Annual Report 2019

HKU-Pasteur Research Pole

7/F Jockey Club Building for Interdisciplinary Research

5, Sassoon Road, Hong Kong SAR

Roberto Bruzzone, Co-Director

Malik Peiris, Co-Director

INDEX

Summary

Mission

The HKU-Pasteur Research Pole (HKU-PRP) is a joint laboratory, established by The University of Hong Kong (HKU) and the Institut Pasteur (IP), under the School of Public Health (SPH) of the Li Ka Shing Faculty of Medicine of the University of Hong Kong. HKU-PRP aims to confront the challenges posed by viral infections by developing research and education programs that willcontribute to providing solutions to mitigate the impact of infectious diseases.

Research

We have organized our activity around Group Leaders who are engaged in competitive research projects aligned with scientific priorities of HKU and IP, namely on emerging and re-emerging infectious diseases (respiratory and mosquito-borne viruses) and, with the recruitment of a new Group Leader, antimicrobial resistance (AMR). With respect to influenza research, we are combining clinical studies and basic research investigations to gain insight into the mechanistic aspects of disease pathogenesis and adaptive immunity for improved protection. Collaboration with the State Key Laboratory of Respiratory Disease of the Guangzhou Medical University, where laboratory space has been made available to HKU-PRP, has also been expanded with the signing of a cooperation project in the framework of the Guangdong-Hong Kong-Macao Greater Bay Area. We are studying both the innate and adaptive immune response to viral infection with a broad objective to investigate the underlining mechanisms relevant to disease pathogenesis and how this could be harnessed and optimized by vaccination to improve protection from diverse influenza virus infection. With respect to arboviruses, we have designed a functional screening strategy to identify novel host factors, which are co-opted by the virus to facilitate its replication, biogenesis, trafficking, and egress. This approach offers novel therapeutic possibilities by interfering with host factors, instead of viral components, as treatment targets. With respect to AMR, we use conventional microbiology and molecular biology techniques, cutting-edge sequencing technologies, coupled with bioinformatics, statistical and epidemiological approaches to study human and animal microbiomes and monitor AMR bacteria and resistome with a holistic One Health approach. HKU-PRP has published over 20 papers since January 2019.

Teaching

Our annual courses draw an increasing number of applications from around the world and have generated a worldwide network of talented trainees. We have completed the Croucher Summer Course in Advanced Imaging with the third and final installment on "Deep Learning in Imaging & Cell Biology". The 15th HKU-Pasteur Virology Course focused on coronavirus biology, a choice of topic that has proven prescient in view of the current outbreak of the new coronavirus. The 9th HKU-Pasteur Cell Biology Course explored proteomics based approaches to probe the cell biology underlying human diseases with an overview of methods spanning conventional to more advanced strategies. The 2019 edition of our Public Health Workshop series at the Pasteur Institute of Ho Chi Minh City (Vietnam), which was supported by the French Regional Scientific Cooperation, discussed the current situation of the measles and rubella eradication program, and the implementation of the proposed Operational Targets set by WHO for 2020.

Perspectives

We have developed a strong identity to promote the missions of HKU, IP and the Institut Pasteur International Network, through research, teaching and public health activities. We plan to recruit another Group Leader in 2020, to spearhead computational biology research programs. We have been awarded a major grant from the Innovation & Technology Commission to establish the Center for Immunology & Infection (C2I), an interdisciplinary research laboratory that will address significant public healthcare challenges through novel technology platforms for biomarker discovery and the development of new vaccine and therapeutic strategies at the Hong Kong Science and Technology Parks. In summary, the results obtained in 2019 are clearly in line with our strategic objective to position HKU-PRP as a cluster of excellence within the School of Public Health and one of the hubs of the Institut Pasteur International Network.

2. Overview of the Programs

2.1 Research

The scientific activity of HKU-PRP is organized around three core research questions that meet the overarching goals of Internationalization, Innovation, Interdisciplinarity and Impact (HKU's 3+1):

1. *How do viruses invade, replicate and escape infected cells?* This question encompasses both the virus point of view of the infectious process – by studying molecules and machinery of the host cells that are hijacked during the viral life cycle, as well as the cellular view – to investigate counterstrategies employed by the host in order to prevent virus infection at various steps, including replication, assembly and release.
2. *What makes a microbe pathogenic?* This question interrogates the behavior and pathogenicity of emerging viruses and bacteria with a multi-layered approach that spans serology, epidemiology, microbiology and pathogenicity to delineate genetic determinants of virulence and the acquisition of traits that favor crossing of species barriers by zoonotic viruses and anti-microbial resistance at the human-animal-environment interface.
3. *How do microbes deal with the host immune response and the environment?* This question zooms in, on the one hand, on innate responses and the complex strategies devised by viruses to foil them and, on the other hand, on adaptive lines of defense of the host and how they could be harnessed and optimized by vaccination to improve protection. By using conventional microbiology, molecular biology and next-generation sequencing, coupled with bioinformatics, statistical and epidemiological approaches we will extend study the composition and function of human and animal microbiomes in health and disease.

The lab of Chris Mok uses a combination of clinical and experimental studies that span the areas of serology, epidemiology and molecular biology to understand the behavior and pathogenicity of emerging viruses. **The major objective of the group is to understand the interplay between the host adaptive immunity and the viral determinants of respiratory viruses such as influenza viruses and coronaviruses using a combination of clinical, virological, immunological and structural approaches**. In collaboration with Nicholas Wu and Ian Wilson (Scripps Research Institute, USA), **they have uncovered and characterized two mutually exclusive evolutionary trajectories for egg adaptation of human H3N2 viruses, which provides important insights into the seed-strain selection for egg-based seasonal influenza vaccines**. It is well-known that egg-based seasonal influenza vaccines are the major preventive countermeasure against influenza virus. However, their effectiveness can be compromised from antigenic changes arising from egg-adaptive mutations on influenza hemagglutinin (HA). This work postulates that pre-introduction of another mutation in the vaccine seed strain will have minimal effect on antigenicity and at the same time, prevent the emergence of mutations that adversely alter antigenicity during egg adaptation. In collaboration with Jincun Zhao's team (Guangzhou Medical University, PR China), they are shedding new light on the reasons undelying the geographical restriction of the vast majority of MERS cases to the Arab Peninsula. Thus, although >70% of MERS-CoV-infected dromedaries are found in Africa, no human infections have been reported from Africa. However, low MERS-CoV sero-prevalence in camel abattoir workers and

those living in camel herding areas has been reported, suggesting that infection may be taking place. One possibility is that viral genetic diversity may be associated with reduced pathogenic potential. They found that MERS-CoV in Africa are phylogenetically distinct from those in the Arabian Peninsula and, furthermore, that the viruses isolated from Saudi Arabia/Korea showed different replication kinetic in the lung of the mice when compared to those isolated from Africa. These results demonstrate that, in vivo, MERS-CoV from Africa have significantly lower replication competence in the lungs of hDPP4 transgenic mice, extending in vitro observations. **Overall, these findings will allow us to understand the range of pathogenic potential to MERS-CoV and, in future studies, to identify the viral genetic determinants of increased pathogenicity observed with the current viruses found in the Arabian Peninsula**. **The Mok lab is now actively working on the novel SARS-CoV-2**, developing serological assays to understand the specificity of antibody responses to SARS-CoV-2 and any cross-reactivity with SARS-CoV and other coronaviruses, which underpins the development of effective vaccines as well as options for passive immunotherapy.

The Sumana Sanyal lab applies a combination of cutting-edge methods spanning biochemistry, cell and molecular biology and immunology to address aspects of host-pathogen interactions. U**sing influenza and flaviviruses as model systems, the Sanyal lab aims to determine the identity and function of specific host factors that are exploited by these viruses to complete their intracellular life cycle**. They also investigate counterstrategies employed by the host – either through upregulation of immune signaling pathways or expression of virus restriction factors – in order to prevent virus infection at various steps, including replication, assembly and release. Among other factors, the lab is particularly interested in ubiquitin and ubiquitin-like post-translational modifiers of protein function, such as ISG15 that play a significant role in modulating different pathways, most of which are innate signaling pathways such as RIG-I, TLR7 and inflammasome activation. **Over the past year the Sanyal lab has revealed how flaviviruses exploit lipid metabolic pathways of the host to promote replication**. The working hypothesis entais that induction of autophagy is a critical aspect to sustain assembly of progeny virions. Consumption of lipid droplets (lipophagy) generates the necessary fatty acids utilized by dengue and a metabolic flux that facilitates virus biogenesis. Amongst the host factors that facilitate egress of dengue virus particles through the secretory pathway are the KDEL receptors (KDELRs), class-II Arfs and several Src-family kinases (SFKs). By screening a number of SFKs to determine their impact on intracellular transport of dengue and Zika viruses, the lab identified Lyn kinase as having a significant impact on release of both flaviviruses. **These experiments have revealed the mechanism through which SFKs activate an autophagy-dependent unconventional secretory process that is specifically triggered upon infection and facilitates release of infectious viral progenies**. Another aspect of the research carried out by the Sanyal lab is directed at understanding the test of strength between the innate immune response to viral infections is through upregulation of the interferon type I and II pathways and the counter strategies implemented by viruses through either inhibition of IFN response or by activation of proteins that inhibit the function of interferon-stimulated genes (ISGs). Using a combination of CRISPR/Cas9 knockouts and protein interaction assays, the lab is currently exploring the functional relevance of these modifications during influenza infection, centered on two host proteins: (i)Tsg101 and (ii) MGRN1 - an E3-ligase that ubiquitylates Tsg101.

The group of Hein Min Tun uses conventional microbiology and molecular biology techniques, cutting-edge sequencing technologies, coupled with bioinformatics, statistical and epidemiological approaches to: 1) **study the composition, function, and dynamics of human and animal microbiomes in health and disease**; and 2) **monitor antimicrobial resistance (AMR) bacteria and resistome in humans, animals, and the environment using a holistic One Health approach**. Their overarching goal is to contribute to improving scientific understanding on the impact of microbiome and AMR in public health. Antimicrobial resistance (AMR) constitutes an increasing health hazard worldwide. The extensive overuse and misuse of antibiotics in both humans and animals is fueling AMR, especially in, but not limited to, South (East) Asia. The exponential increase in international travel to these regions may substantially contribute to the emergence and spread of AMR, since it allows resistant bacteria or bacterial mobile genetic elements (MGEs) carrying resistance genes (e.g. plasmids) to be rapidly transported between regions. The extent to which foreign travel poses a risk for the acquisition of AMR remains largely unknown, as the presence of resistant bacteria in the normal human microbiota following travel remain undetected unless they cause manifest infections. With this in mind **the Tun lab launched the "Hong Kong Traveler Cohort" by sending recruitment information to HKU students and staff via email or posting flyers around campus**. A total of 113 travelers enrolled in the study. From this pilot cohort, they identified travel associated risk factors for the acquisition of ESBL bacteria and other AMR genes, which are also influenced by the diversity of gut microbiota. These findings led to develop a model to predict both acquisition and decolonization of AMR bacteria and genes using baseline microbiota and traveler associated risk factors. A related project deals with the growing body of evidence demonstrating that environmental bacteria are resistant to a multitude of antibiotic substances and that this environmental reservoir of AMR is still growing. Thus, feasible measures are required to reduce the risks posed by AMR genes and resistant bacteria that occur in the environment. **The Tun lab set up protocols to strengthen environmental surveillance of AMR bacteria and investigate antimicrobial resistant (AMR) phenotypes of *E. coli* isolated from air-conditioner and seawater**. The vast majority of isolates were phenotypically resistant to at least one antimicrobial compound and six resistance patterns were found, including to an antimicrobial agent which is uncommon used for outpatients, and mainly used in hospital settings. This raised the possible dissemination of hospital-related AMR bacteria in the environment. These findings indicate that surveillance of **AMR bacteria in Hong Kong's environment should be considered as an approach in the One Health approach to AMR surveillance**.

The main objectives of the group of Sophie Valkenburg are to define immune correlates of protection for influenza viruses from infection and vaccination. **The research projects are centred on the role of protective heterologous T and B cell immunity in mouse and human systems, by investigating novel vaccines and immune correlates of protection for influenza**. The primary focus is to study adaptive immunity to influenza, and how this could be harnessed and optimized by vaccination to improve protection from diverse influenza virus infection. Hemagglutinin (HA)-specific antibodies can block influenza infection, whereas T cells recognize influenza-infected cells. A vaccine which ultimately combines antibody and T cell-based immunity for influenza will provide a full-proof immunological barrier to influenza infection, which these studies will ultimately help develop. In collaboration with Leo LM Poon (School of Public Health

at HKU), and Liyange Perera and Thomas Waldmann (NIH, USA), **the lab is determining the mechanism of protection of a Vaccinia Wyeth vaccine vector encoding 5 influenza proteins, with a molecular IL-15 adjuvant to enhance vaccine memory responses**. The vaccine elicits effective influenza-specific T cell memory responses that establish early local T cell responses upon influenza challenge, significantly reducing viral lung titers and thus survival. The vaccine is being further investigated to determine the role T cell mediated immune pressure may play in viral escape by next generation sequencing to identify mutations at T cell epitopes. Circumventing virus escape is important for the design of next generation influenza vaccines. In collaboration with Leo Poon, Benjamin Cowling and Yat Hang Tam (School of Public Health at HKU), **the lab was involved in a randomized clinical trial to determine the benefit of re-vaccinating the elderly by comparing subjects who received one dose of the updated vaccine versus two doses of vaccine**. Overall, we found that twice annual influenza vaccination had no impact on the quality T- and B-cell responses. Further immune correlates such as the subjects immune genotype background and IgG subclasses are now being tested. This 2015-2016 randomized clinical trial led to the establishment of two trials via a co-operative agreement with the US CDC, to assess longitudinal vaccine responses in older adults over 5 years in Hong Kong. Specifically, we are investigating whether already available enhanced vaccines (recombinant, adjuvant, high dose) are more immunogenic than standard vaccines, and whether an alternating vaccine regime of enhanced vaccines would have further synergy, resulting in an 11-arm clinical trial of nearly 2,000 older adults. The same enhanced and seasonal inactivated vaccines were assessed in a mouse vaccination and challenge model to determine vaccine memory and survival from lethal influenza challenge. **A 5-year Theme based Research Scheme (TRS) project grant was awarded by the Research Grants Council (RGC) to Benjamin Cowling (HKU) to investigate population and individual immunity to influenza in Hong Kong, of which Sophie Valkenburg is a co-investigator and will contribute significantly to it over the coming years**.

