List of Capstone Projects available for prospective students

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S/N	Principal Investigator	Project title with brief abstract
1	Dr Chris Sham Lok To miclts@nus.edu.sg Department of Microbiology & Immunology	**A gene regulatory network that controls carbohydrate utilization and facilitates epithelial cell binding in Streptococcus pneumoniae** Despite a global vaccination effort and nearly a century of intensive research, Streptococcus pneumonia (pneumococcus) remains a major public health threat. The success of S. pneumoniae as a human pathogen can be partly attributed to the complex regulatory network in controlling gene expression in the host. This network allows the bacteria to respond to the environment appropriately. A genetic screen was done to identify factors that control capsular polysaccharide expression in pneumococcus. Unexpectedly, the screen reported two genes that regulate carbohydrate utilization and facilitate airway epithelial cell binding. This project aims to elucidate the mechanism by which they function in the cell to promote virulence. *Domain(s): Infectious Diseases Management*
2	Dr Volker Patzel micvp@nus.edu.sg Department of Microbiology & Immunology	**A novel RNA structure-based mRNA design for genetic therapy and vaccination** The principle of genetic therapy or vaccination relies on the concept to deliver nucleic acids (DNA or RNA) coding for a therapeutic protein or antigen (viral or tumour antigen) into target cells in vivo. As DNA always harbours a theoretical risk of genomic integration, RNA-based therapeutics and vaccines are considered safer though their production is more difficult and costly. In vivo, RNA is readily degraded by ribonucleases and, hence, RNA vaccines have to be chemically modified and/or protected by encapsulation. The standard mRNA design refers to the optimization of the primary structure (sequence) and typically comprises codon optimization, the elimination of cryptic splice sites, GC content optimization, the elimination of miRNA binding sites, 5’ capping, 3’ polyadenylation and for endogenously transcribed RNA the implementation of an intron and a post-transcriptional regulatory element. In addition, RNAs often are chemically modified to improve stability and delivery. However, the standard design does not consider intense secondary and tertiary RNA structure design. The aim of this project is to investigate a novel structure design for mRNA therapeutics and vaccines that improves RNA stability in the extracellular matrix and within cells, RNA translatability and transgene expression, and the efficiency of RNA encapsulation. By applying the RNA trans-splicing technology, gene expression can be rendered cell type

		specific. In addition, minimalistic dumbbell-shaped DNA vectors will be used to deliver such optimised sequences. Dumbbell vectors are much more stable than RNA, cheaper to produce, and allow us to target distinct populations of target cells or subpopulations of cells including immune cells to achieve a more tailored therapeutic effects or immune responses. The methods cover computational (in silico) RNA structure design, in vitro techniques including cloning, PCR, and RT-PCR, and experiments with tissue culture cells including transfection, nucleofection, reporter gene assays, functional assays, flow cytometry, confocal microscopy, gene expression and eventually with additional support studies in mice. This project is highly translational and can support the development of novel vectors for genetic therapy and vaccination. *Domain(s): Vaccinology and Immunotherapy, Applied Biomedicine*
3	Prof Andrea Britta Maier a.maier@nus.edu.sg Department of Medicine	**Advancing longevity: CURATE.AI for Customized NMN Utilization And Treatment Enhancement (ACCURATE) clinical trial** Blood Nicotinamide Adenine Dinucleotide concentration (NADc) declines with chronological age in animals and humans. The dietary supplementation of Nicotinamide mononucleotide (NMN) has been shown to increase the level of NADc in the blood of middle-aged and older individuals; however, with high interindividual variability in the response. CURATE.AI is a platform for optimizing dosing. This study assesses the effectiveness of CURATE.AI dosing compared to conventional dosing of NMN in enhancing blood NAD concentrations and other aging-related biomarkers. *Domain(s): Drug Discovery and Development, Applied Biomedicine*
4	A/Prof Chen Ee Sin bchces@nus.edu.sg Department of Biochemistry	**Artificial intelligent identification of cancer driver mutations from human cancer genome** Advancement in genome-wide sequencing technology permits the sequencing of large amount of genome data of patients from almost every type of cancers. However, it is still an unsurmountable challenge to derive meaningful insights from this huge reservoir of information to impact clinical treatment. This project will attempt to use several approaches including AI-related protocol to look for cancer driver mutations in online cancer databases with focus on colorectal cancer. Depending on time, the student may be able to test the physiological impact of the mutations they have identified in the yeast and/or cancer cells, which are good models for studying proliferation related regulations.

		Domain(s): Applied Biomedicine
5	A/Prof Citra Nurfarah binte Zaini Mattar citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	**Bone Marrow-on-a-Chip for HSC-targeted Gene Therapy** We aspire to build human-relevant models of gene therapy that provide preclinical data at granular and multifaceted levels, to boost confidence in the success and safety of clinical vectors. Human-animal differences significantly limit extrapolation of physiological data to clinical trials, and human immunological and genotoxic effects are not always predicted from animals. We will design a human-derived Bone Marrow-on-a-chip (BMoC) for high-throughput analyses of haemopoietic stem cells following transduction with clinical gene therapy vectors at cellular and molecular levels, determining concomitant effects on bone marrow niche physiology and crosstalk with the liver, often a bystander target of these vectors. *Domain(s): Gene therapy*
6	Dr Zhang Jingjing j.zhang@nus.edu.sg Department of Diagnostic Radiology	**Cancer Theranostics and Development of Novel Tracers for Multimodality Molecular Imaging and Targeted Radioligand Therapy in Combination with Immunotherapy in Multiple Types of Cancer** Cancer theranostics, an approach that integrates advanced diagnostic techniques with targeted therapy, revolutionizing the way we identify, treat, and monitor cancer. The word “theranostics” itself is a portmanteau of “therapeutics” and “diagnostics”. The foundation of theranostics lies in personalizing patient care, ensuring that individuals receive the right treatment at the right time based on their unique physiological and molecular profiles; biomarkers, molecular imaging, imaging-guided therapy, and more integrated theranostic platforms are all part of the wider theranostic spectrum. Radiotheranostics with multimodality molecular imaging and molecular targeted radioligand therapy represents a promising advancement in both cancer diagnosis and treatment. Our NUS Theranostics Centre of Excellence (TCE) Lab aimed to spearhead the advancement of theranostics by pioneering innovative research and technology, developing new drugs, translating discoveries into transformative clinical solutions, and fostering interdisciplinary partnerships. The centre has a well-equipped research facility with an integrated imaging platform consisting of nanoSPECT/CT, nanoPET/MRI, microPET/CT, Second Near-Infrared bioimaging (NIR-II), IVIS spectrum in vivo imaging system, ultrasound/photoacoustic imaging (PAI), and so on. It is also a leading platform for radiopharmaceutical development with a chemical synthesis

		unit, a radiolabelling hot lab (radio-HPLC, Radio-iTLC, gamma counter), a tissue culture room, and an animal holding room. Our research in the field of molecular imaging, particularly within cancer theranostics, is driving its way to use an integrated approach. The collective advancements in molecular imaging are ushering in a new epoch of medical treatment. *Domain(s): Drug Discovery and Development*
7	A/Prof Justin Chu Jang Hann miccjh@nus.edu.sg Department of Microbiology & Immunology	**Characterising the molecular mechanisms of vaccine mutations for live attenuated flavivirus vaccines** The mosquito-borne flaviviruses are a group of human pathogens that pose a significant threat to human health and life. They include dengue virus, yellow fever virus, and Zika virus. Live attenuated vaccines have proven to be the most cost-effective method of preventing flavivirus infection. Flavivirus vaccine strains possess a good balance of attenuation and immunogenicity. This phenotype of attenuation and immunogenicity is driven by vaccine strain mutations that alter the molecular biology of the virus. This project will characterise the underlying molecular mechanisms of these vaccine strain mutations. Specifically, this project will look at how these vaccine mutations affect the vaccine strain at various stages of the virus replication cycle. The project will also look how these vaccine mutations alter viral interaction with host factors and host pathways, especially the immune sensing and immune response pathway. This study will give us understand the molecular mechanisms that help flavivirus vaccine strains achieve their desired phenotype. This will help us design future vaccines for the mosquito-borne flaviviruses. *Domain(s): Vaccinology and Immunotherapy, Infectious Diseases Management*
8	Dr Chester Drum mdccld@nus.edu.sg Department of Biochemistry	**Chemical synthesis of complex biological therapies** Can chemical engineering and machine learning fundamentally change macromolecular creation? In this project you will use a novel set of technologies invented in our lab (Nature Comms, PMID: 29129910) to create biological therapeutics using pure chemical synthesis. A centre piece output is the first ever chemical production of a therapeutic antibody and the application of this novel process to multiple large-market therapeutics. The project is a continuation of research begun at Massachusetts Institute of Technology and funded by the Singapore MIT Alliance for Research and Technology (SMART). There is opportunity for multiple new patents and very high impact publications.

