolic targets to modulate mesenchymal cell differentiation and composition.

The student will employ advanced techniques, including confocal and intravital imaging, single-cell and spatial transcriptomics, metabolic profiling, and state-of-the-art mouse transgenics. Overall, this study aims to uncover the mechanisms driving bone pathology in metabolic diseases like diabetes, providing a foundation for targeted therapeutic strategies.

8.0 Understanding the tumor microenvironment: High-resolution 3D and multiplex imaging approach for deciphering cancer progression

Endothelial cells are pivotal architects of blood and lymphatic vessel integrity, forming the inner lining that regulates inflammation, immune cell trafficking, and organ-specific vascular functions. Perivascular and mesenchymal stromal cells dynamically shape vascular microenvironments, playing essential roles in tissue homeostasis and disease. In cancer, the tumor microenvironment (TME) drives disease progression by orchestrating a complex interplay among cancer cells, vascular networks, and stromal components. This dynamic milieu enhances metastatic potential and contributes to therapeutic resistance. Central to this process is epithelial-mesenchymal transition (EMT), which equips cancer cells with invasive properties. Critically, stromal and vascular cells are key enablers of EMT and therapy resistance, making them highly attractive targets for innovative therapeutic strategies.

Despite their significance, the complexity, heterogeneity, and spatial interactions of tumor stroma and vasculature remain poorly understood across different stages of cancer progression. This knowledge gap limits the development of precision therapies. To address this challenge, we propose leveraging cuttingedge high-resolution light-sheet microscopy and

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multiplex imaging to define, at an unprecedented level, the spatial interactions between vascular, stromal, and cancer cells throughout disease progression. Our approach focuses on three malignancies with distinct clinical and biological challenges: head and neck cancers, glioblastoma, and breast tumors. This study aims to illuminate the spatial interactions within the TME, providing a foundation not only for the development of targeted interventions to disrupt the stromal-vascular axis in cancer progression but also for precise diagnostic and prognostic strategies throughout the course of the disease

8. Microbiome Medicine

8.1 Investigating the role of gut microbiome in cardiometabolic diseases

In recent years, it has become evident that the gut bacteria living in our intestine significantly impact health and disease. This influence extends beyond intestinal disorders like inflammatory bowel disease encompass a wide range of conditions including obesity, diabetes, and neurodegenerative diseases. Our laboratory has previously reported that certain gut bacteria contributes to the progression cardiovascular disease (PMID: 30397344, 37279756). This PhD project focuses on gut microbiota and lipid metabolism, employing state-of-the-art technologies such as anaerobic culture systems, mouse models, and next-generation sequencing to advance research in this field.

Systematically Investigating Molecular Mechanisms Underlying Aging-Related Human Diseases through Multi-Omics Profiling

Aging is a complex biological process characterized by a gradual decline in physiological functions, which increases susceptibility to diseases and death. This process is influenced by a myriad of genetic,

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8.2

environmental, and lifestyle factors. To better understand aging and study the relationship between aging and aging-related diseases, our research group is focused on building predictive models using machine learning techniques. The model is to integrate multiomics datasets, focusing specifically on gut microbiome and metabolomics data. The comprehensive analysis of these multi-omic datasets aims to unveil crucial molecular indicators, intricate biological pathways, and influential regulatory circuits that play a role in the aging process and the pathogenesis of age-associated disorders. Such an understanding is likely to be helpful development of innovative therapeutic interventions to promote healthy aging and to address the onset and progression of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases.

8.3

Comprehensive Multi-omics Analysis of Human Aging Using the Large Language Module based Functional Module Annotation

Multi-omic methods provide great opportunities to systematically reveal the critical molecular alterations of aging from a multidimensional perspective, while matching and investigating the biological information and functions from multi could be a heavy subjective work. Large Language Models (LLMs) has shown high efficiency and accuracy in repetitive search and collection work, which will help us to extensively and quickly investigate potential research objects and validate them with published works to prove their roles and molecular mechanism. So in this project, we aim to build up a tool utilizing LLM, such as GPT4, to accelerate and improve the biological investigation in multi-omics data for aging research.

8.4

Gut Microbiome Signatures in Colorectal Cancer Molecular Subtypes and Tumour Metabolism

This project will investigate the role of the gut microbiome in modulating molecular subtypes and **Asst Prof Shen Xiaotao**

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tumour metabolism in colorectal cancer. Recent studies have highlighted the importance of the gut microbiome in influencing cancer development and progression. This project aims to elucidate the specific microbial signatures and metabolic pathways associated with different molecular subtypes of colorectal tumours. The findings could lead to the development of microbiomebased biomarkers and therapeutic strategies targeting the tumour microenvironment.

8.5

Exploring Gastrointestinal Interoception, Microbiome, and Nutrients in Disorders of GutBrain

This project will explore the gut-brain axis and its role in various neurological and psychiatric disorders. The study will investigate the mechanisms underlying gastrointestinal interoception, the microbiome-gut-brain signalling, and the influence of nutrition on these pathways. By understanding the complex interplay between the gut and the brain, the project aims to provide insights into the pathogenesis of gut-brain disorders and identify potential therapeutic targets.