Work on the sero-epidemiology of MERS-CoV and Ebola virus is coordinated by **Malik Peiris**. His recent findings, obtained in collaboration with several teams worldwide, confirm the widespread distribution of the virus in camels across Africa and the Middle East. A systematic active surveillance and longitudinal studies for MERS-CoV are, therefore, needed to understand the epidemiology of the disease and dynamics of viral infection. **In collaboration with a team of the Institut Pasteur du Maroc, they provided evidence of zoonotic transmission of MERS-CoV in Morocco in people who have direct or indirect exposure to dromedary camels**. Furthemore, genetic analysis of dromedary camel coronavirises showed interspecies events of recombination, supporting the possibility that the zoonotic pathogen MERS-CoV, which also cocirculates in the same camel species, may have undergone similar recombination events facilitating its emergence and spillover to humans, or may do so in its future evolution.

The presence of **James Di Santo**, a Visiting Research Professor from the Institut Pasteur since 2016, **has been instrumental in the preparation of a major project to understand the genetic and environmental determinants of immune responsiveness in normal individuals, which has been combined with other workpackages and submitted for funding to the Innovation and Technology Commission within the framework of InnoHK**, a recent collaborative scientific research scheme set up set up by

the Government of the Hong Kong Special Administrative Region. **The program, which expands the scope of the partnership between HKU and IP, has been approved with a major, 5-year grant totaling over 40 million euros to establish the Center for Immunology & Infection (C2I)**. C2I will work around four major research programs to face public health challenges and making Hong Kong a global center of excellence for precision medicine population strategies. Through C2I, we will contribute to Hong Kong's transformation into an international innovation and technology hub of the Greater Bay Area of Guangdong, Hong Kong and Macau.

2.2 Teaching and Education

HKU-PRP has pioneered in Hong Kong a teaching program of excellence that has been established to train in biomedical sciences a selected group students coming from all over the world. We offer three major international courses on an annual/biennial basis – Cell Biology, Virology and Immunology – which feature lectures from leading scientists and have received increasing support from extramural funding. All HKU-Pasteur courses have been approved by the Research Postgraduate Committee of HKU for inclusion in the coursework curriculum of MPhil/PhD students. All Group Leaders are actively engaged in our international courses as well as in the undergraduate and postgraduate curriculum of HKU.

The **HKU-Pasteur Cell Biology Course**, which reached the 9th edition in 201 9, continued our exploration of proteomics based approaches to probe the cell biology underlying human diseases. Novel targets for drug development have emerged as a result of such methods that take into account active enzymatic states that can be specifically inhibited in the context of human pathologies. Hence a combination of genomic and transcriptomic approaches together with proteomics of cell biology is illuminating how biological networks operate in normal physiology and human diseases. The faculty of the course featured scientific leaders in the integration of methods in classical biochemistry and mass spectrometry spanning conventional to more advanced approaches, which enable the analysis of dynamic biological networks under normal physiology and during diseased states such as pathogen infection.

The **15th HKU-Pasteur Virology Course** offered a full immersion into coronavirus biology, a choice of topic that has proven prescient in view of the current outbreak of the new coronavirus. Most endemic coronaviruses (CoV) cause mild respiratory and intestinal infections in animals and humans. The identification of two novel and highly pathogenic coronaviruses as the cause of SARS and MERS outbreaks has illustrated the risks associated with zoonotic infections from this family of viruses. The Faculty reviewed our current understanding and knowledge gaps, with special emphasis on the origin, evolution, transmissibility, molecular biology, epidemiological and clinical features of the highly pathogenic SARS-CoV and MERS-CoV. Lessons from the outbreaks of SARS-CoV and MERS-CoV in different parts of the world were discussed with experts who played a prominent role in the identification of the viruses and the implementations of measures to control their spread.

We have co-organized with Musa Mhlanga at the University of Cape Town (South Africa), and George Tsao (HKU) the third and final edition of the **Croucher Summer Course in Advanced Imaging**. This course series aimed to advance imaging and high-resolution microscopy for single cell and single molecule imaging which are essential technology

platforms in cell and molecular biology. The third and final edition focused on the application of leading deep learning framewroks for microscopy image restoration to various biological tasks. The series, which started in 2015, was a major effort to promote advanced imaging analysis and share with young as well as established researchers recent advances and breakthroughs made at the intersection of high throughput biology and imaging microscopy and their applications in basic and translational research. We believe that this course was timely and successful in achieving the transfer of the state-of-the-art imaging technology s and their applications in various aspects of cell and molecular biology to an international group of investigators.

The **Public Health Workshop series at the Pasteur Institute of Ho Chi Minh City** is attracting increasing number of applications and has become a benchmark for a world-class training program for epidemiologists, researchers and public health officials in the region. The topic of the 2019 edition, organized in close partnership with the Pasteur Institute of Ho Chi Minh City, was "**Measles and Rubella Elimination: Options for Public Health Interventions**", two vaccine-preventable diseases that can cause serious complications in children and adult women during pregnancy. The workshop discussed the current situation of the eradication program, the efforts of the health sector towards the elimination of measles and rubella and the implementation of the proposed Operational Targets set by WHO for 2020. The faculty, comprising specialists with strong links to the WHO also reviewed the response to the most recent outbreaks with emphasis on regional approaches.

We have hosted nine international students for their laboratory placement, from **France**, **The Netherlands**, **PR China**, **Singapore** and the **UK**, as well as several interns from local institutions, including the Hong Kong Institute of Vocational Education.

2.3 Other Major Activities

We retain leadership roles in a number of global projects. **Roberto Bruzzone** has served in 2019 as the **Interim Chair** of the **International Severe Acute Respiratory and Emerging Infection Consortium** (www.isaric.tghn.org), a network of networks which aims at ensuring that clinical researchers have the open access protocols and data-sharing processes needed to facilitate a rapid response to emerging diseases. He was appointed as the new Chair by the Board of Directors of ISARIC at the end of 2019 for a duration of three years and attended in this capacity the Member Assembly that took place at the Fondation Meriwux (Annecy, France) in February 2020. **Malik Peiris** is the **Coordinator of the Theme-based Research Scheme**: "Viral, host and environmental determinants of influenza virus transmission and pathogenesis", which has been awarded a HK$75 million grant. This large-scale multidisciplinary project, which aims at enhancing global public health by identifying the viral and host determinants of influenza virus transmission and pathogenesis leading to evidence-based interventions, will end in 2020. **Malik Peiris** continues to serve on a number of **WHO working groups** in relation to both avian and swine origin influenza virus and is the **Co-Director of the WHO H5 Reference Laboratory** at HKU. **Roberto Bruzzone** is an **Associate Editor of the Virology Journal** and **Member of the International Affairs Committee of the American Society for Cell Biology**. **Group Leaders** have actively participated in major international conferences (Keystone Symposia, EMBO meetings, Gordon Research Conferences) and are regularly invited to give lectures and seminars at major universities and research institutions worldwide.

3. Progress Report

3.1 Chris Ka Pun MOK Lab

Main Objectives and Strategy

The major objective of our group is to understand the interplay between the host adaptive immunity and the viral determinants of respiratory viruses such as influenza viruses and coronaviruses using a combination of clinical, virological, immunological and structural approaches. We have established a long-term collaboration with the teams of Jincun Zhao (Guangzhou Medical University, PR China) and Ian Wilson (Scripps Research Institute, USA) to investigate T cell and B cell adaptive immunity in humans upon infection/vaccination with influenza virus. We are investigating how the experience of a previous infection influences the immune response against a subsequent infection by a similar virus. In addition, we are also interested to understand the viral factors that contribute to the pathogenicity of zoonotic infection by avian influenza viruses or coronaviruses in mammalian host.

Achievements and Ongoing Research

Preventing an antigenically disruptive mutations in egg-based H3N2 seasonal influenza vaccines by mutational incompatibility [Funding: HMRF]

Egg-based seasonal influenza vaccines are the major preventive countermeasure against influenza virus. However, their effectiveness can be compromised from antigenic changes arising from egg-adaptive mutations on influenza hemagglutinin (HA). We have shown that the L194P mutation frequently occurs in egg-based H3N2 vaccine seed strains and significantly alters HA antigenicity and its immunogenicity.

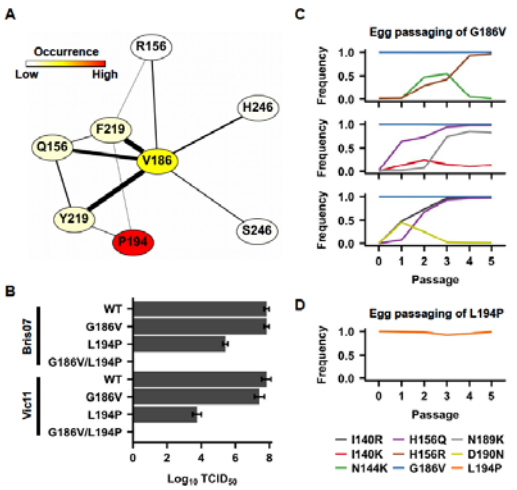


Figure 1. Incompatibility of egg-adaptive mutations HA L194P and G186V. (**A**) A network diagram was constructed that describes the co-occurrence of egg-adaptive mutations, and was based on the sequence analysis of egg-passaged human H3N2 viruses in the GISAID database. Each node represents an egg-adaptive mutation. Two mutations that co-occur more than once are connected by an edge. The width of the edge is proportional to the co-occurrence frequency. The occurrence frequency of each egg-adaptive mutation is color-coded. Egg-adaptive mutations that do not co-occur with other egg-adaptive mutation are not shown. (**B**) The fitness effects of different mutants were examined by a virus rescue experiment. The titer was measured by $TCID_{50}$. Error bars indicate the standard deviation of three independent experiments. (**C**, **D**) Bris07 HA G186V mutant virus **(C)** and Bris07 HA L194P mutant virus (**D**) were passaged five rounds in eggs. The emergence of egg-adaptive mutations in the receptor-binding domain (HA1 residues 117-265) was monitored by next-generation sequencing. Only those mutations that reached a minimum of 10% occurrence frequency are plotted. Three independent passaging experiments were performed for Bris07 HA G186V mutant virus in (**C**) and one passaging experiment was performed for Bris07 HA L194P mutant virus in (**D**). Passage 0 indicates the input virus.

We demonstrated that emergence of L194P during egg passaging can be impeded by pre-existence of a G186V mutation, revealing strong incompatibility between these mutations (**Figure 1**). We further demonstrated that the HA antigenicity and the immunogenicity were disrupted by the HA-L194P mutation from the sera samples collected from the mice immunized by the H3N2 viruses carrying different mutations (**Figure 2**). While the HA-L194P mutation is frequently observed in the H3N2 vaccine strains over the years, we further hypothesize that different H3N2 strains carrying HA-G186V mutation can also prevent the occurrence of HA-L194P during the passage of the vaccine seed strain in embryonated chicken eggs. We postulate that pre-introduction of G186V in the vaccine seed strain will have minimal effect on antigenicity and at the same time, permit high virus replication for the vaccine production in eggs.

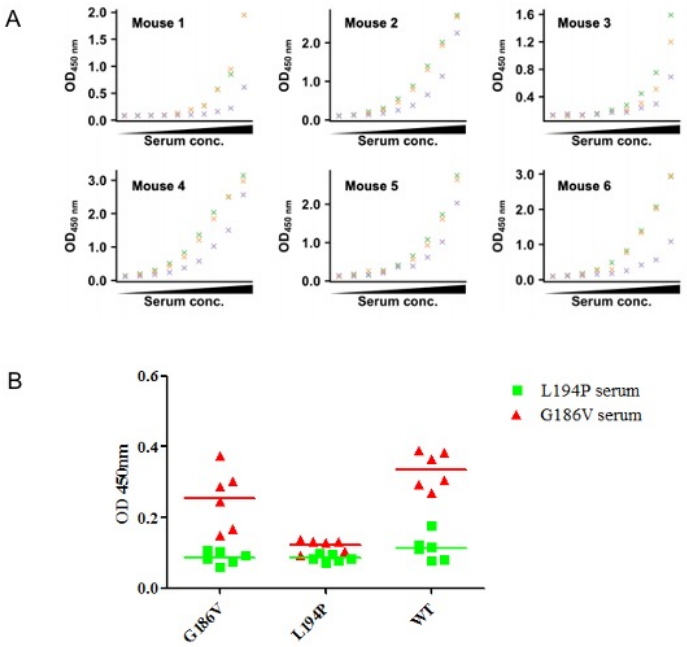


Figure 2. Antigenic and immunogenicity characterization of G186V and L194P. (**A**) Mice were immunized with Bris07 WT virus (6:2 reassortant on a PR8 backbone). Sera from immunized mice were collected after 14 days and tested for binding to WT, G186V mutant, and L194P mutant of recombinant Bris07 HA using ELISA. Each line represents one serum sample. (**B**) Mice were immunized with Bris07 carrying HA-L194P or HA-G186V for 14 days. Sera from immunized mice were tested for binding to recombinant HA of Bris07 WT, G186V mutant, and L194P mutant using ELISA.

Determination of the pathogenicity of MERS-CoV isolated in Africa

[Funding: HMRF)

MERS coronavirus (MERS-CoV) has been identified by WHO as one of eight emerging infections of greatest concern for global public health for which there is an urgent need to develop counter-measures. Emerging viruses transmitting via the respiratory route are of greatest concern, because of the rapidity they may spread worldwide. The source of MERS-CoV zoonotic infection is dromedary camels. Although >70% of MERS-CoV-infected dromedaries are found in Africa, no human infections have been reported from Africa. However, low MERS-CoV sero-prevalence in camel abattoir workers and those living in camel herding areas has been reported, suggesting that infection may be taking place. We have hypothesized that viral genetic diversity may be associated with reduced pathogenic potential. We found that MERS-CoV in Africa belong to clade C and are phylogenetically distinct from those in the Arabian Peninsula (clade A and B). We further

compared the phenotypic characteristics of MERS-CoV from East Africa, with viruses from Saudi Arabia, Korea and West / North Africa, using a well-established experimental model of transgenic mice expressing human Dpp4, the MERS-CoV receptor. We found that the viruses isolated from Saudi Arabia/Korea showed different replication kinetic in the lung of the mice when compared to those isolated from Africa. These results demonstrate that, in vivo, MERS-CoV from Africa have significantly lower replication competence in the lungs of hDPP4 transgenic mice, extending in vitro observations. Overall, these findings will allow us to understand the range of pathogenic potential to MERS-CoV and, in future studies, to identify the viral genetic determinants of increased pathogenicity observed with the current clade B viruses found in the Arabian Peninsula.

Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections [Funding: NSFC/RGC Joint Research Scheme 2018/19]

A novel coronavirus, SARS-CoV-2, has emerged as the cause of severe pneumonia and has been recognized by the World Health Organization as a public health emergency of international concern. Understanding the specificity of antibody responses to SARS-CoV-2 and any cross-reactivity with SARS-CoV and other coronaviruses underpins the development of effective vaccines as well as options for passive immunotherapy. We found that cross-reactive antibody responses between SARS-CoV-2 and SARS-CoV are elicited during SARS-CoV-2 infection, mostly but not exclusively targeting the regions of the spike (S) protein other than the receptor-binding domain (RBD). Our work shows that antibody responses in the SARS-CoV-2 infected patient cohort are generated to both S protein and RBD in the majority of the patients. Furthermore, cross-reactivity with SARS-CoV can be detected in these plasma samples as well as in mice studies. These cross-reactive antibody responses mostly target non-RBD regions. Consistently, higher sequence conservation is found between the S2 domains of SARS-CoV-2 and SARS-CoV (90% amino-acid sequence identity) as compared to that of their RBDs (73% amino-acid sequence identity). Nonetheless, some SARS-CoV-2-infected patients were able to produce cross-reactive antibody responses to SARS-CoV RBD. While cross-reactive antibody binding responses to both SARS-CoV-2 and SARS-CoV S proteins appears to be relatively common in this cohort, cross-neutralizing responses are rare. Such identification of cross-neutralizing epitopes on the coronavirus S protein will be important for vaccine development, not only against SARS-CoV-2, but also for a more universal coronavirus vaccine analogous to those currently in development for influenza virus.

Publications

1) **Lv H**, Wu NC, Tsang OT, Yuan M, Perera RAP, Leung WS, **So RT**, Chan JMC, **Yip GK**, Chik TSH, **Wang Y**, Choi CYC, **Lin Y**, **Ng WW**, Zhao J, Poon LLM, ***Peiris JSM***, Wilson IA, **Mok CKP** (2020) Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections. *Cell Rep*, in review; *bioRxiv* doi: https://doi.org/10.1101/2020.03.15.993097.

2) **Mok CKP**, Zhu A, Zhao J, Lau EHY, Wang J, Chen Z, Zhuang Z, **Wang Y**, Wang W, Tan W, **Liang W**, Oladipo JO, Kuranga SA, **Peiris M**, Zhao J (2020) Specific T cell responses provide evidence of MERS coronavirus infection in people with occupational exposure to dromedary camels in Nigeria. *Lancet Infect Dis*, in revision.

3) Perera RAP, **Mok CKP**, Tsang OTY, **Lv H**, Ko RLW, Wu NC, Yuan M, Leung WS, Chan JMC, Chik TSH, Choi CYC, Leung K, Chan KH, Chan KCK, Li KC, Wu JT, Wilson IA, Monto AS, Poon LLM, *Peiris M* (2020) Serological assays for SARS-CoV-2. *Eurosurveill*, in press.

4) ***Jahan AS***, Biquand E, Muñoz-Moreno R, ***Le Quang A***, **Mok CKP**, ***Wong HH***, ***Teo QW***, ***Valkenburg SA***, Chin AWH, Poon LLM, Te Velthuis A, Garcia-Sastre A, Demeret C, ***Sanyal S*** (2020) OTUB1 is a key regulator of RIG-I-dependent immune signaling and is targeted for proteasomal degradation by influenza A NS1. *Cell Rep* **30**:1570–1584.

5) Wang Y, Li X, Liu W, Gan M, Zhang L, Wang J, Zhang Z, Zhu A, Li F, Sun J, Zhang G, Zhuang Z, Luo J, Chen D, Qiu S, Zhang L, Xu D, **Mok CKP**, Zhang F, Zhao J, Zhou R, Zhao J (2020) Discovery of a subgenotype of human coronavirus NL63 associated with severe lower respiratory tract infection in China, 2018. *Emerg Microbes Infect* **9**:246-255.

6) Yuan M, Wu NC, Zhu X, Lee CCD, **So RTY**, **Lv H**, **Mok CKP**, Wilson IA (2020) A highly conserved cryptic epitope in the receptor-binding 4 domains of SARS-CoV-2 and SARS-CoV. *Science*, Apr 3:eabb7269. doi: 10.1126/science.abb7269.

7) Chan LLY, Hui KPY, Kuok DIT, Bui CHT, Ng KC, **Mok CKP**, Yang ZF, Guan W, Poon LLM, Zhong N, ***Peiris JSM***, Nicholls JM, Chan MCW (2019) Risk assessment of the tropism & pathogenesis of the highly pathogenic avian influenza A/H7N9 virus using ex vivo & in vitro cultures of human respiratory tract. *J Infect Dis* **220**:578-588.

8) Tang YS, Lo CY, **Mok CK**, Chan PK, Shaw PC. (2019) The extended C-terminal region of influenza C nucleoprotein is important for nuclear import and RNP activity. J Virol. pii: JVI.02048-18.

9) Wu NC, **Lv H**, Thompson AJ, Wu DC, **Ng WWS**, Kadam RU, Lin CW, Nycholat CM, McBride R, **Liang W**, Paulson JC, **Mok CKP**, Wilson IA. (2019) Preventing an antigenically disruptive mutation in egg-based H3N2 seasonal influenza vaccines by mutational incompatibility. *Cell Host Microbe* **25**:836-844.

Seminars and Invited Presentations

1) Chris Mok (2019) Guangzhou Medical University Annual Meeting, Guangzhou, PR China.

2) Chris Mok (2019) Outbreak Preparedness and Readiness in the Lancang Mekong Cooperation Region, Kunming, PR China.

Presentations at meetings

1) **Liang W**, **Lv H**, **Ng WWS**, **Mok CKP** (2019) Establishment of avian influenza virus/*Acinetobacter baumannii* co-infection model in mice. *Options for the Control of Influenza X*, Singapore (**Poster**).

2) **Lv H**, **Mok CKP** (2019 Preventing an antigenically disruptive mutation in egg-based H3N2 seasonal influenzavaccines by mutational incompatibility. *The 2nd Science and Technology Summit for Youth Scholar on Virology*, Wuhan, PR China (**Oral**).

3) **Lv H**, Wu NC, Paulson JC, Wilson IA, **Mok CKP** (2020) Preventingan antigenically disruptive mutation in egg-based H3N2 seasonal influenzavaccines by mutational incompatibility. *New Horizons in B Cell Biology, Cell Press Symposium*, Shanghai, PR China (**Poster**).

Teaching

1) Chris Mok (2019) 15th HKU-Pasteur Virology Course, The University of Hong Kong, Hong Kong SAR (*Course Director and Tutor*).

2) Chris Mok (2019) Health Research Project, The University of Hong Kong, Hong Kong SAR (*Tutor*).

3) Chris Mok (2019) Introduction to the Art and Science of Medicine – Problem Based Learning (MBBS Year 1), The University of Hong Kong, Hong Kong SAR (*Tutor*).

4) Chris Mok (2019) Haematology/Immunology System – Problem Based Learning (MBBS Year 2), The University of Hong Kong, Hong Kong SAR (*Tutor*).

5) Chris Mok (2019) OITF Course: Introduction to Outbreak Investigation and Response, Institut Pasteur du Cambodge, Cambodia (*Lecturer and Tutor*).

Collaborations

1) **Nan-Shan Zhong, Jin-cun Zhao, Zi-Feng Yang** (State Key Laboratory of Respiratory Disease, Guangzhou, PR China): Clinical and laboratory studies on emerging infectious diseases in Guangzhou.

2) **Michael Chan** (School of Public Health, The University of Hong Kong) and **Ron Fouchier** (Erasmus Medical Center, The Netherlands): Pathogenicity and transmissibility of influenza virus.

3) **Ian Wilson, Nicholas Wu (**The Scripps Research Institute, USA): Bioinformatic and structural study on influenza research.

Funding

1) Preclusion of an antigenically disruptive mutation in egg-based H3N2 seasonal influenza vaccines by mutational incompatibility (**Principal Investigator**; Health and Medical Research Fund – Ends: 04/2022).

2) Investigation on the immunological cross-protection between different human coronaviruses (**Co-Investigator**; National Natural Science Foundation of China/Research Grants Council Joint Research Scheme 2018/19 – Ends: 12/2022).

3) Evaluation of anti-influenza properties of antrafenine and its analogs (**Co-Investigator**; Health and Medical Research Fund – Ends: 05/2021).

4) Investigation on a pinanamine derivative as an antiviral agent against influenza A virus infection (**Principal Investigator**; Health and Medical Research Fund – Ends: 12/2020).
5) Comparison of the transcriptomic profiles between lung and peripheral blood in mice infected by avian influenza virus (**Principal Investigator**; HKU – Seed Funding for Basic Research – Ends 06/2020).
6) Viral, Host and Environmental Determinants of Influenza Virus Transmission and Pathogenesis (**Co-Investigator**; Research Grants Council/Theme-based Research Scheme – Ends: 06/2020).
7) Importin-alpha protein as the host determinant of influenza B virus replication in human (**Principal Investigator**; HKU – Seed Funding for Basic Research – Ends 04/2019).
8) Building Up Reverse Genetics Technique and Production of Recombinant Influenza Viruses (**Co-Investigator**; Korea Research Institute of Bioscience and Biotechnology (KRIBB), Korea – Ends: 12/2019).
9) Study of Avian Influenza Variation Based on International Collaboration (**Co-Investigator**; Wonkwang University acting through Zoonosis Research Centre, Korea – Ends: 12/2019).

Personnel

Name	Position
Chris MOK	Research Assistant Professor
Tomas LV	PhD student
Ray SO	PhD student
Garrick YIP	MPhil student
Yihan LIN	MPhil student
Weiwen LIANG	Research Assistant
Wilson NG	Research Assistant
Yiquan WANG	Research Assistant
Max Van DIEPEN	Student Intern, Erasmus Medical Center Rotterdam, The Netherlands (7 October 2019 to 1 November 2019)
Adrian LEE	Student Intern, Ngee Ann Polytechnic, Singapore (4 March 2019 to 22 June 2019)
Wing Kei WONG	Student Intern, Hong Kong Institute of Vocational Education, Hong Kong SAR (2 July 2019 to 30 August 2019)
Chak Man HUI	Student Intern, Hong Kong Institute of Vocational Education, Hong Kong SAR (2 July 2019 to 30 August 2019)
Yin Wing CHAN	Student Intern, Hong Kong Institute of Vocational Education, Hong Kong SAR (2 July 2019 to 30 August 2019)
Man Kit LIAO	Student Intern, Hong Kong Institute of Vocational Education, Hong Kong SAR (2 July 2019 to 30 August 2019)

3.2 Sumana SANYAL LAB

Main Objectives and Strategy

The main objectives of the lab are to combine methods of molecular biology and immunology to address aspects of host-pathogen interactions. Using influenza and dengue as model systems, we aim to determine the identity and function of specific host factors that are exploited by these viruses to complete their intracellular life cycle. We also investigate counterstrategies employed by the host – either through upregulation of immune signaling pathways or expression of virus restriction factors – in order to prevent virus infection at various steps, including replication, assembly and release. Among other factors, we are particularly interested in ubiquitin and ubiquitin-like post-translational modifiers of protein function, such as ISG15 that play a significant role in modulating different pathways, most of which are innate signaling pathways such as RIG-I, TLR7 and inflammasome activation. Our major research projects are listed below.

Achievements and Ongoing Research

Since joining HKU-PRP in November 2013, we have expanded on projects that were initiated at the Whitehead Institute/MIT while creating new directions at the current setting. We have successfully submitted grant applications to RGC/GRF, HMRF as well as Transversal Research Grants (PTR) of the Institut Pasteur. Our research has been published in Proc Natl Acad Sci USA, J Biol Chem, Cell Host Microbe, Cell Rep and also summarized in invited review articles in the Frontiers series.

Characterization of host factors involved in virus infections [Funding: RGC/GRF; PTR-Institut Pasteur; HMRF]

A molecular understanding of host cellular factors involved in virus infections is crucial not only to provide novel insights into pathways hijacked by them, but also for development of effective antimicrobials against such pathogens. Identification of host factors that can be targeted for developing novel anti-viral compounds has the additional benefit of avoiding potential resistance acquired in viruses by mutation and selection.

(a) ***Exploitation of lipid metabolic pathways in flavivirus infection:*** The complexity of the assembly and release of dengue virus provides a potentially rich source of host targets for interference. Propagation of dengue virus (DENV), Zika virus (ZIKV) and other members of the family appears to involve extensive membrane and lipid remodeling to facilitate virus replication, trafficking, assembly and egress. However, we have been severely limited in our understanding of the role of fundamental biological pathways typically hijacked by flaviviruses. We recently discovered that Aup1 – a lipid droplet associated protein – is upregulated upon dengue infection. Dengue NS4A interacted with Aup1 to exploit its acyltransferase function that in turn induced lipophagy. In addition, the sterol regulatory element binding proteins were activated to induce *de novo* sterol and fatty acid biosynthesis. We are currently extending our findings with dengue virus to explore similarities and differences that exist in Zika.

(b) ***Role of Tsg101 in influenza virus infection:*** A major response of mammalian cells to viral infections is through upregulation of the interferon type I and II pathways. Viruses in turn implement counter strategies through either inhibition of IFN response or by

activation of proteins that inhibit the function of interferon-stimulated genes (ISGs). The function of Tsg101 appears to be dictated by several post-translational modifications including ISG15, phosphorylation and ubiquitylation. Using a combination of CRISPR/Cas9 knockouts and protein interaction assays, we are currently exploring the functional relevance of these modifications during influenza infection, centered on (i)Tsg101 and (ii) MGRN1 - an E3-ligase that ubiquitylates Tsg101.

(c) ***Mechanism of Src-family kinase (SFK)-mediated signaling during flavivirus infections***: Amongst the host factors that facilitate egress of dengue virus particles through the secretory pathway are the KDELR, class-II Arfs and several Src-family kinases. We recently screened a number of SFKs to determine their impact on intracellular transport of dengue and Zika. Deficiency of Lyn through siRNA-mediated suppression as well as pharmacological inhibition had a significant impact on release of both dengue and Zika virus particles. We have elucidated the mechanism through which these SFKs activate an autophagy-dependent unconventional secretory process that is specifically triggered upon infection and facilitates release of infectious viral progenies.

Targeting deubiquitylases as therapeutic strategies against viral infections [Funding: HMRF; PTR-Institut Pasteur]

Influenza virus is responsible not only for annual epidemics, but also for frequent outbreaks of pathogenic avian flu strains that have become a serious public health issue worldwide. The ubiquitylation machinery is frequently exploited by a number of pathogens either to masquerade as host proteins or to inhibit immune signaling cascades. We have employed a chemoenzymatic strategy to identify deubiquitylating enzymes (DUBs) that are specifically activated upon influenza infection and are currently investigating the role of these DUBs. Our ongoing studies involve characterization and pharmacological inhibition of these DUBs in order to attenuate influenza infection. Our current data support the hypothesis that influenza takes advantage of DUBs to suppress signaling pathways such as RIG-I and inflammasome activation that require ubiquitin modification for recruitment of downstream effectors. We also propose to test small molecules that target these DUBs both in vitro and in vivo. Our published data describe the mechanism of OTUB1-dependent innate immune responses, which is countered by influenza A NS1.