		Domain(s): Drug Discovery and Development, Vaccinology and Immunotherapy
9	A/Prof Thai Tran phstt@nus.edu.sg Department of Physiology	**Deciphering the molecular mechanisms underlying steroid-induced increase in viral infections** Due to its potent anti-inflammatory effects, GCs have been used to treat severe influenza infections. However, studies have shown that GCs increase IAV virulence and exacerbate disease-related mortality, making the use of GCs controversial. The underlying mechanism for this is attributed to the immunosuppressive properties of GCs; however, it is not well understood. Preliminary studies by our group demonstrated that CD151 levels in airway smooth cells are increased in a concentration-dependent manner when treated with GCs. These studies suggest potential CD151-related signalling events that drive GC-induced aggravations of IAV infection, independent of immunosuppression. Since GCs increase CD151 levels, and CD151 enhances IAV replication, GCs may enhance IAV replication through CD151-mediated mechanisms. Clinically, this would provide a mechanistic basis on the benefits and risks of using GCs in IAV infections, offering insights into potential novel avenues for developing "better" GCs or informed GC treatment regimens. We hypothesize that the GC-induced increase in IAV replication, IAV titre, and disease-related mortality is CD151-mediated. *Domain(s): Infectious Diseases Management, Drug Discovery and Development*
10	A/Prof Justin Chu Jang Hann miccjh@nus.edu.sg Department of Microbiology & Immunology	**Deciphering the potential of a synthetic derivative as an antiviral agent against dengue virus** Dengue virus (DENV) is the primary causative agent which upon infection, leads to the development of dengue fever, a potentially fatal disease which is endemic in over 100 countries especially in the tropical and subtropical regions. DENV is mainly acquired by humans via bites of infected mosquitoes, Aedes spp in particular, which have resulted in at least 100 million cases of annual DENV infections and more than 20,000 deaths worldwide. Given the consistently high levels of active DENV infections, there is a dire need for an effective antiviral drug or prophylactic vaccine to combat this arboviral disease, which hitherto remain absent. Over the years, various natural compounds have been discovered to exhibit promising inhibitory effects against DENV replication. Subsequently, in order to identify the specific active group(s) involved in the observed efficacious antiviral properties, structure-based analyses involving different chemical

		modifications of the parent compounds were performed with the aim of improving their bioavailability, toxicity and antiviral profiles. In this study, a synthetic derivative of a natural compound will be screened for its in vitro cytotoxicity and anti-DENV inhibitory effects in mammalian cell lines. The compound will then be subjected to different biological and biochemical mechanistic assays to identify the specific stage(s) of DENV replication cycle and target protein(s) on which it exerts its antiviral activity. The outcome of this study will provide more in-depth insight into the potential anti-DENV properties exhibited by the synthetic derivative of interest as well as the underlying mechanism(s) involved. *Domain(s): Infectious Diseases Management, Drug Discovery and Development*
11	Dr Volker Patzel micvp@nus.edu.sg Department of Microbiology & Immunology	**Design and investigation of next-generation dumbbell-shaped DNA vectors and trans-splicing RNAs** Spliceosome-mediated RNA trans-splicing represents a form of alternative splicing in which sequences from two distinct pre-mRNAs are joined with the help of the spliceosome to produce chimeric RNAs and proteins. As trans-splicing enables labeling and reprogramming of genetic information at the level of the pre-mRNA, researchers have been exploring trans-splicing for diagnostic or therapeutic interventions. We developed and tested a novel trans-splicing RNA design. Compared with the previous state-of-the-art, our new trans-splicing RNAs exhibit up to 1000-fold improved activity and about 10-fold higher on-target specificity. We are currently using RNA trans-splicing to achieve cell type specificity of gene expression. For cellular delivery of trans-splicing and other RNAs, we developed safe, non-integrating dumbbell-shaped DNA minimal vectors which exhibit 10-100-fold enhanced nuclear targeting and gene expression compared with plasmids and conventional dumbbells. In addition, these vectors are not silenced in primary cells and trigger prolonged transient expression. The aim of this project is to use RNA secondary structure design to further improve the trans-splicing RNAs, to explore synergies between the RNA trans-splicing technology and other RNA technologies such as RNA interference, CRISPR Cas genome editing, or mitochondrial delivery vector technologies, and to design and investigate advanced dumbbell-shaped DNA to deliver these RNAs into target cells. The methods cover computational (in silico) RNA structural design, in vitro techniques including cloning, PCR, RT-PCR, and dumbbell production, and experiments with tissue culture cells including transfection, nucleofection, reporter

		gene assays, flow cytometry, confocal microscopy and functional assays. These technologies can have high impact towards the development of novel genetic therapies of yet incurable human diseases. *Domain(s): Applied Biomedicine*
12	Dr Le Thi Nguyet Minh phcltnm@nus.edu.sg Department of Pharmacology	**Designing a delivery platform to enhance the bioavailability of extracellular vesicles for cancer treatment** Extracellular vesicles (EVs) serve as highly promising carriers for delivering nucleotide-based therapeutics for cancer treatment, particularly in delivering antisense oligonucleotides to target specific mutations in cancer cells. However, systemic administration of EVs into living bodies have shown limited circulation time in the bloodstream and low accumulation in tumours, hindering their clinical translation. The short half-life of EVs is primarily due to their phagocytosis by mononuclear phagocyte systems (MPS), leading to their accumulation and degradation in livers and spleens. To enhance EVs' efficacy in cancer therapy, this project aims to develop a micro-nano-hybrid delivery platform, shielding EVs from MPS phagocytosis and enhancing the therapeutic efficacy of loaded agents against cancers. *Domain(s): Drug Discovery and Development*
13	Prof Wang Linfa linfa.wang@duke-nus.edu.sg Duke-NUS Medical School	**Developing bat-inspired protein-based topical anti-inflammatory therapies for human skin inflammatory diseases** Bats are the only flying mammals capable in hosting numerous viruses asymptomatically with no/minimal sign of diseases. Previous studies from our lab demonstrated altered inflammasome in bats including genomic loss of PYHIN genes (Sci Rep 2016), dampened NLRP3 expression (Nat Micro 2019) and reduced Caspase-1 and cleavage of IL-1b activities (PNAS 2020). The recent work from our lab (Cell 2023) has shown that bat ASC2 is a powerful negative regulator of inflammasomes. We further identified four key residues responsible for bat ASC2's gain-of-function. By incorporating these key residues, we developed a patented modified human ASC2, called hupa4 ASC2, with high potency of inflammasome inhibition. For this project, we aim to develop an effective topical anti-inflammatory therapies for human skin inflammatory diseases, based on hupa4 ASC2 via different methods of delivery. Mouse in vivo study will be performed and patient skin biopsy samples will be collected to validate our drug candidates in this project.