8.6

Gut Microbiome Dysbiosis and Its Role in Metabolic-Associated Cancers

This project will investigate the interplay between the gut microbiome, metabolic disorders. and the development of metabolic-associated cancers. Emerging evidence suggests that dysbiosis of the gut microbial community can contribute to the pathogenesis of obesity, type 2 diabetes, and related metabolic conditions, which are known risk factors for certain types of cancer. The study aims to elucidate the specific microbial signatures, metabolic pathways, inflammatory mechanisms that link gut microbiome alterations to the initiation and progression of metabolicassociated cancers, such as hepatocellular carcinoma and endometrial cancer. The findings could inform the development of microbiome-based diagnostic and therapeutic strategies.

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8.7

Gut Microbiome, Dietary Patterns, and Metabolic Health in a Multi-Ethnic Asian Population: A Singapore-Based Study

Singapore is a highly urbanised and multiethnic country in Southeast Asia, with a diverse population comprising primarily Chinese, Malay, and Indian ethnic groups. Dietary patterns and food cultures vary significantly across these ethnic communities, which may influence the gut microbiome and overall health outcomes. This project aims to investigate the complex interplay between the gut microbiome, dietary habits, and nutritional status in the Singaporean population. The findings can inform the development of culturally-relevant nutritional interventions and microbiome-based strategies to address public health challenges in Singapore and similar urban, multiethnic settings.

8.8

Modulation of digestive enzyme activity as a safe approach to improve metabolism and health

This project aims to design new therapeutic targets, with structure-function lead optimisation of compounds that inhibit luminal carbohydrate enzymes. Guided by naturally occurring plant-based compounds, this project involves side-chain modifications to improve enzyme inhibition selectivity and specificity. From chemistry to biology, this project will continue with the characterization of luminal carbohydrate digestion modulation on the recipient host. Investigations will include an assessment of intestinal health, alterations in gut microbiome, impact on immunology and finally carbohydrate metabolism and homeostasis.

8.9

Gut-brain neurobiology: microbiome control of neural circuits and behaviour

The trillions of bacteria living in our body encode over 46 million genes – suggesting tremendous functional

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capacity (by contrast, the human genome has less than a thousandth of that). Moreover, emerging evidence suggests that the gut microbiota profoundly influences host physiology and behaviour. In this project, we will investigate the fundamental biological basis of "gutfeelings", how microorganisms and chemicals in the gut signal to brain to modulate neural substrates that control physiology and behaviour. We employ a range of experimental techniques in mice to study the mammalian gut-brain axis including sequencing, metabolomics, in vivo neural imaging/recording, and genetically-guided functional interrogation.

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9. Medical Education

9.1 Climate and health – mapping the impacts towards positive action

This PhD is located within a wider multidisciplinary project NTU "Climate Transformation Program" that seeks to map and model impacts of climate change. World Health Organization (WHO) emphatically noted that the risks of the climate crisis to human health extend way beyond physical impact(s) to mental health and called for intervention(s), mitigation and adaptation. The evidence however on mental health impacts in Singapore and Southeast Asia is limited. The PHD project will integrate evidence synthesis and observational mixed methods approached to identify mental health risks and at risk populations.

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10. Others

10.1 Chemistry and Bioengineering

Modulation of digestive enzyme activity as a safe approach to improve metabolism and health

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10.2 NIE, Exercise Physiology

Nutritional intervention and the impact on muscle health in elderly health

This project aims to molecularly dissect pathways that are altered under (i) intermittent fasting conditions and (ii) plant-based nutritional intake. These dietary interventions are increasingly being suggested as disease-modifiers, but the molecular mechanisms that support these claims are still not well-defined. With a focus on insulin sensitivity, immunology and metabolic organ homeostasis and health, the candidate will undertake a series of in vitro and in vivo experiments to understand the role of intracellular lipid regulation response to both dietary interventions. In collaboration with exercise physiologists from the National Institute of Education, candidate will also undertake a human study to validate translation and clinical relevance.

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10.3 Cancer Research

Modeling Tertiary Lymphoid Structures in Solid Tumors: Unveiling Immune Modulation and Therapeutic Potential

This PhD project aims to model tertiary lymphoid structures (TLS) in solid tumors to investigate their influence on the tumor microenvironment and response to cancer therapy. Using advanced in vitro techniques, the project will create a robust model system that mimics TLS formation, allowing us to explore interactions between immune cells and tumor cells. The student will gain experience with cutting-edge technologies in immunology and cancer biology and contribute to crucial discoveries in the tumor immune landscape. This research will offer new insights into TLS functions in cancer, with potential applications in developing more effective cancer treatments.

Modeling Tumor-Immune Interactions in Glioblastoma

Join our lab to develop an advanced glioblastoma (GBM) model that integrates the blood-brain barrier and immune components to better understand tumorimmune interactions. This PhD project focuses on investigating the role of tertiary lymphoid structures (TLS) within the GBM microenvironment and exploring immunotherapy strategies targeting both GBM and TLS. This interdisciplinary project offers hands-on experience in cutting-edge cancer biology techniques, advanced model development, and preclinical testingideal for students passionate about driving innovation in cancer immunotherapy and tumor microenvironment research.

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