Regulation of immune signaling by deubiquitylases [Funding: RGC/GRF; HMRF]

Signaling cascades require tight control over activation and suppression to maintain downstream activities for appropriate durations. Such regulation is often executed by post-translational modifications such as phosphorylation and ubiquitylation. We are interested in deciphering the role of deubiquitylases (DUB) in the context of a number of innate and adaptive immune responses. We have identified DUBs that are either specifically recruited or inactivated in the T-cell receptor-signaling cascade, presumably to optimize the length and magnitude of downstream activities. Usp12, which resides in the nucleus, is redistributed to the cytosol in a TCR stimulus specific manner. In the absence of Usp12 surface expression of the TCR is drastically reduced. This phenotype is recapitulated upon inhibition of Usp12 translocation from the nucleus to the cytosol. Using proximity based labeling we identified LAT and Trat1 to be substrates of Usp12.

We are also pursuing a set of DUBs, including Usp4, identified through functional screening in mouse T-lymphocytes that function to suppress TCR signaling.

Publications

1. **Li MY**, **Naik TS**, **Siu LYS**, Acuto O, Spooner E, Wang P, Yang X, Lin Y, ***Bruzzone R***, Ashour J, **Sanyal S** (2020) Activation of Src-family kinases orchestrate secretion of flaviviruses by targeting mature progeny virions to secretory autophagosomes. *Nat Microbiol*, in revision; *bioRxiv* doi: https://doi.org/10.1101/2020.01.12.903062.
2. **Jahan AS**, Biquand E, Munoz R, **Le Quang A**, **Mok CK**, **Wong HH**, **Teo Q**, ***Valkenburg SA***, Chin AWH, Poon LLM, te Velthuis A, García-Sastre A, Demeret C, **Sanyal S** (2020) OTUB1 functions as a ubiquitin sensor for RIG-I activation and is targeted for proteasomal degradation by Influenza A virus NS1. *Cell Rep* **30**:1570–1584.
3. **Wong HH**, **Sanyal S** (2019) Manipulation of autophagy by (+) RNA viruses. *Semin Cell Dev Biol*, in press.

Seminars and Invited Presentations

1. Sumana Sanyal (2019) Department of Cell Biology and Infection of the Institut Pasteur Retreat, San Feliu de Guixols, Spain.
2. Sumana Sanyal (2019) Pasteur Network Fighting Emerging Threats, Seoul, Korea.
3. Sumana Sanyal (2019) Icahn School of Medicine at Mt Sinai, New York City, USA.

Presentations at Meetings

1. **Ho J, Sanyal S** (2020) Zika Virus Infection can Induce MHC-I Downregulation on the Cell Surface. *Third International Conference on Zika and Aedes Related Infections*, Washington DC, USA **(Poster).**
2. **Wong HH, Sanyal S** (2020) Investigating Host Components Utilised for Translation of Zika Virus Proteins. *Third International Conference on Zika and Aedes Related Infections, Washington DC*, USA **(Poster).**
3. **Li MY**, **Naik TS**, **Siu L**, Porciello N, Spooner E, Ashour J, Wang P, Yang X, Lin Y, ***Bruzzone R***, **Sanyal S** (2019) Activation of Src-family kinases orchestrate secretion of flaviviruses by targeting mature progeny virions to secretory autophagosomes. *2019 ASCB/EMBO Meeting*, Wahington DC, USA (**Poster**).
4. **Teo Q**, **Sanyal S** (2019) USP25 Functions as a Restriction Factor during Influenza A Virus Infection. *EMBO Conference: Ubiquitin and Ubiquitin-like Modifiers*, Cavtat, Croatia (**Poster**).
5. **Teo Q**, **Sanyal S** (2019) Roles of USP25 during Influenza A Virus Infection. *Options for the Control of Influenza X*, Singapore (**Poster**).

Teaching

1. Sumana Sanyal (2019) Basic Metabolism (BSc Biochemistry Year 3 students) The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
2. Sumana Sanyal (2019) Essentials in Proteomics (BBMS Year 3) The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
3. Sumana Sanyal (2019) Recent Advances in Biotechnology (MMPH) The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
4. Sumana Sanyal (2019) Cancer Screening – Problem Based Learning (MBBS Year 4 students) The University of Hong Kong, Hong Kong SAR (*Tutor*).
5. Sumana Sanyal (2019) Introduction to the art and science of medicine – Problem Based Learning (MBBS Year 1 students) The University of Hong Kong, Hong Kong SAR (*Tutor*).
6. Sumana Sanyal (2019) Endocrine and Reproductive Systems – Problem Based Learning (MBBS Year II students) The University of Hong Kong, Hong Kong SAR (*Tutor*).
7. Sumana Sanyal (2019) 9th HKU-Pasteur Cell Biology Course, The University of Hong Kong, Hong Kong SAR (*Course Director, Lecturer and Tutor*).

Collaborations

1. **Adolfo García-Sastre** (Mount Sinai School of Medicine, New York, USA): Function of ubiquitin like modifiers and their mode of restricting RNA virus infections.
2. **Leo Poon** (The University of Hong Kong, Hong Kong SAR): Functional characterization of PB2 ubiquitylation.
3. **Christoph Thiele** (LIMES Institute, University of Bonn, Germany): Role of lipid droplets in virus infections.
4. **Caroline Demeret** (Institut Pasteur, Paris, France): Role of deubiquitylases in influenza virus infections.
5. **Joseph Ashour** (Boehringer Ingelheim/Mount Sinai School of Medicine, New York, USA): Manipulation of host factors in influenza and dengue infections.
6. **Hidde Ploegh** (The Whitehead Institute for Biomedical Research, MIT, Cambridge, MA, USA): Studying host factors and their mechanism of function during influenza virus biogenesis centered on ubiquitylation.

Funding

1. Targeting E3 ubiquitin ligases as a therapeutic intervention for cytotoxic T-cell killing of Dengue virus infected cells (**Principal Investigator**; Health and Medical Research Fund – Ends: 2022).
2. Altered protein acylation regulates mitochondrial function and viral replication during flavivirus infections (**Principal Investigator**; Research Grants Council/General Research Fund – Ends: 06/21).

3. Croucher Foundation Start Up Funds (**Principal Investigator**; Croucher Foundation – Ends: 02/2020).
4. Regulation of the intracellular life cycle of Influenza A virus by targeting the cellular E3 ubiquitin-protein ligase MGRN1 (**Co-Investigator**; Health and Medical Research Fund – Ends: 04/2020).
5. Viral Host and Environmental Determinants of Influenza virus transmission and pathogenesis (**Co-investigator**; Research Grants Council/Theme-based Research Scheme – Ends: 06/2020).
6. Host lipid metabolism as a potential target for Zika antiviral therapy (**Co-Investigator**; Health and Medical Research Fund – Ends: 06/2020).
7. A chemical proteomics-based strategy for target discovery in flavivirus infections (**Principal Investigator**; Health and Medical Research Fund – Ends: 08/2020).
8. Targeting lipid droplet metabolism as therapeutic intervention during dengue virus infections (**Principal Investigator**; Health and Medical Research Fund – Ends: 06/2019).
9. Regulation of dengue virus life cycle by KDEL receptor-dependent signaling pathway: a new target to interfere with viral infection and pathogenesis (**Co-Investigator**; Health and Medical Research Fund – Ends: 08/2019).
10. Mechanism of OtuB1 mediated regulation of influenza virus infection (**Principal Investigator**; Research Grants Council/General Research Fund – Ends: 12/2019).
11. Role of Usp4 in T cell receptor signaling (**Principal Investigator**; HKU – Seed Funding for Basic Research – Ends 12/2019).
12. Perturbation of cellular cholesterol homeostasis during virus infections (**Principal Investigator**; HKU – Seed Funding for Basic Research – Ends 12/2019).

Personnel

Name	Position
Sumana SANYAL	Assistant Professor
Yun LAN	Postdoctoral Fellow
Mingyuan LI	Postdoctoral Fellow
Qiwen TEO	PhD Student
Ho Him WONG	PhD Student
Julian HO	MPhil Student
Lewis SIU	Senior Technician
Akhee Sabiha JAHAN	Research Assistant I (Contract ended 30 June 2019)
Lynn CHEN	Research Assistant I (Contract ended 30 June 2019)
Julia FERNANDO	Research Assistant II
Leslie LAU	Research Assistant II
Trupti NAIK	Research Assistant II (Contract ended 31 July 2019)
Sophie VAN LEUR	Student Intern, Erasmus Medical Center, Rotterdam, The Netherlands (29 November 2018 to 28 July 2019), Research Assistant II (January 1 2020)
Sun Man KWOK	Student Intern, The University of Hong Kong, Hong Kong SAR, (24 June 2019 to 20 August 2019)
Vrinda MATHUR	Student Intern, The University of Hong Kong Science and Technology, Hong Kong SAR, (1 June 2019 to 20 August 2019)
Karen Wai Sze CHAN	Executive Assistant

3.3 Hein Min TUN LAB

Main Objectives and Strategy

Our group uses conventional microbiology and molecular biology techniques, cutting-edge sequencing technologies, coupled with bioinformatics, statistical and epidemiological approaches to study: 1) the composition, function, and dynamics of human and animal microbiomes in health and disease; and 2) to monitor antimicrobial resistance (AMR) bacteria and resistome in humans, animals, and the environment using a holistic One Health approach. Our goal is to contribute to improving scientific understanding on the impact of microbiome and AMR in public health.

Achievements and Ongoing Research

In the year 2019, there were several achievements within the group. Hein Min Tun's presentation was awarded "the Best Presentation Award" at AllerGen 2019 Research Conference (Toronto, Canada). He was also honored with a visiting fellowship by the National Center for Infectious Diseases (NCID) and National University of Singapore (NUS) and he was invited to give lectures at NCID, NUS and National University Hospital. Several proposals have been funded by the HMRF Fellowship Scheme, Research Impact Fund and PTR – Transverse Research Program of the Institut Pasteur in Paris. Hein Min Tun was also invited by USDA and OIE to give a keynote lecture at 3rd Alternatives to Antibiotics (ATA) Conference (Bangkok, Thailand) and also asked to become a member of STAR-IDAZ working group on AMR and the development of ATA. He was also elected as the only young scientist member to join the Scientific Steering Committee of the Institute Pasteur International Network (COS-RIIP).

Unwanted Souvenirs for Hong Kong Travelers: A prospective epidemiological approach to study the emergence and dissemination of antimicrobial resistance

Antimicrobial resistance (AMR) constitutes an increasing health hazard worldwide. Recently, the World Health Organization produced a global map of AMR, warning that a 'post- antibiotic' world could soon become reality. Drugs that were once lifesavers are now useless and treatment of many infectious diseases now relies on just one or two drugs. Furthermore, AMR jeopardizes the achievements of modern medicine, since the success of interventions such as organ transplantation, chemotherapy and major surgery depends on effective antimicrobial agents for prevention and treatment of infections. With a dearth of novel antibiotics in the pipeline, the conservation of existing ones is imperative. Adequate global surveillance of AMR is a prerequisite for informing global strategies, monitoring the effectiveness of interventions and detecting new trends and threats. Despite successful regional surveillance programs in Europe, North America, and Australia, global surveillance of AMR generally is neither coordinated nor harmonized comprising the ability to assess and monitor the situation. Moreover, many low and middle-income countries in Africa and Asia, often with a high AMR prevalence, lack a surveillance programs entirely. Last but not least, current national and regional surveillance programs are often based on samples taken from patients with severe (nosocomial) infections neglecting the AMR problem in the community. Therefore, we

should aim for alternative ways to monitor AMR around the world in its full breadth in a standardized and flexible fashion.

The extensive overuse and misuse of antibiotics in both humans and animals is fueling AMR, especially in, but not limited to, South (East) Asia. The exponential increase in international travel to these regions may substantially contribute to the emergence and spread of AMR, since it allows resistant bacteria or bacterial mobile genetic elements (MGEs) carrying resistance genes (e.g. plasmids) to be rapidly transported between regions. The intercontinental spread of novel resistance genes via travelers has been demonstrated by the reported transfer of Enterobacteriaceae with New Delhi metallo-beta-lactamase-1 from the Indian subcontinent to Europe. Additionally, case reports of infections with KPC-, VIM-, and OXA-48-producing Enterobacteriaceae in developed countries have been associated with visiting and being hospitalized in endemic areas such as the USA, Greece and Israel for KPCs, Greece for VIMs and the Middle East for OXA-48. The extent to which foreign travel poses a risk for the acquisition of AMR remains largely unknown, as the presence of resistant bacteria in the normal human microbiota following travel remain undetected unless they cause manifest infections.

The gastrointestinal tract is an open system, which every day encounters myriad of bacterial acquisitions originating from the environment (e.g. from food, water, soil, and other humans or animals). These incoming bacteria acquired in countries with a high prevalence of antimicrobial resistance often harbor AMR genes. In case of opportunistic pathogens of environmental or food-borne origin, such AMR bacteria can pose a direct threat to the host. Alternatively, these incoming microbes might transfer their resistance elements through horizontal gene transfer to the indigenous microbial communities. Next to this lateral gene transfer, AMR microorganisms can also spread from the traveler to other family members and beyond through the fecal-oral route. Travelers can therefore be viewed as interactive biological units who pick up, process, carry and drop off microbial genetic material. Consequently local emergence of AMR can rapidly become a worldwide health problem.

To date, only two studies have been published analyzing geographical differences in the human resistome by means of sequence-based metagenomics. Both cross-sectional studies showed strong correlations between antibiotic consumption and the abundance and type of resistance genes on a population level, clearly proving the strength of resistome analyses. In particular, it remains unknown to what extent traveling to geographic areas with high rates of AMR affects one's resistome. Moreover, information on AMR in countries with a lack of surveillance, like many countries on the African and Asian continent, is currently missing. The proposed project provides a unique opportunity to prospectively study the shifts in the resistome of Hong Kong travelers following travel to different countries. At the beginning of 2018 December, we launched the "Hong Kong Traveler Cohort" by sending the recruitment information to HKU students and staffs via email or posting flyers around the campus. After sending out the first recruitment email, a total of 113 travelers enrolled in the study. rom our pilot cohort, we have generated a manuscript based on AMR and Microbiota data of 90 travelers. In our study, we identified travel associated risk factors for the acquisition of ESBL bacteria and other AMR genes, which are also influenced by the diversity of gut microbiota. This led to develop a model to predict both acquisition and decolonization of AMR bacteria and genes using baseline microbiota and traveler associated risk factors.