		Domain(s): Drug Discovery and Development
14	Dr Cheok Chit Fang patcfc@nus.edu.sg Department of Pathology	**Developing drug analogues of mitochondrial inhibitors as therapeutics** While metabolic changes characteristic of tumours were known nearly a century ago, understanding of cancer cell metabolism has undergone a resurgence in the past decade. A number of metabolic inhibitors have recently entered clinical trials for treatment of advanced and refractory cancers. We recently identified a metabolic pathway selectively targeting p53-defective cancers. We discovered that mitochondrial uncouplers lead to metabolic catastrophe and apoptosis in p53-defective cancers, elucidating a first-in-class mechanism exploiting this class of inhibitors against p53 mutations (that occur in more than 50% of all cancers). The purpose of this project is to further develop this concept, by adopting chemical screens as well as targeted development of drug analogues. *Domain(s): Applied Biomedicine*
15	Dr Volker Patzel micvp@nus.edu.sg Department of Microbiology & Immunology	**Developing novel RNA-based mitochondrial delivery vectors for mitochondrial targeting of nucleic acids towards mitochondrial gene therapy and for anti-aging** Defects of all protein-coding mitochondrial genes have been associated with human, mainly neurodegenerative disorders or with aging. Many mitochondria harbour both, healthy and defect mitochondrial genomes (heteroplasmy) and defects accumulate with aging. Mitochondrial gene therapy could provide cure of mitochondrial disease and dysfunction but is hampered by the lack of an efficient mitochondrial gene delivery system. We developed an efficient novel scalable mitochondrial targeting vector based on RNA subdomains of a long non-coding viral RNA. We demonstrated that this vector system can efficiently target functional recombinant coding (mRNA) or non-coding (antisense) RNA to the mitochondria resulting in mitochondrial gene expression or knockdown of gene expression. Here, we will further improve and explore this novel mitochondrial delivery vector system towards mitochondrial gene therapy. The aim of this project is to improve the mitochondrial targeting vectors and to explore them for mitochondrial delivery of healthy gene functions and or of the CRISPR Cas system to selectively destroy defect mitochondrial genomes. A first medical target will be Lebers Hereditary Optic Neuropathy LHON, an orphan disease that causes sudden blindness in young adults.

		The methods cover computational (in silico) RNA structural design, in vitro techniques including cloning, PCR, RT-PCR, the CRISPR/Cas technology, and experiments with tissue culture cells, eventually cybrids, and Rho-zero cells including transfection, nucleofection, and reporter gene assays. The approach may help to prevent/restore LHON-associated vision loss and can be explored for mitochondrial gene therapy of yet incurable human diseases and for anti-aging. *Domain(s): Applied Biomedicine*
16	Prof Wang Linfa linfa.wang@duke-nus.edu.sg Duke-NUS Medical School	**Development of a cross-species liver organoid model to identify novel drug targets for mitigating liver insulin resistance** Liver insulin resistance is a critical component of metabolic disorders such as type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). Both experimental and epidemiological evidence have established a causative link between modern diets rich in simple sugars, particularly fructose, and the development of peripheral tissue insulin resistance. Novel approaches for targeting liver insulin sensitivity or inhibiting the onset of insulin resistance are urgently needed. In the mammalian kingdom, a diet primarily relying on the nectar of angiosperm flowers, termed nectarivory, is exceptionally rare. A small number of bat species, including Eonycteris spelaea—the key model organism under research in the laboratory of Prof. Wang Lin-Fa—are specialist nectarivores. Nectar has a high concentration of fructose and sucrose (a disaccharide containing fructose). It is hence hypothesized that E. spelaea has evolved specific mechanisms to avoid the development of liver insulin resistance. Liver organoids generated from adult primary tissue are a recent development which provide a physiologically relevant platform for studying disease mechanisms and drug discovery. In this study, we will first establish and characterize liver organoids derived from both mouse and E. spelaea liver tissue. By exposing these organoids to insulin resistance-inducing conditions and performing high-throughput screening, we aim to uncover species-specific and conserved mechanisms of liver insulin resistance. This comparative approach leverages the unique metabolic adaptations of E. spelaea, providing insights that are not possible with traditional mouse models alone, and seeks to identify novel drug targets for improving insulin sensitivity in humans. *Domain(s): Drug Discovery and Development*

17	Prof Antonio Bertoletti antonio@duke-nus.edu.sg Duke-NUS Medical School	**Development of a rapid whole-blood assay for the detection of T-cells against zoonotic viruses** Emerging infections pose a significant burden on the healthcare systems and economic loss for societies worldwide as exemplified by the COVID-19 pandemic. Early detection of spill over events is critical to informing coordinated responses but existing surveillance platforms are based on molecular methods and hospitalised patients, and therefore, fail to capture early cases and those with asymptomatic or mild infection. In addition, the incidence of past infection in defined populations is often evaluated by survey detecting antibodies against the pathogen. T cells against viruses have been instead rarely evaluated for clinical or epidemiological purposes mainly due to the technical complexity of conventional T-cell assays. However, antigen-specific memory T-cell responses against SARS-CoV-2 have been shown to persist in individuals where antibody levels were either never detected or waned within weeks post-infection, particularly in individuals with asymptomatic infections. Serosurveys also undercount infections with other viruses, such as MERS-CoV, where T cell responses were found to be present in seronegative individuals. The aim of the study is to develop T cell assays specific for zoonotic viruses and test their ability to detect individuals who have been infected with such viruses. We will design pools of peptides covering different proteins of distinct zoonotic viruses (i.e. Avian Influenza, Bunjaviridae) and test their ability to detect T cells in individuals with known or unknown contact with such viruses with conventional (ELISPOT or Intracellular cytokine staining) or rapid cytokine detection in whole blood. Serological assays will also be performed to understand whether T cells might be better suited to define previously infected populations. *Domain(s): Vaccinology and Immunotherapy, Infectious Diseases Management*
18	Dr Ding Lingwen patdl@nus.edu.sg Department of Pathology	**Development of Cancer Vaccines: RNA vaccine against public tumor antigens and individualized neoantigens** Immune checkpoint blockade antibodies, such as anti-PD1 antibody, have dramatically altered the therapeutic landscape of many cancers and have recently become the first-line therapy for several major cancers. Despite the remarkable achievements, the response rate is relatively low (10-20%), and only a subset of patients can benefit from the treatment. Mechanistic studies suggest that the preexistence of tumor antigen recognition T cells is the key to the success

		of PD1 immunotherapy. Among the different strategies developed to overcome PD1 resistance, cancer vaccines show great promise to elicit T cell responses against cancer-specific antigens, converting 'cold' tumors to 'hot' tumors and thus improving PD1 antibody therapy. In this study, we will develop a circular mRNA-LNP (lipid nanoparticle encapsulated circular mRNA) vaccine platform to generate RNA vaccines against the most prevalent, experimentally verified common cancer antigens (e.g., neoantigens derived from hotspot mutations of TP53, KRAS, and PIK3CA and tumor-associated antigens). This platform features our improved mRNA design (such as motifs to enhance MHC presentation and mRNA translation/stability). Based on TCGA pan-cancer sequencing data, over 10% of (pan)cancer patients harbor at least one of the above mutations and may benefit from our cancer vaccine. The therapeutic effect of the generated mRNA-LNP vaccine will be verified using syngeneic murine models and humanized murine models. *Domain(s): Vaccinology and Immunotherapy, Drug Discovery and Development*
19	A/Prof Justin Chu Jang Hann miccjh@nus.edu.sg Department of Microbiology & Immunology	**Discovery of Biomarker for the Detections of Enterovirus D68 infection** Enterovirus D68 (EV-D68) has garnered attention over the recent past years with global outbreaks of Acute Respiratory Infection (ARI) in the American and East Asia Region. In paediatric cohort, EV-D68 can cause hospitalization and fatality due to asthma exacerbation and acute flaccid myelitis. There are no effective vaccines and antiviral drugs, research in the development and evaluation of Enterovirus D68 is much needed as pandemic preparation against future outbreaks in Singapore. This project takes a novel approach to engage in single cell RNA sequencing analysis of organotypic culture to identify novel pathways and biomarker using that can be purposed as disease identifier and possible drug targets. *Domain(s): Infectious Diseases Management, Applied Biomedicine*
20	A/Prof Nguyen Nam Long bchnnl@nus.edu.sg Department of Biochemistry	**Discovery of ligands for membrane transporters to use for functional drug screening assays** The project here is to discover the small molecules for membrane transporters and use this discovery knowledge for developing functional assays for drug discovery. *Domain(s): Drug Discovery and Development*
21	Dr Shi Jiahai jh.shi@nus.edu.sg	**DNA based non-viral gene therapy**

	Department of Biochemistry	The traditional production of DNA depends on bacteria, which requires 3-4 weeks for production and subsequently requires extensive purification, which may still give rise to traces of bacterial endotoxins. We aimed to develop a cell-free DNA synthesis system and does not require the presence of bacterial element. Compared to mRNA therapy, DNA therapy offers prolonged effectiveness and stable expression over time. However, DNA-based gene therapy faces challenges in achieving efficient nuclear entry, primarily due to barriers such as endosomal entrapment, cytosolic sequestration, and nuclear exclusion. To address these issues, we utilize red blood cell extracellular vesicles (RBCEVs) as delivery vehicles for the DNA cassette. RBCEVs are promising due to their high biocompatibility with various cell types and their potential to penetrate multiple cellular and organelle membranes. By leveraging RBCEVs, this project aims to mitigate the current limitations of non-viral DNA gene therapy, particularly focusing on overcoming endosomal trapping and avoiding the drawbacks associated with viral delivery vectors, such as immunogenicity and potential integration risks. *Domain(s): DNA gene therapy*
22	A/Prof Chen Ee Sin bchces@nus.edu.sg Department of Biochemistry	**Epigenetic Oncomutations regulating drug efficacy and carcinogenesis of colorectal cancer** Epigenetic is a mechanism that is imposed over the genetic (DNA seqeunces) control of the genome. This mechanism determines the usage of the genomic sequences and such regulation is often compromised during cancer development that result in uncontrolled proliferation and metastasis of the cancer cells. Due to the importance of epigenetic regulation, it is not unexpected that many mutations have been shown to facilitate cancer initiation. Many of these mutations exist in enzymes that catalyses the addition or removal of 'epigenetic marks' on the chromatin. In this project, we will study one particular class of epigenetic regulators that act on the scaffolding that wraps and organize the DNA, called histones. Using bioinformatics tools, including some artificial intelligent-assisted ones, we will identify cancer driver mutations, with focus on colorectal cancer. *Domain(s): Applied Biomedicine*
23	A/Prof Chan Shiao-yng obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	**Exploring the utility of inositols in modulating placental metabolism of lipids and inositol-derivatives in gestational diabetes** Gestational diabetes affects around 1 in 5 pregnant women in Singapore. Many studies demonstrate that maternal

		hyperglycaemia perturbs placental lipid metabolism, which has consequences for fetal growth and developmental programming of future health outcomes for the offspring postnatally. Current treatments such as metformin and insulin, while able to regulate maternal glycaemia well, can have undesired effects for long-term offspring health or are difficult to administer. Hence, there is a need for alternative therapies. Inositols belong to the class of nutraceuticals and some inositol isoforms have shown promising effects in improving insulin sensitivity. However, their impact on placental lipid metabolism remains poorly understood. The candidate will examine how different inositol isomers affect placental lipid metabolism using a variety of techniques including in vitro placental cultures, molecular biology and liquid chromatography-mass spectrometry (LC-MS). *Domain(s): Drug Discovery and Development, Nutraceuticals*
24	A/Prof Toh Wei Seong tohws@nus.edu.sg Department of Orthopaedic Surgery	**Extracellular vesicles (EVs) and EV-mimetic therapies for intervertebral disc regeneration** Low back pain (LBP) is a leading cause of disability that imposes an enormous socioeconomic burden. With looming threat of an ever-aging population, the prevalence of LBP is increasing drastically and is estimated to affect >90% of people over 50 years of age. The major cause of LBP is intervertebral disc (IVD) degeneration that can further aggravate and give rise to severe spine problems. Current treatments that include physiotherapy, anti-inflammatory/analgesic medication, and surgery may relieve the symptoms and reduce disability to a limited extent, but do not repair the degenerated IVD. Thus, there is an unmet need for development of disease-modifying therapies that can effectively alleviate IVD pain, inflammation, and degeneration to facilitate IVD repair and regeneration. Our research team has long-standing interest on the design and development of next-generation extracellular vesicles (EVs) and EV-mimetics as immunotherapeutic agents against musculoskeletal disorders such as osteoarthritis, sarcopenia and IVD degeneration. We recently reported that EVs from mesenchymal stromal cells (MSCs) are immunomodulatory with the ability to enhance M2 over M1 macrophage polarization through CD73/ecto-5´-nucleotidase activity. To overcome the issues of isolation yield and laborious purification process with native EVs, we have further developed EV-mimetic strategies with the generation of macrophage membrane-coated nanoparticles and cell-derived nanovesicles (fused with liposomes) as EV-mimetics, and demonstrated comparable biophysical properties,

		biochemical compositions, and pharmacological activities as their parental EVs. Based on these prior studies, we hypothesize that EVs and their mimetics have similar biophysical and biochemical properties and exhibit comparable immunomodulatory effects beneficial for IVD regeneration. *Domain(s): Vaccinology and Immunotherapy, Drug Discovery and Development, Applied Biomedicine*
25	Dr Le Thi Nguyet Minh phcltnm@nus.edu.sg Department of Pharmacology	**Extracellular vesicles deliver therapeutics targeting KRAS to for treatment of pancreatic cancer and metastasis** Pancreatic cancer is the fourth most significant cause of cancer-related death globally. Pancreatic ductal adenocarcinoma (PDAC) is the most common histological type of pancreatic cancer, which ranks among the most lethal cancer entities, has a poor prognosis with a 5-year survival rate of 5%. PDAC metastasis most commonly occurs in the liver and peritoneum, causing morbidity and mortality of patients with no effective treatment options. Mutations in the GTPase KRAS are commonly encountered in PDAC and these drive initiation, progression and metastasis. Here we investigate whether extracellular vesicles (EVs) can function as efficient carriers of antisense oligonucleotides (ASOs) targeting oncogenic KRAS and sought out to develop direct and specific treatment for PDAC and mestatasis. *Domain(s): Vaccinology and Immunotherapy, Applied Biomedicine*
26	Dr Le Thi Nguyet Minh phcltnm@nus.edu.sg Department of Pharmacology	**Extracellular vesicles delivering RNA therapeutics for inflaming the pancreatic tumor microenvironment for cancer immunotherapy** Pancreatic cancer is the leading cancer-caused death with few therapeutic targets and poor effective treatments. Recently, tremendous attention has been paid to RNA-based therapeutics, including small interference RNAs (siRNAs) and antisense oligonucleotides (ASOs), due to their great potential in specifically targeting numerous undruggable oncogenes. This project aims to employ red blood cell-derived extracellular vesicles (RBCEVs) as a delivery vehicle for ASOs to specifically target driver mutations in pancreatic cancer. Additionally, we seek to co-deliver immunomodulatory RNA (immRNA) that binds to retinoic acid-inducible gene I receptor (RIG-I) to activate the RIG-I pathway in pancreatic cancer cells, resulting in IFNs-mediated anti-tumor polarization. *Domain(s): Vaccinology and Immunotherapy, Drug Discovery and Development*
27	A/Prof Nguyen Nam Long	**From AI to drug discovery for membrane transporters**

	bchnnl@nus.edu.sg Department of Biochemistry	Membrane transporters are great drug targets. Some of the known drug targets such as SGLT2, neuronal neurotransmitter transporters such as VMAT2... has been exploited for drug development. Our lab is interested in screening drugs such as small molecules for several transporters that we have discovered. *Domain(s): Drug Discovery and Development*
28	A/Prof Citra Nurfarah binte Zaini Mattar citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	**Gene Modification Therapies targeting induced Pluripotent Stem Cells, Haemopoetic reprogramming and transplantation in a Humanized Murine Model: Therapeutic approached for Major Haemoglobinopathies** β-thalassaemia major (βTM) is challenging to correct with gene therapy as there are >300 causative point mutations. Current gene modification therapies (GMT) require ex vivo haemopoetic stem cell (HSC) transduction using integrating vectors delivering the β-globin transgene or CRISR/Cas9 editing tools, increasing cost and morbidity from autologous transplantation. In vivo GMT pose different challenges, including low-efficacy HSC transduction with non-integrating vectors. We are currently developing HSC-targeting adeno-associated viral vector (AAV)-mediated in vivo base editing strategies to precisely correct point mutations causing transfusion-dependent βTM, but despite the widespread application of in vivo AAV-mediated GMT in clinical trials for diverse diseases, we acknowledge the significant concerns regarding the immunotoxicity of high-dose AAV. Additionally, HSC-directed gene editing is challenging due to low transduction efficacy and the paucity of true long-term repopulating stem and progenitor cells (<0.01% in peripheral blood). We have formulated an alternative strategy for HSC gene editing that combines patient-derived induced pluripotent stem cells (IPSC), base editing and vector technologies. This stems from our current data that demonstrate the low efficacy of transducing HSC with single-strand ssAAV6, the serotype identified in screening studies as having the most tropism for HSC, which has a payload too small to carry large base editing tools, necessitating alternative strategies such as split-intein AAV. This restriction drives us to explore alternative vehicles to achieve HSC correction, including lipid nanoparticles (LNP) and non-integrating viral vectors (NILV) that have larger payloads for carrying large base editors. NILV offer the promise of higher HSC targeting efficacy without integration mutagenesis while LNP can be modified to improve cell targeting while reducing immunotoxicity.