The impact of early-life antibiotic exposure on infant gut microbiome and resistome

Neonates are exposed to antibiotics both before and after birth, often empirically due to risk factors for infection. Surprisingly limited data is available on the impact of early life antibiotics in the harboring antibiotic resistance (AR) genes by the gut microbiota. A proof-of-concept study was employed to examine the impact of early life exposure to antibiotics on the gut resistome of 3 months old infants. Among ten randomly selected infants, five infants were exposed to antibiotics/antifungal either at birth or during their first 3 months of life. History of antibiotic exposure was obtained from hospital records and/or questionnaires. Fecal samples were collected at 3 months for genomic DNA extraction and followed by shotgun metagenomics sequencing. Sequence data were subjected to quality check, trimming and then annotation based on AR genes database (CARD). The gut metagenome of infants harbored diverse AR genes mainly genes involved in RND, ABC, and MFS efflux pumps, tetracycline resistant, beta-lactams resistant, and polymyxin resistant. However, unsupervised clustering of AR genes population showed a clear separation between antibiotic-exposed infants and antibiotic-naïve infants, with the exception that an infant with re-hospitalisation history, and one with history of antifungal use are clustered into high AR gene abundance group although they did not receive antibiotics. Moreover, the relative abundance of AR genes was significantly higher in the infant group which mostly had exposed to antibiotics in their early life ($P<0.01$). Our study indicates that early life exposure to antimicrobial drugs contributes selective pressure for the development of resistance genes. The presence of AR genes in antibiotic-naïve infants also suggested that the acquisition of antimicrobial resistance can be impacted by maternal and environmental microbes during and after delivery.

Antimicrobial resistant E. coli recovered from aero- and hydro-environment

Antimicrobial resistance (AMR) is a threat to public and animal health on the global scale. The origin of the genes associated with resistance has long been unknown. There is a growing body of evidence, however, demonstrating that environmental bacteria are resistant to a multitude of antibiotic substances and that this environmental reservoir of AMR is still growing. The analysis of the genomes of bacterial pathogens indicates that they have acquired their resistance profiles by incorporating different genetic elements through horizontal gene transfer. The ancestors of pathogenic bacteria, as well as the origin of resistance determinants, lay most likely in the environmental microbiota. Indeed, there is some evidence that at least some clinically relevant resistance genes have originated in environmental bacterial species. Thus, feasible measures are required to reduce the risks posed by AMR genes and resistant bacteria that occur in the environment. Our study aims to demonstrate antimicrobial resistant (AMR) phenotypes of *E. coli* isolated from air-conditioner and seawater as a preliminary data to strengthen environmental surveillance of AMR bacteria. Dust samples from air conditioner (n=12) and seawater samples (n=6) were collected and subjected for *E. coli* isolation. Briefly, swabs from air conditioning filter and seawater filtrated membranes were pre-enriched with buffer peptone water (BPW) prior to isolation of Enterobacteriaceae on MacConkey agar and followed by specific identification of *E.coli* on selective Eosin-Methylene Blue (EMB) agar. Identified *E. coli* were tested for antimicrobial susceptibility using Kirby-Bauer

Disk Diffusion method according to Clinical and Laboratory Standard Institude (CLSI) guideline. A total of 12 antimicrobial agents including ampicillin (AMP), chloramphenicol (CHP), ciprofloxacin (CIP), norfloxacin (NOR), tetracycline (TET), gentamicin (GEN), amoxycillin-clavulanate (AMC), tobramycin (TOB), ceftaxidime (CAZ), cafaxitin (FOX), azithromycin (AZM), and meropenem (MEP) were examined in this study. A total of 12 *E. coli* isolates were identified and tested for antimicrobial susceptibility. 91.6% of isolates were phenotypically resistant to at least one antimicrobial compound and six resistance patterns were found. A MP resistant was the most prevalent resistant pattern, found in 50% of isolates, followed by AMP & TET resistance (16.6%). Three isolates showed resistance to at least three types of antimicrobial agents, thus they can be considered as Multidrug resistance (MDR) *E. coli*. Surprisingly, one out of three MDR isolates conferred resistance to MEP together with other antimicrobial agents such as AMP, AMC, TOB, CAZ, FOX, and AZM. Because MEP is an antimicrobial agent uncommon used for outpatients, and related to hospital. This raised the possibility of dissemination of hospital-related AMR bacteria in the environment. Our findings indicate that surveillance of AMR bacteria in Hong Kong's environment should be considered as an approach in One Health initiative of AMR surveillance.

Impact of outdoor nature-related activities on mental health and gut microbiota

Due to rapid urbanization, children today have fewer opportunities to interact with nature, causing greater risk for stress, depression and poor cognition. Outdoor nature-related activities can enhance human general well-being, as can be seen in demonstrably increased physical activity, a healthier diet, better sleep, and reduced stress. However, the underlying mechanisms are not fully delineated. A two-arm, randomised-controlled trial study was conducted with 54 preschool children, aged two to five, at the beginning of 2018. The preschool children were recruited to participate in 10 consecutive weeks of weekly sessions of the structured nature-related "Play&Grow" program. The parameters measured included Connectedness to Nature questionnaire for preschool children, age-specific mental health questionnaire, fecal serotonin levels and gut microbiota among children pre- and post-program. The intervention improved children's Connectedness to Nature and their responsibility towards it. The gut microbiome of children who participated in the intervention was improved, especially by stabilizing the abundance of Roseburia and the related fecal-serotonin level. Moreover, we also observed a reduction in the anger frequency among these children.

Publications

1. Drall KM, **Tun HM**, Morales-Lizcano NP, Konya TB, Guttman DS, Field CJ, Mandal R, Wishart DS, Becker AB, Azad MB, Lefebvre DL, Mandhane PJ, Moraes TJ, Sears MR, Turvey SE, Subbarao P, Scott JA, Kozyrskyj AL (2019) *Clostridioides difficile* Colonization Is Differentially Associated With Gut Microbiome Profiles by Infant Feeding Modality at 3-4 Months of Age. *Front Immunol* **10**:2866.
2. Tan Q, Orsso CE, Deehan EC, Triador L, Field CJ, **Tun HM**, Han JC, Müller TD, Haqq AM (2019) Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review. *Obes Rev* 10.1111/obr.12992.

3. **Tun HM**, *Bruzzone R* (2019) Early-life antibiotic exposure, gut microbiome, and colonization resistance. *J Health Sci Altern Med* **1**:1-5.

Seminars and Invited Presentations

1. Hein Min Tun (2019) National University of Singapore, Singapore.
2. Hein Min Tun (2019) National University Hospital, Singapore.
3. Hein Min Tun (2019) National Center for Infectious Diseases of Singapore, Singapore.
4. Hein Min Tun (2019) Childhood Infections and Pollution Consortium Workshop, Jaipur, India.
5. Hein Min Tun (2019) School of Life Sciences, Chinese University of Hong Kong, Hong Kong SAR.
6. Hein Min Tun (2019) The Rowett Institute, University of Aberdeen, United Kingdom.
7. Hein Min Tun (2019) 3rd Alternatives to Antibiotics (ATA) Conference, Bangkok, Thailand.

Presentations at Meetings

1. **Tun HM**, Konya T, Chari R, Field CJ, Guttman DS, Becker AB, Azad MB, Mandhane PJ, Morea TJ, Sears MR, Turvey SE, Subbarao P, Scott JA, Kozyrskyj AL (2019) Delayed gut microbiota maturation during infancy is associated with food sensitization in children. *AllerGen 2019 Research Conference*, Toronto, Canada (**Oral**).

Teaching

1. Hein Min Tun (2019) CMED6227 – Biological Basis of Disease (Master of Public Health), The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).

Collaborations

1. **Anita Kozyrskyj** (Department of Paediatrics, University of Alberta, Edmonton, Canada): Gut microbiota maturation during infancy.
2. **Andrea Haqq** (Department of Pediatrics, University of Alberta, Edmonton, Canada): Gut microbiota profile in children with Prader-Willi Syndrome
3. **John Penders** (Department of Medical Microbiology, Maastricht University, Maastricht, The Netherlands): Antimicrobial dissemination in international travellers.
4. **Tanja Sobko** (School of Biological Sciences, The University of Hong Kong, Hong Kong SAR): Impact of nature connectedness on gut microbiome and mental health of children.

Funding

1. Antimicrobial resistance comprehensive etiology Study (ACES) (**Co-Principal Investigator**; Research Grants Council/Research Impact Fund – Ends: 03/2022).
2. Cross-sectional study of antimicrobial use pattern, antimicrobial resistant pathogen and bacterial genomic association in urinary tract infection patients.(**Co-Investigator**; HKU – Seed Funding for Basic Research – Ends: 06/2021).
3. Bacterial carriage in the upper respiratory tract among community healthy subjects in Hong Kong and Guangzhou (**Co-Investigator**; HKU – Seed Funding for Basic Research – Ends: 01/2021).
4. Bacterial carriage in the upper respiratory tract among community healthy subjects in Hong Kong and Guangzhou (**Co-Investigator**; HKU – Enhanced New Staff Start-up Research Grant – Ends: 01/2021).
5. Computational imaging of the spatiotemporal distribution of forces in gut tissue: a study of the cross talk between cell mechanics, microbiome and infectious processes (**Principal Investigator**; Institut Pasteur – PTR 232 Grant – Ends: 09/2021).
6. Acquisition and persistence of antimicrobial resistance following travels to resource-limited countries: a multi-layered metagenomic epidemiological study (**Principal Investigator**; Health and Medical Research Fund – Ends: 11/2021).
7. Unwanted souvenirs for Hong Kong travelers: a prospective epidemiological approach to study the emergence and dissemination of antimicrobial resistance (**Principal Investigator**; HKU – Seed Funding for Basic Research – Ends: 04/2020).
8. Understanding aspects of common, complex chronic diseases in urban households: FAMILY Cohort. (**Co-Investigator**; Health and Medical Research Fund Commissioned Research – Ends: 06/2020).
9. A chemical-proteomics based approach for target discovery in Zika virus infection (**Co-Investigator**; Health and Medical Research Fund – Ends: 08/2020).
10. Intergenerational transmission of antimicrobial resistance and microbiome during labour at home vs hospital: a proof-of-principle study (**Principal Investigator**; Calmette & Yersin Intra-Pasteur Network Grant – Ends: 12/2019).
11. Childhood infections and pollution (CHIP): a UCL-HKU one health technology enabled citizen science approach to better manage and prevent infections in children in Jaipur's urban slums (**Co-Investigator**; HKU – UCL Strategic Partnership Fund – Ends: 12/2019).

Personnel

Name	Position
Hein Min TUN	Research Assistant Professor
Kanchana POONSUK	Postdoctoral Fellow
Darren Chak Lun CHAN	PhD Student
Suisha LIANG	PhD Student
Ye PENG	PhD Student
Gigi CHOW	Research Assistant II
Hilda ON	Research Assistant II
Bo YAN	Student Intern, Nanjing Medical University, PR China (10 March 2019 to 30 June 2019)
Qing WANG	Student Intern, Nanjing Medical University, PR China (10 March 2019 to 30 June 2019)
Zhen Ye SIN	Student Intern, University of Durham, United Kingdom (15 July 2019 to 30 August 2019)
Maurine MORGAN	Student Intern, Clermont-Auvergne University, France (24 June 2019 to 7 September 2019)
Sze Wang LI	Student Intern, The University of Hong Kong, Hong Kong SAR (1 July 2019 to 28 August 2019)

3.4 Sophie VALKENBURG Lab

Main Objectives and Strategy

The main objectives of the lab are to define immune correlates of protection for influenza viruses from infection and vaccination. Our research is centred on the role of protective heterologous T and B cell immunity in mouse and human systems, by investigating novel vaccines and immune correlates of protection for influenza. Our primary focus is to study adaptive immunity to influenza, and how this could be harnessed and optimized by vaccination to improve protection from diverse influenza virus infection. Hemagglutinin (HA)-specific antibodies can block influenza infection, whilst T cells recognize influenza-infected cells. A vaccine which ultimately combines antibody and T cell-based immunity for influenza will provide a full-proof immunological barrier to influenza infection, which our studies will ultimately help develop. Our major research projects, which aim to elucidate how cross-reactive T and B cell responses to influenza provide broad immunity, are listed below.

Achievements and Ongoing Research

Over the past year the research output from my team has consolidated, with a number of ongoing projects, submitted grants and international symposiums. Further movement within my research team saw the recruitment of a new research assistant (Glenn Hao LI) with the departure of another (Jodi CHAN), and placements by a number of student interns (Jordan CHUNG, Matthew KHWONG, Margaux STAMM). A 5-year Theme based Research Scheme (TRS) project grant was awarded by the Research Grants Council (RGC) to Professor Benjamin Cowling to investigate population and individual immunity to influenza in Hong Kong, of which I am a co-investigator and will contribute significantly to over the next coming years.

Broadly reactive immune correlates for improved influenza vaccines

[Funding: RGC/GRF; CDC; CEIRS]

A vaccine that is broadly protective against different strains and subtypes of influenza is needed *in lieu* of the current seasonal vaccine that requires yearly update and is not protective against pandemic or outbreak strains.

(a) A T-cell based universal vaccine: In collaboration with Leo LM Poon at HKU, and Liyange Perera and Thomas Waldmann at NIH, our group is determining the mechanism of protection of a Vaccinia Wyeth vaccine vector encoding 5 influenza proteins, HA, NA, NP and Matrix 1 and 2 proteins, with a molecular IL-15 adjuvant to enhance vaccine memory responses, termed Wyeth/5Flu/IL-15. The vaccine has been highly effective in mice providing protection against avian, pandemic and seasonal strains of influenza. The vaccine elicits effective influenza-specific T cell memory responses that establish early local T cell responses upon influenza challenge, significantly reducing viral lung titers and thus survival. Importantly, depletion of T cell subsets showed that memory CD4 T cell responses were necessary for vaccine mediated protection, an under-appreciated role of helper subset. The vaccine is being further investigated to determine the role T cell mediated immune pressure may play in viral escape by next generation sequencing to

identify mutations at T cell epitopes. Circumventing virus escape is important for the design of next generation influenza vaccines.

(b) Single protein immune mouse serum (SPIMS): Influenza A viruses contain 8 genes encoding at least 11 proteins. However, recombinant HA only protein vaccines have been recently licensed and available for human use. More conserved vaccine targets may provide greater protection from influenza infection. Therefore, we are characterising human immune serum to alternate protein targets before and after human and mouse influenza infection to identify immunodominant antibody targets.

(c) Enhanced inactivated influenza vaccines and repeat vaccination for older adults: The 2014/2015 Northern hemisphere winter influenza season had excess mortality in over 65-year old's due to vaccine mismatch between the H3N2 circulating strain and vaccine strain (A/Texas/50/2012). The updated vaccine containing the A/Switzerland/9715293/2013 virus became available after the peak of the influenza season. In collaboration with Leo Poon, Benjamin Cowling and Yat Hang Tam (School of Public Health at HKU), we conducted a randomized clinical trial to determine the benefit of re-vaccinating the elderly in establishing H3N2-Switzerland specific T and B cell and ADCC responses was assessed by comparing subjects who received one dose of the updated vaccine versus two doses of vaccine. Overall, we found no difference that twice annual influenza vaccination had no impact on in the quality of ADCC responses but decreased influenza-specific $CD4^+$ T cell responses and increased antibody avidity, and reduced boosting of HAI antibodies but sustained levels of sera-protection. Further immune correlates such as the subjects' immune genotype background and IgG subclasses are now being tested.