		We have produced IPSC from oral epithelial cells and peripheral blood mononuclear cells, and have had initial success with reprogramming IPSC to HSC. IPSC being developmentally immature are more efficiently transduced, edited and expanded than are HSC. In response to some of the difficulties producing and using AAV for gene editing, we will explore customizable non-integrating lentiviral vectors (NILV) and lipid nanoparticles (LNP) for HSC-directed GMT. We are also producing base editors specific to the most common Asian βTM-causing point mutations, and with this we can offer off-the shelf personalised GMT. We propose to genetically edit patient-derived IPSC carrying specific β-globin mutations in vitro with the appropriate base editors delivered by AAV6, non-integrating lentiviral vectors or lipid nanoparticles, to compare transduction efficacies. These corrected IPSC (screened out for incorrect editing and off-target mutations) will be expanded and reprogrammed into HSC carrying the normal β-globin gene. Reprogrammed HSC will be assessed in vitro and in vivo for haemopoetic phenotype, multilineage differentiation, engraftment and repopulating function via primary and secondary transplantation in a humanized mouse model. On- and off-target mutations and editing efficacy will be assessed in both IPSC and reprogrammed HSC. This proposed approach will allow patient-derived gene-edited IPSC to be used as GMT vehicles, corrected in vitro and reprogrammed to HSC that carry the patient's unique epigenetic markers and can be autologously transplanted, offering a viable alternative to in vivo GMT and ex vivo HSC GMT, and expanding the library of molecular therapies for haemoglobinopathies. *Domain(s): Applied Biomedicine*
29	Dr Hu Chunyi hu_dbs@nus.edu.sg Department of Biochemistry	**Harnessing CRISPR-Cas to Shape Modern Therapeutic Landscapes** The CRISPR-Cas system has emerged as a revolutionary tool in genetic engineering, offering unprecedented precision in gene editing. This proposal explores the transformative potential of CRISPR-Cas technology in the development of novel therapeutic strategies. By leveraging its capability to modify genetic material with high accuracy, we aim to address genetic disorders, enhance disease resistance, and create personalized medicine approaches. Our research will focus on optimizing CRISPR-Cas delivery methods, improving target specificity, and minimizing off-target effects to ensure safety and efficacy. Additionally, we will investigate its applications in various therapeutic contexts, including cancer

		treatment, neurodegenerative diseases, and rare genetic conditions. Through rigorous experimentation and clinical trials, we aspire to demonstrate the feasibility and benefits of CRISPR-Cas-based therapies. This work promises to reshape the landscape of modern therapeutics, offering hope for more effective and tailored treatments, ultimately improving patient outcomes and advancing the field of precision medicine. *Domain(s): Drug Discovery and Development, Infectious Diseases Management, CRISPR-Cas, Gene-editing*
30	Dr Cui Jianzhou cjz@nus.edu.sg Medicine Dean's Office-Immunology Translational Research Programme A/Prof Lim Hsiu Kim, Lina linalim@nus.edu.sg Department of Physiology	**Heparin-Artesunate Nanoparticle Delivery System for Enhanced Sorafenib Efficacy in Hepatocellular Carcinoma** Sorafenib is a multikinase inhibitor that promotes apoptosis, inhibits angiogenesis, and suppresses tumor cell proliferation. It is currently an effective first-line therapy for late-stage hepatocellular carcinoma (HCC). However, its clinical applications are significantly restricted due to poor solubility, rapid metabolism, and low bioavailability. To address these challenges, the use of nanoparticles to improve drug targeting, enhance therapeutic efficacy, and overcome sorafenib resistance has become increasingly prevalent. Our previous data have shown that nanoparticles encapsulating sorafenib can significantly improve in vivo distribution within tumors and suppress tumor growth in mice. In this project, we aim to utilize our well-characterized Heparin-Artesunate Nanoparticles (NP) encapsulating sorafenib to investigate the underlying mechanisms by which this NP system effectively overcomes sorafenib resistance in HCC both in vivo and in vitro. Additionally, we will explore potential targets of sorafenib through transcriptome data analysis during the tumor suppression process. Furthermore, depending on time, we will investigate the combination of cytotoxic chemotherapeutic agents and molecular targeted agents, such as those targeting EGFR and the PI3K/AKT/mTOR signaling pathway, to further enhance the efficacy of NP-encapsulated sorafenib in overcoming drug resistance. *Domain(s): Drug Discovery and Development*
31	A/Prof Gautam Sethi phcgs@nus.edu.sg Department of Pharmacology	**Identification of a novel agent that can suppress proliferation, induce apoptosis and overcome chemoresistance in hepatocellular carcinoma** In association with the dissemination of hepatitis B and C virus infection, hepatocellular carcinoma (HCC) ranks as the sixth most common cancer and the third leading cause of

		cancer-related deaths worldwide [1]. The prevalence of this cancer is expected to increase by 55% from 2020 to 2040. Although surgery remains to be the first choice for HCC, tumor size, hepatic functional reserve and/or portal hypertension may all restrict surgical ablation. Multi-targeted tyrosine kinase inhibitors (TKIs) including sorafenib, lenvatinib, and regorafenib have been approved for systemic treatment of advanced HCC, but overall survival benefits have been relatively modest and highlight the unmet medical need among patients with HCC. Therefore, the need to develop novel therapeutic strategies for HCC is of paramount importance. Hence, the project aims to identify a novel agent that can inhibit proliferation, induce apoptosis and overcome chemoresistance in different HCC cell lines. The agent will be identified by screening small molecule inhibitors library available in the laboratory. The effect of identified agent on signaling pathways that contribute to survival and chemoresistance in HCC will also be investigated in detail. Furthermore, detailed investigation, using, in vivo HCC mice models will be carried out. The potency of novel agent will also be teste din combination with some of the existing therapies for HCC. Overall this project will lead to discovery of a novel drug that can help to enhance treatment efficacy, reduce toxicity, and overcome chemoresistance in HCC patients. *Domain(s): Drug Discovery and Development, Infectious Diseases Management*
32	A/Prof Justin Chu Jang Hann miccjh@nus.edu.sg Department of Microbiology & Immunology	**Identification of novel proviral host factors for positive-sense RNA viruses** Positive-sense RNA viruses consist of many medically important human pathogens which have resulted in multiple significant outbreaks across the globe. To facilitate effective virions production from infected cells, RNA viruses actively hijack and utilize host cell metabolism to support viral life cycles and to modulate host antiviral defence mechanisms. Previous studies have shown that RNA viruses form replication complexes made up of viral and host proteins, indicating the significant role(s) of cellular component(s) in successful completion of intracellular virus replication. Hence, this study aims to identify crucial interactions between specific host factor(s) with viral protein(s) or genomic contents, which promote the replication capacity of selected positive-sense RNA viruses. Target host protein(s) will be overexpressed in human cell lines using mammalian expression vectors harbouring tagged coding sequence(s) of

		respective gene(s) of interest. Viral components (proteins or RNA) bound to the specific host factor(s) will be identified via pulldown assays followed by western blot or RT-PCR. The potential of respective host pathway(s) as antiviral targets for specific positive-sense RNA viruses will be subsequently evaluated using chemical or siRNA inhibitors. *Domain(s): Drug Discovery and Development*
33	A/Prof Gautam Sethi phcgs@nus.edu.sg Department of Pharmacology	**Identification of novel small molecule compounds as autophagy regulators for treatment of cancer** Cancer is one of the leading causes of mortality which accounts around ten million deaths per year globally. Regardless of various treatment strategies including surgery, chemotherapy and radiotherapy are available for cancer treatment still, it is quite challenging due to its recurrence supported by therapy resistance and stemness. In this connection, autophagy, the self-cannibalism process can act as a potentially effective strategy for treatment of cancer. In cancer, autophagy acts as a double-edged sword at the interface of cell survival and cell death in a context-dependent manner based on cancer type, stage, and cancer genetics. Its pro-survival activity helps the cancer cells to survive under nutrient depletion conditions by adopting various mechanisms such as remodeling metabolism, resistant to therapeutics through inducing apoptosis resistance, resistance to anoikis, and genome integrity and so on. Alternatively, the pro-death functions kill cancer cells which is mediated in response to oxidative stress, accumulation of protein aggregates and degradation of a cell survival proteins. Therefore, there is a great effort in developing small molecule drugs for inducing toxic autophagy or blocking pro-survival autophagy that can result in effective therapeutic strategy against cancer. Thus, the current project aims to screen the small molecule anticancer compounds available in the laboratory for autophagy induction in cancer cell lines. Then the nature of autophagy i.e. either contributing to cell survival or cell death will be investigated at the molecular level in vitro and in vivo models. *Domain(s): Drug Discovery and Development, Vaccinology and Immunotherapy*
34	Dr Ni Qiangian qqian.ni@nus.edu.sg Department of Diagnostic Radiology	**Improved lipid nanoparticle technology for messenger RNA delivery and gene editing** Among various nucleic acids therapeutics (i.e., antisense oligonucleotides (ASO), small interfering RNA (siRNA), DNA adjuvants), messenger RNA (mRNA) is no doubt one of the most promising therapeutic modalities as billions of