This 2015-2016 randomized clinical trial led to the establishment of two trials via a co-operative agreement with the US CDC, to assess longitudinal vaccine responses in older adults over 5 years in Hong Kong. Specifically, whether already available enhanced vaccines (recombinant, adjuvant, high dose) were more immunogenic than standard vaccines, and whether an alternating vaccine regime of enhanced vaccines would have further synergy, resulting in an 11-arm clinical trial of nearly 2,000 older adults. So far, we have collected PBMCs and plasma from 3 seasons of vaccination from 180 subjects for 1,620 samples to assess vaccine immunogenicity on T cell and antibody response magnitude and quality. The same enhanced and seasonal inactivated vaccines were assessed in a mouse vaccination and challenge model to determine vaccine memory and survival from lethal influenza challenge. Furthermore, annual vaccination of older adults and susceptible individuals, is recommended by many health authorities worldwide due to vaccine strain updates and waning immunity. However, there is emerging evidence that repeated vaccination with antigenically similar vaccine viruses may result in reduced vaccine efficacy and protection from infection. We have been collecting and bio-banking PBMCs and plasma samples for over 7 vaccination seasons since 2017 from 80 subjects for 1,680 samples again to assess vaccine immunogenicity on T cell and antibody response magnitude and quality.

Publications

1. **Kavian N**, **Hachim A**, Wang Y, Poon LLM, **Valkenburg SA** (2020) Vaccination with ADCC activating HA peptide epitopes provides partial protection from influenza infection. *In review*.
2. *Jahan AS*, Biquand E, Muñoz-Moreno R, *Le Quang A*, *Mok CKP*, *Wong HH*, *Teo QW*, **Valkenburg SA**, Chin AWH, Poon LLM, Te Velthuis A, Garcia-Sastre A, Demeret C, *Sanyal S* (2020) OTUB1 is a key regulator of RIG-I-dependent immune signaling and is targeted for proteasomal degradation by influenza A NS1. *Cell Rep* 30:1570–1584.
3. **Kavian N**, **Hachim A**, **Li APY**, **Cohen CA**, Chin AHW, Poon LLM, Fang VJ, Leung NHL, Cowling BJ, **Valkenburg SA** (2020) Assessment of enhanced influenza vaccination finds FluAd advantage in mice and older adults. *Clin Transl Immunol* **9**:e1107.
4. Cowling BJ, Perera RAPM, **Valkenburg SA**, Leung NHL, Iuliano AD, Tam YH, Wong JHF, Fang VJ, **Li APY**, So HC, Ip DKM, Azziz-Baumgartner E, Fry AM, Levine MZ, Gangappa S, Sambhara S, Barr IG, Skowronski DM, *Peiris JSM*, Thompson MG (2020) Comparative immunogenicity of several enhanced influenza vaccine options for older adults: A randomized, controlled trial. *Clin Infect Dis* doi: 10.1093/cid/ciz1034. PMID: 31828291.
5. **Valkenburg SA**, Cowling BJ (2020) Turning influenza vaccinology on its head to reveal the stalk. *Lancet Infect Dis* **20**:5-7.
6. **Valkenburg SA**, Fang VJ, Leung NH, Chu DK, Ip DK, Perera RA, Wang Y, **Li AP**, *Peiris JM*, Cowling BJ, Poon LLM (2019) Cross-reactive antibody-dependent cellular cytotoxicity antibodies are increased by recent infection in a household study of influenza transmission. *Clin Transl Immunol* **8**:e1092.
7. **Valkenburg SA**, Li OTW, *Peiris JSM*, Perera LP, Poon LLM (2019) Vaccine-induced T cell protection from influenza viruses. *Hong Kong Med J* **25**(Suppl 7):33–36.
8. Yan LM, Li OTW, Poh CM, Perera RAPM, **Valkenburg SA**, *Peiris M*, Poon LLM (2018) Combined use of live-attenuated and inactivated influenza vaccines to enhance heterosubtypic protection. *Virology* **525**:73-82.

Seminars and Invited Presentations

1. Sophie Valkenburg (2019) Kitasato Institute, Tokyo, Japan.
2. Sophie Valkenburg (2019) The University of Hong Kong, Hong Kong SAR.

Presentations at Meetings

1. **Bull MB**, **Valkenburg SA** (2019) Identification of influenza escape mutants in the context of T-cell mediated vaccination. *1st Immunological Correlates for Next Generation Influenza Vaccines, International Society for Influenza and Other Respiratory Virus Diseases (ISIRV),* Siena, Italy (**Oral**).

2. **Bull MB**, **Valkenburg SA** (2019) Investigation of T cell immune pressure on the Influenza genome within a universal vaccination model. *Options for the Control of Influenza X*, Singapore (**Poster**).
3. **Kavian N**, **Valkenburg SA** (2019) Parallel assessment of immune responses to enhanced seasonal influenza vaccination finds an advantage for FluAdfor cross-protection in mice. *Options for the Control of Influenza X*, Singapore (**Poster**).
4. **Li APY**, **Valkenburg SA** (2019) Enhanced annual influenza vaccination strategies in older adults for the establishment of high-quality antibody responses. *1st Immunological Correlates for Next Generation Influenza Vaccines, International Society for Influenza and Other Respiratory Virus Diseases (ISIRV)*, Siena, Italy (**Poster**).
5. **Li APY**, **Valkenburg SA** (2019) Enhanced annual influenza vaccination generates higher quality immune responses in older adults. *Options for the Control of Influenza X*, Singapore (**Poster**).
6. **Valkenburg SA** (2019) Antibody responses to twice-annual vaccination due to 2014/2015 H3N2 antigenic mismatch in Hong Kong. *CEIRS 12th Annual meeting*, Baltimore, USA (**Oral**).
7. **Valkenburg SA** (2019) Reduced antibody function correlates with influenza infection in a household model of transmission. *1st Immunological Correlates for Next Generation Influenza Vaccines, International Society for Influenza and Other Respiratory Virus Diseases (ISIRV)*, Siena, Italy (**Oral**; **ISIRV Oral presentation award**).

Teaching

1. Sophie Valkenburg (2019) "Biological Basis of Disease" (Master of Public Health, CMED-6227), School of Public Health, The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
2. Sophie Valkenburg (2019) Health Research Project, The University of Hong Kong, Hong Kong SAR (*Tutor*).

Collaborations

1. **Benjamin Cowling** (School of Public Health, The University of Hong Kong, Hong Kong SAR): Determining the correlation between baseline T cell responses and protection from transmission in a household transmission setting; Longitudinal impact of repeat vaccination in the Hong Kong Elderly.
2. **Leo LM Poon** (School of Public Health, The University of Hong Kong, Hong Kong SAR): Broadly reactive influenza vaccines in mouse models.
3. **Ragahavan Varadarajan** (Indian Institute of Science, Bangalore, India): Characterization of a headless-trimeric pre-fusion conformation HA recombinant protein vaccine in a mouse model to generate broadly reactive HA-stem antibodies.
4. **Amy Chung** (University of Melbourne, Australia): Antibody effector functions after influenza exposure by multiplex assay.

5. **Adam Wheatley** (University of Melbourne, Australia): Recombinant influenza protein expression system.
6. **Jennifer Nayak** (University of Rochester, USA): Paediatric influenza vaccine responses.
7. **Mark Hogarth** (Burnet Institute, Australia): Reagents for antibody effector functions.
8. **Weisan Chen** (Monash University, Australia) and **Jonathan Yewdel**l (NIH, USA): Recombinant vaccinia virus panel for single influenza protein antibodies.

Funding

1. Control of influenza: individual and population immunity (**Co-investigator**; Research Grants Council/Theme based Research Scheme – Ends 2024).
2. The protective role of antibody effector functions for influenza in mice and humans (**Principal investigator**; Research Grants Council/General Research Fund – Ends 06/2022).
3. Multiplexed antibody function for protection from influenza (**Principal investigator**; HKU – Seed Funding for Basic Research – Ends: 03/2021).
4. Research on the epidemiology, vaccine effectiveness and treatment of influenza and other respiratory viruses in Southeast Asia and the Western Pacific (**Co-Investigator**; US Center for Disease Control – Ends: 07/2021).
5. Repeated elderly influenza vaccination and underlying factors contributing to antibody quality and cellular immunity (**Co-Investigator**; CEIRS NIH – Ends: 08/2020).
6. Influenza viruses adapt to escape T cell responses (**Principal Investigator**; Research Grants Council/General Research Fund – Ends: 12/2020).
7. Influenza ADCC-antibody responses in vaccination and infection of children as a correlate of protection (**Principal Investigator**; Health and Medical Research Fund – Ends: 08/2020).
8. Repeated elderly influenza vaccination and establishing cellular immune responses (**Co-Investigator**; CEIRS NIH – Ends: 08/2019).

Personnel

Name	Position
Sophie VALKENBURG	Research Assistant Professor
Niloufar KAVIAN	Postdoctoral fellow
Maireid BULL	PhD Student
Carolyn COHEN	PhD Student (HKPF awardee)
Athena LI	PhD Student
Fionn MA	Research Assistant I
Jodi CHAN	Research Assistant II (Contract ended 5 July 2019)
Asmaa HACHIM	Research Assistant II
Glenn Hao LI	Research Assistant II
Jordan CHUNG	Student Intern, Brunel University, London, United Kingdom (3 November 2018 to 31 July 2019)
Matthew KWONG	Student Intern, The University of Hong Kong, Hong Kong SAR
Margaux STAMM	Student Intern, Clermont-Auvergne University, France, (24 July to 7 September 2019)

3.7 Teaching and Education

HKU-Pasteur Course Series

HKU-PRP has pioneered a unique course series in Hong Kong and in the region that provides state of the art lectures and practical workshops in a "Master class" setting to outstanding postgraduate students and postdoctoral fellows coming from countries with markedly different resources. Our alumni network demonstrates that this educational program helps intensify human and scientific links between HKU-PRP, the School of Public Health at HKU and the Institut Pasteur International Network, and will continue to attract to Hong Kong top scientists and highly motivated students. HKU-Pasteur courses are supported with external grants from the Institut Pasteur International Network, the French Consulate in Hong Kong and Macau, the Regional Health Cooperation Office of the French Ministry of Foreign Affairs the Pasteur Foundation Asia and other private donations. In 2019 we have organized and co-organized four international courses, 3 in Hong Kong (Cell Biology, Advanced Imaging, Virology) and 1 in Ho Chi Minh City ,Vietnam (Measles and Rubella Elimination: Options for Public Health Interventions). We received more than 200 applications from over 25 countries; 100 students with global geographic representation were selected for participation. Our courses are extremely competitive and comparable in quality to that of established benchmarks, such as EMBO and Cold Spring Harbor courses and, therefore, are solidifying the reputation of HKU-PRP and Hong Kong as the premier regional hub for biomedical education. HKU-Pasteur Courses have been approved by the Research Postgraduate Committee of HKU for inclusion in the coursework curriculum of MPhil/PhD students.

The **9th HKU-Pasteur Cell Biology Course** focused on proteomics based approaches to probe the cell biology underlying human diseases. With the advent of more sophisticated technology and instrumentation in mass spectrometry, a strong interest has emerged to assess and interrogate biology at the level of protein networks along with the more conventional genomic and transcriptomic approaches. The ability to determine changes at the protein level including post-translational modifications that dictate protein states and their corresponding function is revealing a new texture to biology. Both systems-wide as well as targeted proteomic strategies have proved critical for generating hypotheses in various cellular perturbations. Novel targets for drug development have emerged as a result of such methods that take into account active enzymatic states that can be specifically inhibited in the context of human pathologies. The program of the 9th HKU-Pasteur Cell Biology Course brought together scientific leaders in the integration of methods in classical biochemistry and mass spectrometry spanning conventional to more advanced approaches, which enable the analysis of dynamic biological networks under normal physiology and during diseased states such as pathogen infection. The seminars, methods and technologies used during the course highlighted the power of using mass spectrometry and proteomics combined with quantitative analysis to probe signaling networks that are typically perturbed in various diseased states. We received 34 applications from 9 countries and selected 20 students coming from (in alphabetical order): Brazil (1), France (1), Greece (1), Hong Kong (14), Korea (1), Malaysia (2). The objective of the HKU-Pasteur Cell Biology course is to foster the development of this discipline, which is becoming the centerpiece of not just basic research, but also of studies that address questions relevant to the quality of human life and public health.

The **15th HKU-Pasteur Virology Course** offered a full immersion into coronavirus biology, a choice of topic that has proven prescient in view of the current outbreak of the new coronavirus. Most endemic coronaviruses (CoV) cause mild respiratory and intestinal infections in animals and humans. The identification of two novel and highly pathogenic coronaviruses as the cause of SARS and MERS outbreaks has illustrated the risks associated with zoonotic infections from this family of viruses. The Faculty reviewed our current understanding and knowledge gaps, with special emphasis on the origin, evolution, transmissibility, molecular biology, epidemiological and clinical features of the highly pathogenic SARS-CoV and MERS-CoV. Lessons from the outbreaks of SARS-CoV and MERS-CoV in different parts of the world were discussed with experts who played a prominent role in the identification of the viruses and the implementations of measures to control their spread. The practical workshop challenged participants to design experimental strategies to mitigate the impact of CoV infections. The workshop was built around the preparation of a multidisciplinary grant proposal to address the main scientific questions that we are facing in coronavirus research. Students worked in small groups focusing on a particular research area; they were required to identify relevant question(s), generate hypothesis and propose experimental approaches to address them. At the end of the practicum each group presented their grant proposal, which stimulated further discussion on the themes of the course. The HKU-Pasteur Virology course has been approved by the Research Postgraduate Committee of HKU for inclusion in the coursework curriculum of MPhil/PhD students.

Additional teaching and training

We have co-organized with **Musa Mhlanga at the University of Cape Town** (South Africa), and George Tsao (HKU) the third and final edition of the **Croucher Summer Course in Advanced Imaging**. This course series aimed to advance imaging and high-resolution microscopy for single cell and single molecule imaging which are essential technology platforms in cell and molecular biology. The ability to image and define subcellular and molecular events involved in crucial biochemical pathways of normal physiological and disease processes allows monitoring of pathological event during disease progression and is having a strong impact on the directions taken by biomedical research at large. The third and final edition focused on the application of leading deep learning framewroks for microscopy image restoration to various biological tasks. The series, which started in 2015, was a major effort to promote advanced imaging analysis and share with young as well as established researchers recent advances and breakthroughs made at the intersection of high throughput biology and imaging microscopy and their applications in basic and translational research. We believe that this course was timely and successful in achieving the transfer of the state-of-the-art imaging technology s and their applications in various aspects of cell and molecular biology to an international group of investigators. We received 80 applications from 7 countries. We selected 30 students coming from (in alphabetical order): China (4), Greece (1), Hong Kong (16), Korea (2), Singapore (6), UK (1). This is the third and final edition of this course series.