		administered doses of COVID-19 mRNA vaccines have convinced its safety and efficacy. The advances of mRNA technology have also enabled successful protein replacement therapies with some of the cases are already in early clinical trials for the treatment of a broader range of diseases beyond infectious diseases and cancer vaccinations. Specifically, clustered regularly interspaced short palindromic repeat (CRISPR)-based gene editing systems represent a promising therapeutic strategy for correction of gene mutations, which is of great interest in prevention and treatment of diseases. Systemic delivery of CRISPR-Cas cargos using non-viral delivery systems has attracted increasing attention because the transient nature confers increased safety over viral delivery and allows repeat dosing. This project aims to address the current pain in mRNA-based CRISPR-Cas9 gene editing system by enhancing the protein production yield of delivered mRNA, increasing the efficiency of CRISPR-Cas9-based genome editing, and enabling safe and more efficient therapeutic efficacy that target extrahepatic tissues. *Domain(s): Drug Discovery and Development, Applied Biomedicine*
35	Dr Daniel Teh Boon Loong danielteh@nus.edu.sg Department of Ophthalmology	**Interdisciplinary Optogenetic in Eye and Brain** We are utilizing optogenetics and phototherapeutics to identify the role of membrane excitability in the onset of aged-related degenerative diseases of the brain and eye. This include ultra-sensitive channelrhodopsin and photodynamic therapy as therapeutics of age-related macular degeneration, glaucoma, neurodegenerative diseases and peripheral nervous system such as neuromuscular junction. Our laboratory is inviting students to test out some of our wireless optogenetic and photodynamic therapy technologies for chronic application in in vitro and in vivo model. *Domain(s): Interdisciplinary technologies in neuroscience and vision research (optogenetics & photodynamic therapy)*
36	Dr Chen Jinmiao micchenj@nus.edu.sg Department of Microbiology & Immunology	**Investigate tumour complexity and drug response of peripheral T-cell lymphoma with subcellular resolution spatial multi-omics** Lymphoma is currently the 5th and 6th commonest cancer for male and female, respectively in Singapore. Peripheral T-cell lymphoma (PTCL) represents an Asia-centric subgroup that accounts for 15% of all lymphoma diagnoses. PTCLs are highly heterogeneous, aggressive, and present significant treatment challenges. As PD-1 and PD-L1 expressions are detectable in both PTCL and immune cells within the tumour microenvironment, immune checkpoint inhibitors (ICIs) and

		related agents have been actively explored to treat PTCL over recent years. Studies on breast cancer and ovarian cancer have suggested that PARP inhibition (PARPi) can induce immunostimulatory micromilieu and its combination with ICIs displays significant synergistic activity8–10. At Singapore General Hospital, an ongoing clinical trial of anti-PD-L1 durvalumab in combination of PARPi olaparib has showed an encouraging response rate in PTCL patients. Working with clinician scientists Dr Jason Chan and Dr Choon Kiat Ong, we will dissect the tumour heterogeneity and tumour-immune crosstalk in PTCL responders and non-responders using the latest subcellular resolution spatial multi-omics technologies, aiming to uncover the cellular and molecular mechanisms underlying different treatment outcomes. We will collect both fresh and fixed tumour specimens from 25 PCTL patients before drug treatment. With the fresh samples, we will use Stereo-seq or CosMx 1 multi-omics technology to obtain spatially resolved co-profiling of high-plex protein and whole transcriptome from the same tissue slice11. For the fixed samples, we will acquire serial sections and profile protein and gene expressions on adjacent tissue slices using the latest CosMx1 or MERSCOPE3 technologies. We will analyse the data with our AI analytical platform. *Domain(s): Vaccinology and Immunotherapy*
37	A/Prof Chan Shiao-yng obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	**Investigating the impact of inositol on uterine contractility in postpartum haemorrhage** Postpartum haemorrhage (PPH) is a leading cause of maternal morbidity and mortality, accounting for >100,000 deaths per annum globally. The most common aetiology is impaired uterine contraction after childbirth. Although uterotonic agents to enhance uterine contraction are routinely give post-delivery, they do not completely prevent PPH. Therefore, complementary approaches are needed to address PPH more effectively. Clinical studies suggest that inositol may be one such candidate to reduce postpartum blood loss. Inositols belong to a class of nutraceuticals and the myo-inositol isomer demonstrates promising effects in promoting uterine contractility in an animal model. However, the mechanisms by which myo-inositol affects uterine contractility remains unclear. The candidate will investigate the effect of myo-inositol on uterine contractility using a variety of techniques including in vitro cultures, functional assays and molecular biology. *Domain(s): Drug Discovery and Development, Nutraceuticals*
38	A/Prof Vincent TK Chow	**Investigation of antiviral and host-directed combination therapy against coronavirus infection**

	micctk@nus.edu.sg Department of Microbiology & Immunology	This project aims to evaluate the efficacy and synergism of combinations of clinically approved drugs with antiviral activity against coronavirus infection. It will employ the mouse hepatitis virus (MHV) model of infection for analyzing these combination therapies, including optimization of drug concentrations and their mechanisms of action. *Domain(s): Infectious Diseases Management, Drug Discovery and Development*
39	A/Prof Dan Yock Young / Dr Adrian Low mdcdyy@nus.edu.sg / adlow@nus.edu.sg Department of Medicine	**Isolation and characterization of microbes from the human gut** The gastrointestinal tract is a habitat to a rich diversity of microbes that produce metabolites that affect the gut environment, and microbiota and may even induce host response. Deciphering the metabolic function and role of each microbe in vivo is challenging. Isolation of gut microbes allows the characterization of metabolic profiles of individual species or as a consortium. In our research, we are interested in microbes that produce 1) short-chain fatty acid particularly isovaleric acid and valeric acid, or 2) secondary bile acids. These compounds have been associated with diseased and healthy guts. The study is multidisciplinary and involves microbiological techniques, molecular techniques (DNA or RNA), and analytical chemistry. *Domain(s): Infectious Diseases Management, Applied Biomedicine*
40	Prof Gavin Smith gavin.smith@duke-nus.edu.sg Duke-NUS Medical School	**Molecular epidemiology and evolution of human influenza viruses** Influenza viruses circulate year-round in Singapore, with two biennial peaks aligning with the winter seasons in the Southern and Northern hemispheres. During the COVID-19 pandemic, the global circulation of seasonal influenza viruses experienced an unprecedented halt, with almost no influenza activity for two years. However, since late 2022, human influenza viruses have re-emerged, causing a rise in influenza infections worldwide. Here we aim to investigate the shifts in genomic diversity that contribute to the occurrence of epidemics. Specifically, we will test the hypothesis that reduced levels of population immunity have led to the emergence of both advantageous and non-advantageous mutations within the viral genes. As the human population gradually regains immunity, these viruses are expected to face seasonal bottlenecks, which will lead to the elimination of non-advantageous mutations. The future circulation of seasonal influenza remains uncertain, creating an incentive for closely tracking the trajectories and transmission patterns