The **Public Health Workshop series at the Pasteur Institute of Ho Chi Minh City** has become a benchmark for a world-class training program for epidemiologists, researchers and public health officials in the region. The topic of the 2019 edition, organized in close partnership with the Pasteur Institute of Ho Chi Minh City, the Institut Pasteur du Laos and

the World Health Organization, was "**Measles and Rubella Elimination: Options for Public Health Interventions**". Although vaccines for measles and rubella have been introduced to great effect in the 1960's, there has been a resurgence in the number of cases in recent years. This is particularly true in the case of measles, which is highly contagious, with outbreaks of large proportions in many countries, from Asia to New Zeland, Europe and the United States largely attributed to lowered vaccination rates. We discussed the current situation of the eradication program, the efforts of the health sector towards the elimination of measles and rubella and the implementation of the proposed Operational Targets set by WHO for 2020. The faculty, comprising specialists with strong links to the WHO, also reviewed the response to the most recent outbreaks with emphasis on regional approaches. The course was again oversubscribed and we selected 20 trainees (out of 56 applications) from 11 countries (in alphabetical order): Bangladesh (1), Cambodia (1), China (2), Indonesia (1), Japan (1), Lao PDR (3), Myanmar (2), Philippines (1), Singapore (3), Thailand (4), Vietnam (1). An additional objective of this course series is to create a strong community of researchers, public health and government staff and team leaders in South East Asia equipped with knowledge of best public health practices. Since 2012, when the first edition of this course series took place, we have received more than 550 applications and selected over 200 applicants. We are keeping in contact with them through mails and advertisements and have received strong positive feed- backs from them. We plan to have a scientific meeting with some of the alumni in the future to celebrate the tenth anniversary of this course series. The establishment and sustainability of this training program of excellence has been made possible by unflagging financial support received over the years from the Regional Health Cooperation Office of the French Ministry of Foreign Affairs. We also thank the Pasteur Foundation Asia for its generous contribution.

Besides their involvement in the HKU-Pasteur course series, the **Co-Directors and Group Leaders** at HKU-PRP are also teaching courses in the undergraduate and postgraduate curriculum and the Problem-Based Learning modules for MBBS students (see cpmplete list at the end of this section). HKU-PRP regularly hosts undergraduate/postgraduate students from overseas institutions for internships. In 2019 we welcomed seven international trainees for an internship period:

1. Jordan Chung from Brunel University, London, United Kingdom
2. Bo Yan from Nanjing Medical University, PR China
3. Qing Wang from Nanjing Medical University, PR China
4. Max van Diepen from Erasmus Medical Center, Rotterdam, The Netherlands
5. Sophie van Leur from Erasmus Medical Center, Rotterdam, The Netherlands
6. Margaux Stamm from Clermont-Auvergne University, France
7. Morgan Maurin from Clermont-Auvergne University, France
8. Zhen Ye Sin from University of Durham, United Kingdom
9. Adrian Lee from Ngee Ann Poltechnic, Singapore

We continue our educational program for high school students from the French International School in Hong Kong and have hosted one for the week-long work experience laboratory placement. Moreover, four students from the Hong Kong Institute of Vocational Education (IVE) have trained with us during the summer. We have partnered with IVE for many years and two of their students, after spending time in the

lab, have previously joined HKU-PRP for MPhil research work. Matthew Khong, a second year MBBS student, has continued his attachment to the Valkenburg lab for the second consecutive year.

1. Sze Wang Li, from The University of Hong Kong, Hong Kong SAR
2. Sun Man Kwok from The University of Hong Kong, Hong Kong SAR
3. Matthew Kwong from The University of Hong Kong, Hong Kong SAR
4. Vrinda Mathur from The Hong Kong University of Science & Technology, Hong Kong SAR
5. Wing Kei Wong from the Hong Kong Institute of Vocational Education, Hong Kong SAR
6. Chak Man Hui from the Hong Kong Institute of Vocational Education, Hong Kong SAR
7. Yin Wing Chan from the Hong Kong Institute of Vocational Education, Hong Kong SAR
8. Man Kit Liao from the Hong Kong Institute of Vocational Education, Hong Kong SAR
9. Elena Denis from the French International School, Hong Kong SAR
10. Geraldine Feschet the from French International School, Hong Kong SAR
11. Gabriel Slaoui from the French International School, Hong Kong SAR
12. Caroline Ward from the French International School, Hong Kong SAR

Complete list of taught and international courses

8. Roberto Bruzzone (2019) Molecular Biology of the Cell Course, Institut Pasteur, Paris, France (*Course Director*).
9. Roberto Bruzzone (2019) 9th HKU-Pasteur Cell Biology Course, The University of Hong Kong, Hong Kong SAR (*Course Director*).
10. Roberto Bruzzone (2019) 3rd Croucher Summer Course in Advanced Imaging, The University of Hong Kong, Hong Kong SAR (*Course Director*).
11. Roberto Bruzzone (2019) 15th HKU-Pasteur Virology Course, The University of Hong Kong, Hong Kong SAR (*Course Director*).
12. Roberto Bruzzone (2019) CMED6227 – Biological Basis of Disease (Master of Public Health), The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
13. Roberto Bruzzone (2019) Introduction to the Art and Science of Medicine, Problem Based Learning (MBBS Year 1), The University of Hong Kong, Hong Kong SAR (*Tutor*).
14. Roberto Bruzzone (2019) Measles and Rubella Elimination: Options for Public Health Interventions, Pasteur Institute in Ho Chi Minh City, Vietnam (*Course Director*).
15. Chris Mok (2019) 15th HKU-Pasteur Virology Course, The University of Hong Kong, Hong Kong SAR (*Course Director and Tutor*).
16. Chris Mok (2019) Health Research Project, The University of Hong Kong, Hong Kong SAR (*Tutor*).
17. Chris Mok (2019) Introduction to the Art and Science of Medicine – Problem Based Learning (MBBS Year 1), The University of Hong Kong, Hong Kong SAR (*Tutor*).

18. Chris Mok (2019) Haematology/Immunology System – Problem Based Learning (MBBS Year 2), The University of Hong Kong, Hong Kong SAR (*Tutor*).
19. Chris Mok (2019) OITF Course: Introduction to Outbreak Investigation and Response, Institut Pasteur du Cambodge, Cambodia (*Lecturer and Tutor*).
20. Malik Peiris (2019) 15th HKU-Pasteur Virology Course, The University of Hong Kong, Hong Kong SAR (*Course Director*).
21. Malik Peiris (2019) CMED6104 – Emerging infectious diseases: the "One Health" concept (Master of Public Health), The University of Hong Kong, Hong Kong SAR (*Course Director*).
22. Sumana Sanyal (2019) Basic Metabolism (BSc Biochemistry Year 3 students) The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
23. Sumana Sanyal (2019) Essentials in Proteomics (BBMS Year 3) The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
24. Sumana Sanyal (2019) Recent Advances in Biotechnology (MMPH) The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
25. Sumana Sanyal (2019) Cancer Screening – Problem Based Learning (MBBS Year 4 students) The University of Hong Kong, Hong Kong SAR (*Tutor*).
26. Sumana Sanyal (2019) Introduction to the art and science of medicine – Problem Based Learning (MBBS Year 1 students) The University of Hong Kong, Hong Kong SAR (*Tutor*).
27. Sumana Sanyal (2019) Endocrine and Reproductive Systems – Problem Based Learning (MBBS Year II students) The University of Hong Kong, Hong Kong SAR (*Tutor*).
28. Sumana Sanyal (2019) 9th HKU-Pasteur Cell Biology Course, The University of Hong Kong, Hong Kong SAR (*Course Director, Lecturer and Tutor*).
29. Hein Min Tun (2019) CMED6227 – Biological Basis of Disease (Master of Public Health), The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
30. Sophie Valkenburg (2019) CMED6227 – Biological Basis of Disease (Master of Public Health), The University of Hong Kong, Hong Kong SAR (*Course Director and Lecturer*).
31. Sophie Valkenburg (2019) Health Research Project , The University of Hong Kong, Hong Kong SAR (*Tutor*).

Complete list of interns

Jordan CHUNG	Brunel University, London, United Kingdom
Bo YAN	Nanjing Medical University, PR China
Qing WANG	Nanjing Medical University, PR China
Max Van DIEPEN	Erasmus Medical Center, Rotterdam, The Netherlands
Sophie VAN LEUR	Erasmus Medical Center, Rotterdam, The Netherlands
Morgan MAURIN	Clermont-Auvergne University, France
Margaux STAMM	Clermont-Auvergne University, France
Zhen Ye SIN	University of Durham, United Kingdom
Adrian LEE	Ngee Ann Polytechnic, Singapore
Sze Wang LI	The University of Hong Kong, Hong Kong SAR
Sun Man KWOK	The University of Hong Kong, Hong Kong SAR
Matthew KHONG	The University of Hong Kong, Hong Kong SAR
Vrinda MATHUR	The Hong Kong University of Science & Technology, Hong Kong SAR
Yin Wing CHAN	Hong Kong Institute of Vocational Education, Hong Kong SAR
Chak Man HUI	Hong Kong Institute of Vocational Education, Hong Kong SAR
Man Kit LIAO	Hong Kong Institute of Vocational Education, Hong Kong SAR
Wing Kei WONG	Hong Kong Institute of Vocational Education, Hong Kong SAR
Elena DENIS	French International School, Hong Kong SAR
Geraldine FESCHET	French International School, Hong Kong SAR
Gabriel SLAOUI	French International School, Hong Kong SAR
Caroline WARD	French International School, Hong Kong SAR

3.8 Other Major Activities

HKU-PRP exerts a leadership role in a number of research and educational programs of global scope.

International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)

Roberto Bruzzone was appointed as the Interim Chair in December of 2018 and became the Chair at the beginning of 2020, for a three-year term. ISARIC launched in 2011, is a consortium of over 40 clinical research networks operational in 131 countries (http://isaric.tghn.org/). ISARIC's vision is to change the approach to collaborative, patient-oriented research between and during epidemics of rapidly emerging public health threats, in order to generate new evidence-based knowledge, maximize the availability of clinical information and, thereby, save lives. ISARIC has played a major role in the Ebola virus crisis and has urged the deployment of alternative trial designs to fast-track the evaluation of new Ebola treatments. It has been involved in the coordination of two clinical trials in West Africa. ISARIC has assisted with the deployment of research on Zika virus and has set up a web site for shared resourced and information. It is now actively involved in two randomized clinical trials with COVID-19 patients in China. ISARIC and the Institut Pasteur du Madagascar have received a major grant from the Wellcome Trust to coordinate a clinical study to generate evidence for plague treatment regimens in Madagascar.

Theme-based Research Scheme "Viral, host and environmental determinants of influenza virus transmission and pathogenesis"

Malik Peiris is the Coordinator of the Theme-based Research Scheme (TRS): "Viral, host and environmental determinants of influenza virus transmission and pathogenesis", which has been awarded a HK$75 million grant. The program addresses two outstanding "grand-challenge" research questions in influenza: i) the biological determinants of influenza virus transmission from animals-to-humans and from human-to-humans; and ii) the pathogenesis of severe influenza disease. The specific goals of the TRS are to:

- Understand the viral, host and environmental determinants of influenza virus transmission between humans, and from animals to humans;
- Understand the viral and host determinants of pathogenesis of severe influenza;
- Develop evidence based interventions to reduce transmission and novel therapeutic strategies targeting the host.

This research program, which promotes the implementation of the "One Health" concept to manage influenza risks, will end in 2020.

Establishment of the Center for Immunology & Infection (C2I)

We have been awarded a major 5-year grant, totaling over 40 million euros, from the Innovation and Technology Commission to establish the Center for Immunology & Infection (C2I) within the framework of InnoHK, a recent collaborative scientific research scheme set up set up by the Government of the Hong Kong Special Administrative

Region. This research program, which expands the scope of the partnership between the University of Hong Kong and the Institut Pasteur will work around four major research programs to face public health challenges and making Hong Kong a global center of excellence for precision medicine population strategies. Through C2I, we will contribute to Hong Kong's transformation into an international innovation and technology hub of the Greater Bay Area of Guangdong, Hong Kong and Macau. C2I's major focus will be the immune system, which is responsible for maintaining a healthy state and preventing infection in the majority of cases. However, dysfunction of the immune system can result in increased susceptibility to infections, inflammation, autoimmunity or even development of cancer in some individuals. Moreover, individual heterogeneity in the immune response can have an enormous impact on the likelihood to respond to therapy or the development of side effects secondary to vaccine administration. Thus, knowledge of these parameters in healthy humans, as envisaged in this program, is essential to establish personalized and precision medical care, and disease management. This information will accelerate research to develop new effective vaccines and drug candidates, as well as inform pertinent risk assessment that would facilitate the discovery of solutions for critical issues facing Hong Kong and the world within the next decade, such as pollution, ageing of the population or pandemics. This partnership has the ambition to contribute to Hong Kong's transformation into an international innovation and technology hub of the Guangdong-Hong Kong-Macao Bay Area.

Other key actions

Professor James Di Santo from the Institut Pasteur has been appointed as Visiting Professor in 2016 through the "Visiting Research Professors" scheme of the University Research Committee of HKU. He is one of the leading scientists in the field of human innate immunity and his appointment has been an invaluable asset in building an even stronger program in human immunology. James Di Santo plays also an active role in mentoring postgraduate students and early stage investigators involved in the project. Malik Peiris continues to serve on a number of WHO working groups in relation to both avian and swine origin influenza virus and is the Co-Director of the WHO H5 Reference Laboratory at HKU.