		of these viruses. We will examine how these alternations contribute to an increase in the diversification of lineages, yielding the emergence of novel antigenic variants. *Domain(s): Infectious Diseases Management, Molecular epidemiology and evolution*
41	Dr Alan Prem Kumar apkumar@nus.edu.sg Department of Pharmacology	**New Therapeutic Strategy for Unmet Need in Neovascular Age-related Macular Degeneration (nAMD)** Neovascular age-related macular degeneration (nAMD), characterized by choroidal neovascularization (CNV), is one of the leading causes of incurable blindness worldwide. Current standard treatment involves monthly intravitreal injections of anti- vascular endothelial growth factor (VEGF) agents such as aflibercept (Eylea), ranibizumab (Lucentis) and brolucizumab (Beovu). However, the long-term repeated intravitreal injections can lead to complications and low patient compliance, as well as high financial burden for patients and the healthcare system. Notably, these drugs can only delay progression to blindness without providing cure to patients. Furthermore, about 30% of the patients are non-responsive to these treatments, while 15-20% of patients become resistant to treatment over time. Hence, new, ideally long-lasting, and minimally invasive, therapeutic strategies, are urgently needed for nAMD patients. Several studies have demonstrated the prominent roles of Src Family Kinases (SFKs) in retinal angiogenesis. Lyn kinase is a SFK member, and we have recently developed a new Lyn kinase-specific inhibitor (CHL-4); Patent: Kumar AP et al "COMPOUNDS FOR MODULATING SRC FAMILY KINASES AND USES THEREOF" [SG Patent Application No. 10202260299X, filed 2 December 2022], which possesses anti-angiogenic and anti-epithelial-to-mesenchymal transition (EMT) properties. Therefore, we hypothesize that CHL-4 targets an alternative pathway other than VEGF could be a novel therapeutic agent for nAMD. *Domain(s): Drug Discovery and Development, Applied Biomedicine*
42	Dr Chris Sham Lok To miclts@nus.edu.sg Department of Microbiology & Immunology	**Profiling genetic interactions in the human pathogen Streptococcus pneumoniae** Knowing the sequence of a gene is far from understanding its function. Even in the simplest of cells like Escherichia coli, we do not know the role of about one-third of the genes. Traditional approaches for studying gene function, such as phenotyping knockout mutants, are time-consuming and labour-intensive. To overcome these challenges, my laboratory developed high-throughput methods to study genetic interactions, which helped us understand the function of these "genetic dark matters" in the ever-

		increasing number of sequenced genomes in public databases. Our preliminary results uncovered mechanisms by which cell envelope synthesis is coordinated and identified new factors required for central metabolic pathways. In this project, students will follow up on these findings by constructing deletion mutants of the human pathogen Streptococcus pneumoniae. Uncovering new gene functions will identify new drug targets that fuel the development of novel treatment options. *Domain(s): Infectious Diseases Management*
43	A/Prof Lim Hsiu Kim, Lina linalim@nus.edu.sg Department of Physiology	**Regulation of DNA sensing and recognition in cancer** The host immune system recognizes regions of viral and self RNA via specific receptors that activate host immune responses. Annexin-A1 is an immune response protein which has anti-viral properties. We and others believe that cancer cells express cytosolic DNA which can be sensed by immune cells and cancer cells themselves. Why the immune system does not react to these abundant DNAs/RNAs are unclear. We predict that expression levels of ANXA1 can positively regulate sensitivity of the immune cells and cancer cells to DNA. In fact, our published results show that RNA and DNA stimulation of cancer cells induces cancer cell death, which is dependent on ANXA1. We therefore, plan to determine that ANXA1 enhances DNA and RNA sensing in immune cells and cancer cells in vitro and in vivo. Knowing these mechanisms of how cancers evade immune recognition will bring us closer to finding treatments for cancer. *Domain(s): Vaccinology and Immunotherapy*
44	A/Prof Zhang Yongliang miczy@nus.edu.sg Department of Microbiology & Immunology	**Regulatory role of DUSP4 in cancer and anti-cancer immunity** Our study on a molecule known as DUSP4 showed that it plays important roles in both immune response to microbial infection and in the development of cancer such as colorectal cancer. Interestingly, we found that this molecule functions as a tumor suppressor mainly through its regulation of the immune system. However, its role in liver cancer and anti-cancer immunity is unclear. This project aims to investigate the function of DUSP4 in the pathogenesis of liver cancer by focusing on both the cancer cells and the immune cells in tumor microenvironment. Knowledge gained from this project will elucidate the regulatory function of DUSP4 in liver cancer development and anti-cancer immunity which will help to target this molecule for development of anti-cancer therapies. *Domain(s): Vaccinology and Immunotherapy*

45	Dr Alan Prem Kumar apkumar@nus.edu.sg Department of Pharmacology	**Targeting Protein Tyrosine Kinase 6 and Replication Stress Response to Enhance Immunotherapy Response in Ovarian Cancer** Protein Tyrosine Kinase 6 (PTK6) is aberrantly expressed in many cancers and is associated with poor prognosis. Its expression is also significantly elevated across all ovarian cancer subtypes. PTK6 has been shown to have multiple oncogenic roles in other cancers but its roles in ovarian cancer remain unclear. Our preliminary findings identified a novel link between PTK6 and the DDR network in ovarian cancer. PTK6 depletion in ovarian cancer cells impaired their ability to repair DNA damage induced by cisplatin, a current standard-of-care chemotherapy drug, thus increasing their sensitivity to cisplatin. Furthermore, PTK6-depleted ovarian cancer cells exhibited reduced nuclear accumulation of Replication Protein A 32 (RPA32) in response to cisplatin-induced damage and were thus unable to repair the DNA damage. This suggests that PTK6 might function within the replication stress response (RSR) pathway. Additionally, PTK6 depletion in ovarian cancer cells resulted in an upregulation of immune checkpoint protein PD-L1 expression, which was further enhanced by cisplatin treatment. Therefore, we hypothesize that PTK6 mediates resistance to platinum chemotherapy through the RSR pathway in ovarian cancer. Given that DDR-targeted therapies have significantly improved the efficacy of Immune Checkpoint Inhibitors (ICI) in ovarian cancer patients in several clinical trials, we also hypothesize that PTK6 inhibition with/without cisplatin could be a viable strategy to improve ovarian cancer patient response to ICI therapy, targeting PD-L1. *Domain(s): Vaccinology and Immunotherapy*
46	Dr Ding Lingwen patdl@nus.edu.sg Department of Pathology	**Targeting RNA exonuclease XRN1 to potentiate immune checkpoint blockade therapy** The remarkable achievement of immune checkpoint blockade antibodies has altered the therapeutic landscape of many types of cancer. However, the response rate is relatively low (20-30% in melanoma and even lower in other types of cancer) and only a fraction of patients can benefit from the treatment. Therefore, comprehensively understanding the genes and molecular mechanism controlling the efficiency of immunotherapy is an urgent need. We recently identified several key genes (LNK, SETDB1 and XRN1 etc.) regulating the response of immune therapy using murine melanoma models. In this study, we will focus

		on the most likely druggable target we identified, RNA exonuclease XRN1. Specific Aims & Hypothesis: XRN1 regulates aberrant-RNA mediated interferon (IFN) signaling and innate immune response; therefore, inhibiting XRN1 can potentially enhance the response of immunotherapy. Aim 1 To examine whether our finding of role of XRN1 in potentiating immunotherapy in melanoma models can be extend to other major cancers which are currently been treated with anti-PD1 antibody. Aim 2 To identify the target RNAs which are degraded by XRN1; and to elucidate mechanism of how downstream sensors recognize accumulated aberrant-RNA and activate anti-viral IFN signaling. Activated downstream RNA sensors will be systematically identified using a small customized CRISPR library. Rescue experiments will be conducted in XRN1 silenced cells to examine whether knockdown of the identified sensors can abolish the aberrant RNA induced IFN signaling. We will also examine whether XRN1 silencing enhances the antigens/neoantigens presentation and T cell response. Aim 3 Potential XRN1 inhibitors will by identified by using small molecule library screening, and their potential therapeutic effect will be evaluated. *Domain(s): Vaccinology and Immunotherapy, Drug Discovery and Development*
47	A/Prof Nguyen Nam Long bchnnl@nus.edu.sg Department of Biochemistry	**Targeting sphingosine-1-phosphate transporters for treatment of inflammatory diseases** Sphingosine-1-phosphate (S1P) is a potent signaling lipid which exerts its activity via activation of 5 different G-protein coupled receptors designated as S1PR1-5. Blood sphingosine-1-phosphate (S1P) is highly supplied by erythrocytes and platelets. However, there are specific S1P sources that regulate delicate biological processes such as lymphocyte exit from lymph nodes and tissues. The Spinster Homolog Protein 2 (Spns2) is responsible for S1P production in lymphatic vessels to regulate lymphocyte exit. Inhibition of Spns2 reduces blood lymphocytes that is beneficial in inflammatory conditions such as colon cancers, multiple sclerosis, and arthritis. In this project, student will study the roles of Spns2 in regulation of immune cell egress in response to intestinal inflammations. The goals of this study are to evaluate whether Spns2 can be used as a target for development of drugs. *Domain(s): Drug Discovery and Development, Applied Biomedicine*
48	Prof Antonio Bertoletti antonio@duke-nus.edu.sg	**The secretome of HDV and HBV-specific T cells in HBV/HDV co-infected infected individuals**

	Duke-NUS Medical School	Hepatitis Delta virus (HDV), the only known viroid that infects humans, requires the presence of HBV to complete its infection cycle. Most patients with HBV-HDV co-infection experience a more severe clinical course of chronic hepatitis with limited therapeutic options. Knowledge of the profile of HDV and HBV-specific T cell response in patients and in individuals who have been able to clear HDV are scarce. We propose here to characterize HBV and HDV-specific T cell response utilizing a novel cytokine secretion method recently develop for the analysis of SARS-CoV-2 specific T cells Pool of peptides covering HBV and HDV proteins will be utilized to directly stimulate whole blood of HDV-HBV co-infected patients, healthy controls and individuals who control HDV infection. Cytokines will be analyzed after peptide pools stimulation to understand the pattern of cytokines (secretome) release by the HBV and HDV-specific T cells. Conventional T cell assay will then be used to define the T cell population able to secrete the different cytokines. The study will provide novel knowledge about the antiviral cellular immune profile triggered by HDV and its impact on HBV-specific T cell response. *Domain(s): Infectious Diseases Management*
49	Dr Cui Jianzhou cjz@nus.edu.sg Medicine Dean's Office-Immunology Translational Research Programme	**Unravelling the Underlying Immune Mechanisms, Drug Response, and Vaccine Response in Influenza Infection Using Multi-omics and AI Approaches** Influenza remains a significant global health threat, causing substantial morbidity and mortality annually. Understanding the complex interplay between the host immune system, influenza virus, and therapeutic interventions, including antiviral drugs and vaccines, is crucial for developing effective strategies to combat influenza. Our previous study revealed that influenza infection can cause distinct immune responses in different immune cell types, suggesting that the detailed underlying mechanisms need further study, especially under different drug treatments and vaccine conditions. By analysing publicly available bulk RNA-seq, single-cell sequencing, and spatial transcriptomics datasets and following AI approaches and partial validation studies, students can aim to: 1. Investigate the Transcriptional Landscape: Explore the transcriptional landscape of host immune responses during influenza infection, drug response, and vaccination using bulk RNA-seq, single-cell sequencing, and other multi-omics data (metagenomics, metabolomics, etc.).

		2. Identify Key Immune Components: Identify key immune-related genes, pathways, and cell types involved in influenza pathogenesis, drug response, and vaccine response. 3. Characterize Spatial Immune Responses: Characterize the spatial distribution and cell type-specific immune responses in influenza-infected tissues treated with drugs and vaccines using spatial transcriptomics. 4. Develop Predictive Models: Develop machine learning models to predict the efficacy of antiviral drugs and vaccines in influenza infection based on multi-omics data. 5. Identify Novel Therapeutic Targets: Utilize AI-driven approaches to identify potential novel therapeutic targets and compounds for the prevention and treatment of influenza. 6. Validate Predictions Experimentally: Validate the predictions of machine learning models and AI-driven approaches through experimental studies, including vaccine immunogenicity and efficacy assessments (depending on time). The insights gained from this project will contribute to the development of more effective and targeted strategies for the prevention and treatment of influenza, ultimately improving public health outcomes. *Domain(s): Vaccinology and Immunotherapy;*
50	Prof Andrea Britta Maier a.maier@nus.edu.sg Department of Medicine	**Unveiling Metabolic Signatures: Nicotinamide Adenine Dinucleotide Levels In The SG90 Longitudinal Study Of Successful Aging** Nicotinamide adenine dinucleotide (NAD) is a coenzyme that plays a central role in various biochemical reactions within cells, including those involved in energy metabolism, DNA repair, and maintaining the balance between oxidative stress and antioxidant defences. Blood NAD concentration declines with chronological age in animals and humans. This decline accelerates cellular aging and contributes to the development of various aging-related diseases. The SG90 Longevity Cohort is a longitudinal study designed to assess the mechanisms underlying healthy aging and longevity of Singaporeans aged 90 years and above. In line with the objective of this endeavour, the present project aims to evaluate the basal levels of nicotinamide adenine dinucleotide (NAD) and its association with aging-related clinical outcomes within the members of this cohort. *Domain(s): Drug Discovery and Development, Applied Biomedicine*

51	Dr Matthew Tay Zirui matthew_tay@idlabs.a-star.edu.sg Department of Biochemistry	**Utilization of microfluidics for discovery of antibody-based therapeutics against viruses and antimicrobial-resistant organisms** This project seeks to identify novel vaccine immunogens for combatting emerging and re-emerging infectious diseases. Droplet microfluidics is capable of enabling high-throughput functional studies of monoclonal antibodies. By analysing the targets of such protective antibodies, the antigenic targets conferring protective functional activity can be identified. This project will be conducted at the A*STAR ID Labs, within a multidisciplinary lab environment with lab expertise in bioengineering, virus biology, and antibody biology. *Domain(s): Vaccinology and Immunotherapy, Drug Discovery and Development*
52	A/Prof Lim Hsiu Kim, Lina linalim@nus.edu.sg Department of Physiology	**Vaccination/preexposure to COVID19 and susceptibility to influenza** The coronavirus disease 2019 (COVID-19) epidemic represents one of the most devastating pandemics in modern history. SARS-CoV-2, the etiologic agent of COVID19 has now spread across the planet to 188 countries and devastated the global economy. In the response to the pandemic, countries have taken extreme measures to thwart the spread of the disease and multiple countries, (including Singapore) have closed their borders, created mask mandates and social distancing measures. Although retrospective analyses will no doubt assess the efficacy of various countries' response to this unprecedented event, one potential advantage of Singapore's approach to pandemic management has been the 'knock-on' effect it has had on other common respiratory pathogens such as influenza viruses. Influenza viruses infect millions of people each year and can result in severe or even fatal complications including pneumonia and respiratory distress syndrome. The Singapore Ministry of Health started influenza monitoring 40 years ago to monitor for possible outbreaks and to track influenza strains, and it is the first time since the start of the monitoring that there have been no cases of flu reported through the surveillance system for almost a year. In January 2020, 652 flu-like cases were sent in for analysis and 320 were flu positive (50%). In comparison, in January 2021, 200 flu-like cases were sent in and 0 were flu-positive. This project will study the interaction between influenza and coronaviruses with even subclinical infection by coronaviruses preventing influenza infection These questions are critically important as influenza pandemics have

		historically had far more devastating impact than the current coronavirus pandemic especially among younger people. It is thus key to our understanding of current and future pandemics to determine if and how the influenza virus is going to reappear to cause the next pandemic. *Domain(s): Infectious Diseases Management*
53	A/Prof Justin Chu Jang Hann miccjh@nus.edu.sg Department of Microbiology & Immunology	**Validating the role of Hedgehog signalling pathway as a therapeutic target in viral infections** The COVID-19 pandemic has brought about an unprecedented public health crisis worldwide. While treatments and vaccinations are now available for some viruses to prevent the exacerbation of viral diseases, many of the existing antiviral drugs are targeting against a viral factor for which viruses were known to acquire a resistance for quickly. The evolutionarily conserved hedgehog (HH) pathway has essential functions in embryonic development and tissue homeostasis. Aberrations in the HH signalling pathway have been well-studied in cancer, showing an increased cancer prevalence and mortality with HH signalling activation. Recently, accumulating evidence has shown that HH signalling is targeted by viruses to allow effective viral replication and pathogenesis. This discovery highlights the emerging role of HH signalling in viral infections, and evoked the potential of repurposing small molecule drugs which are targeting HH signalling in the treatment of viral diseases. In this project, we will evaluate the drug repurposing potential of hedgehog inhibitors in virus infections through evaluating its antiviral efficacy and dissecting its mechanism in cell-based and in vivo studies. *Domain(s): Drug Discovery and Development*