4. Scientific Output

4.1 Publications

1. Yan LM, Li OTW, Poh CM, Perera RAPM, Valkenburg SA, Peiris M, Poon LLM (2018) Combined use of live-attenuated and inactivated influenza vaccines to enhance heterosubtypic protection. *Virology* **525**:73-82.
2. Abbad A, Perera RA, Anga L, Faouzi A, Minh NN, Malik SMM, Iounes N, Maaroufi A, Van Kerkhove MD, Peiris M, Nourlil J (2019) Middle East respiratory syndrome coronavirus (MERS-CoV) neutralising antibodies in a high-risk human population, Morocco, November 2017 to January 2018. *Euro Surveill* **24**:1900244.
3. Baudon E, Peyre M, Tung DD, Thi Nga P, Khong NV, Cowling BJ, Peiris M (2019) Surveillance of swine influenza viruses in sentinel familial farms in Hung Yen province in Northern Vietnam in 2013-2014. *Zoonoses Public Health* **10**.1111/zph.12671.doi:10.1111/zph.12671.
4. Chan LLY, Hui KPY, Kuok DIT, Bui CHT, Ng KC, Mok CKP, Yang ZF, Guan W, Poon LLM, Zhong N, Peiris JSM, Nicholls JM, Chan MCW (2019) Risk Assessment of the Tropism and Pathogenesis of the Highly Pathogenic Avian Influenza A/H7N9 Virus Using Ex Vivo and In Vitro Cultures of Human Respiratory Tract. *J Infect Dis* **220**:578-588.
5. Drall KM, Tun HM, Morales-Lizcano NP, Konya TB, Guttman DS, Field CJ, Mandal R, Wishart DS, Becker AB, Azad MB, Lefebvre DL, Mandhane PJ, Moraes TJ, Sears MR, Turvey SE, Subbarao P, Scott JA, Kozyrskyj AL (2019) *Clostridioides difficile* Colonization Is Differentially Associated With Gut Microbiome Profiles by Infant Feeding Modality at 3-4 Months of Age. *Front Immunol* **10**:2866.
6. Kandeil A, Gomaa M, Nageh A, Shehata MM, Kayed AE, Sabir JSM, Abiadh A, Jrijer J, Amr Z, Said M A, 6,. Byarugaba DK, Wabwire-Mangen F, Tugume T, Mohamed NS, Attar R, Hassan SM, Linjawi SA, Moatassim Y, Kutkat O, Mahmoud S, Bagato O, Shama NMA, El-Shesheny R, Mostafa A, Perera RA, Chu DKW, Hassan N, Elsokary B, Saad A, Sobhy H, El Masry I, McKenzie PP, Webby RJ, Peiris M, Makonnen YJ, Ali MA, Kayali G (2019). Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Dromedary Camels in Africa and Middle East. *Viruses* **11**:717.
7. Kandeil A, Gomaa M, Shehata M, El-Taweel A, Kayed AE, Abiadh A, Jrijer J, Moatassim Y, Kutkat O, Bagato O, Mahmoud S, Mostafa A, El-Shesheny R, Perera RA, Ko RL, Hassan N, Elsokary B, Allal L, Saad A, Sobhy H, McKenzie PP, Webby RJ, Peiris M, Ali MA, Kayali G (2019) Middle East respiratory syndrome coronavirus infection in non-camelid domestic mammals. *Emerg Microbes Infect* **8**:103–108.
8. Lai JC, Karunarathna HM, Wong HH, Peiris JS, Nicholls JN (2019) Neuraminidase activity and specificity of influenza A virus are influenced by haemagglutinin-receptor binding. *Emerg Microbes Infect* **8**:327-338.
9. So RTY, Chu DKW, Miguel E, Perera RA, Oladipo JO, Fassi-Fihri O, Aylet G, Ko RL, Zhou Z, Cheng MS, Kuranga SA, Roger FL, Chevalier V, Webby RJ, Woo PCY, Poon LLM, Peiris M (2019) Diversity of Dromedary Camel Coronavirus HKU23 in African Camels Revealed Multiple Recombination Events among Closely Related Betacoronaviruses of the Subgenus Embecovirus. *J Virol* **93**:e01236-19.

10. Tan Q, Orsso CE, Deehan EC, Triador L, Field CJ, Tun HM, Han JC, Müller TD, Haqq AM (2019) Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review. *Obes Rev* 10.1111/obr.12992.

11. Tang YS, Lo CY, Mok CK, Chan PK, Shaw PC (2019) The extended C-terminal region of influenza C nucleoprotein is important for nuclear import and RNP activity. *J Virol* **93**:e02048-18.

12. Tun HM, Bruzzone R (2019) Early-life antibiotic exposure, gut microbiome, and colonization resistance. *J Health Sci Altern Med* **1**:1-5.

13. Valkenburg SA, Fang VJ, Leung NH, Chu DK, Ip DK, Perera RA, Wang Y, Li AP, Peiris JM, Cowling BJ, Poon LLM (2019) Cross-reactive antibody-dependent cellular cytotoxicity antibodies are increased by recent infection in a household study of influenza transmission. *Clin Transl Immunol* **8**:e1092.

14. Valkenburg SA, Li OTW, Peiris JSM, Perera LP, Poon LLM (2019) Vaccine-induced T cell protection from influenza viruses. *Hong Kong Med J* **25**(Suppl 7):33–36.

15. Wong HH, Sanyal S (2019) Manipulation of autophagy by (+) RNA viruses. *Semin Cell Dev Biol*, in press.

16. Wu NC, Lv H, Thompson AJ, Wu DC, Ng WWS, Kadam RU, Lin CW, Nycholat CM, McBride R, Liang W, Paulson JC, Mok CK, Wilson IA (2019) Preventing an antigenically disruptive mutation in egg-based H3N2 seasonal influenza vaccines by mutational incompatibility. *Cell Host Microbe* **25**:836-844.

17. Cowling BJ, Perera RAPM, Valkenburg SA, Leung NHL, Iuliano AD, Tam YH, Wong JHF, Fang VJ, Li APY, So HC, Ip DKM, Azziz-Baumgartner E, Fry AM, Levine MZ, Gangappa S, Sambhara S, Barr IG, Skowronski DM, Peiris JSM, Thompson MG (2020) Comparative immunogenicity of several enhanced influenza vaccine options for older adults: A randomized, controlled trial. *Clin Infect Dis* doi: 10.1093/cid/ciz1034. PMID: 31828291.

18. Jahan AS, Biquand E, Munoz-Moreno R, Le Quang A, Mok CK, Wong HH, Teo Q, Valkenburg SA, Chin AWH, Poon LLM, te Velthuis A, García-Sastre A, Demeret C, Sanyal S (2020) OTUB1 is a key regulator of RIG-I-dependent immune signaling and is targeted for proteasomal degradation by influenza A NS1. *Cell Rep* **30**:1570–1584.

19. Kavian N, Hachim A, Li APY, Cohen CA, Chin AHW, Poon LLM, Fang VJ, Leung NHL, Cowling BJ, Valkenburg SA (2020) Assessment of enhanced influenza vaccination finds FluAd advantage in mice and older adults. *Clin Transl Immunol* **9**:e1107.

20. Perera RAP, Mok CKP, Tsang OTY, Lv H, Ko RLW, Wu NC, Yuan M, Leung WS, Chan JMC, Chik TSH, Choi CYC, Leung K, Chan KH, Chan KCK, Li KC, Wu JT, Wilson IA, Monto AS, Poon LLM, Peiris M (2020) Serological assays for SARS-CoV-2. *Eurosurveill*, in press.

21. Valkenburg SA, Cowling BJ (2020) Turning influenza vaccinology on its head to reveal the stalk. *Lancet Infect Dis* **20**:5-7.

22. Wang Y, Li X, Liu W, Gan M, Zhang L, Wang J, Zhang Z, Zhu A, Li F, Sun J, Zhang G, Zhuang Z, Luo J, Chen D, Qiu S, Zhang L, Xu D, Mok CKP, Zhang F, Zhao J, Zhou R, Zhao J (2020) Discovery of a subgenotype of human coronavirus NL63 associated with severe lower respiratory tract infection in China, 2018. *Emerg Microbes Infect* **9**:246-255.

23. Yuan M, Wu NC, Zhu X, Lee CCD, So RTY, Lv H, Mok CKP, Wilson IA (2020) A highly conserved cryptic epitope in the receptor-binding 4 domains of SARS-CoV-2 and SARS-CoV. *Science*, Apr 3:eabb7269. doi: 10.1126/science.abb7269.

24. Kavian N, Hachim A, Wang Y, Poon LLM, Valkenburg SA (2020) Vaccination with ADCC activating HA peptide epitopes provides partial protection from influenza infection. *In review*.

25. Li MY, Naik TS, Siu LYS, Acuto O, Spooner E, Wang P, Yang X, Lin Y, Bruzzone R, Ashour J, Sanyal S (2020) Activation of Src-family kinases orchestrate secretion of flaviviruses by targeting mature progeny virions to secretory autophagosomes. *Nat Microbiol*, in revision; *bioRxiv* doi: https://doi.org/10.1101/2020.01.12.903062.

26. Lv H, Wu NC, Tsang OT, Yuan M, Perera RAP, Leung WS, So RT, Chan JMC, Yip GK, Chik TSH, Wang Y, Choi CYC, Lin Y, Ng WW, Zhao J, Poon LLM, *Peiris JSM*, Wilson IA, Mok CKP (2020) Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections. *Cell Rep*, in review; *bioRxiv* doi: https://doi.org/10.1101/2020.03.15.993097.

27. Mok CKP, Zhu A, Zhao J, Lau EHY, Wang J, Chen Z, Zhuang Z, Wang Y, Wang W, Tan W, Liang W, Oladipo JO, Kuranga SA, Peiris M, Zhao J (2020) Specific T cell responses provide evidence of MERS coronavirus infection in people with occupational exposure to dromedary camels in Nigeria. *Lancet Infect Dis*, in revision.

4.2 Presentations at Meetings

1. Ho J, Sanyal S (2020) Zika Virus Infection can Induce MHC-I Downregulation on the Cell Surface. *Third International Conference on Zika and Aedes Related Infections*, Washington DC, USA (**Poster**).
2. Wong HH, Sanyal S (2020) Investigating Host Components Utilised for Translation of Zika Virus Proteins. *Third International Conference on Zika and Aedes Related Infections*, Washington DC, USA (**Poster**).
3. Bull MB, Valkenburg SA (2019) Identification of influenza escape mutants in the context of T-cell mediated vaccination. *1st Immunological Correlates for Next Generation Influenza Vaccines, International Society for Influenza and Other Respiratory Virus Diseases (ISIRV),* Siena, Italy (**Oral**).
4. Bull MB, Valkenburg SA (2019) Investigation of T cell immune pressure on the Influenza genome within a universal vaccination model. *Options for the Control of Influenza X*, Singapore (**Poster**).
5. Kavian N, Valkenburg SA (2019) Parallel assessment of immune responses to enhanced seasonal influenza vaccination finds an advantage for FluAdfor cross-protection in mice. *Options for the Control of Influenza X*, Singapore (**Poster**).
6. Li APY, Valkenburg SA (2019) Enhanced annual influenza vaccination generates higher quality immune responses in older adults. *Options for the Control of Influenza X*, Singapore (**Poster**).
7. Li APY, Valkenburg SA (2019) Enhanced annual influenza vaccination strategies in older adults for the establishment of high-quality antibody responses. *1st Immunological Correlates for Next Generation Influenza Vaccines, International Society for Influenza and Other Respiratory Virus Diseases (ISIRV)*, Siena, Italy (**Poster**).
8. Li MY, Naik TS, Siu L, Porciello N, Spooner E, Ashour J, Wang P, Yang X, Lin Y, Bruzzone R, Sanyal S (2019) Activation of Src-family kinases orchestrate secretion of flaviviruses by targeting mature progeny virions to secretory autophagosomes. *2019 ASCB/EMBO Meeting*, Wahington DC, USA (**Poster**).
9. Liang W, Lv H, Ng WWS, Mok CKP (2019) Establishment of avian influenza virus/*Acinetobacter baumannii* co-infection model in mice. *Options for the Control of Influenza X*, Singapore (**Poster**).
10. Lv H, Mok CKP (2019 Preventing an antigenically disruptive mutation in egg-based H3N2 seasonal influenzavaccines by mutational incompatibility. *The 2nd Science and Technology Summit for Youth Scholar on Virology*, Wuhan, PR China (**Oral**).
11. Lv H, Wu NC, Paulson JC, Wilson IA, Mok CKP (2020) Preventingan antigenically disruptive mutation in egg-based H3N2 seasonal influenzavaccines by mutational incompatibility. *New Horizons in B Cell Biology, Cell Press Symposium*, Shanghai, PR China (**Poster**).
12. Teo Q, Sanyal S (2019) USP25 Functions as a Restriction Factor during Influenza A Virus Infection. *EMBO Conference: Ubiquitin and Ubiquitin-like Modifiers*, Cavtat, Croatia (**Poster**).

13. Teo Q, Sanyal S (2019) Roles of USP25 during Influenza A Virus Infection. *Options for the Control of Influenza X*, Singapore (**Poster**).
14. Tun HM, Konya T, Chari R, Field CJ, Guttman DS, Becker AB, Azad MB, Mandhane PJ, Morea TJ, Sears MR, Turvey SE, Subbarao P, Scott JA, Kozyrskyj AL (2019) Delayed gut microbiota maturation during infancy is associated with food sensitization in children. *AllerGen 2019 Research Conference*, Toronto, Canada (**Oral**).
15. Valkenburg SA (2019) Antibody responses to twice-annual vaccination due to 2014/2015 H3N2 antigenic mismatch in Hong Kong. *CEIRS 12th Annual meeting*, Baltimore, USA (**Oral**).
16. Valkenburg SA (2019) Reduced antibody function correlates with influenza infection in a household model of transmission. *1st Immunological Correlates for Next Generation Influenza Vaccines, International Society for Influenza and Other Respiratory Virus Diseases (ISIRV)*, Siena, Italy (**Oral**; **ISIRV Oral presentation award**).

4.3 Seminars and Invited Presentations

1. Roberto Bruzzone (2019) Fourth International Conference on Tropical Medicine and Infectious Diseases, Kuala Lumpur, Malaysia.
2. Roberto Bruzzone (2019) Outbreak Preparedness and Readiness in the Lancang Mekong Cooperation Region, Kunming, PR China.
3. Chris Mok (2019) Guangzhou Medical University Annual Meeting, Guangzhou, PR China.
4. Chris Mok (2019) Outbreak Preparedness and Readiness in the Lancang Mekong Cooperation Region, Kunming, PR China.
5. Malik Peiris (2019) MERS-CoV Consultation Meeting, Addis Ababa, Ethiopia.
6. Malik Peiris (2019) CEIRS 12th Annual Meeting, Baltimore, USA.
7. Malik Peiris (2019) Options for the Control of Influenza X, Singapore.
8. Malik Peiris (2019) 132nd Annual International Medical Congress of the Sri Lanka Medical Association, Colombo, Sri Lanka.
9. Sumana Sanyal (2019) Department of Cell Biology and Infection of the Institut Pasteur Retreat, San Feliu de Guixols, Spain.
10. Sumana Sanyal (2019) Pasteur Network Fighting Emerging Threats, Seoul, Korea.
11. Sumana Sanyal (2019) Icahn School of Medicine at Mt Sinai, New York City, USA.
12. Hein Min Tun (2019) National University of Singapore, Singapore.
13. Hein Min Tun (2019) National University Hospital, Singapore.
14. Hein Min Tun (2019) National Center for Infectious Diseases of Singapore, Singapore.
15. Hein Min Tun (2019) Childhood Infections and Pollution Consortium (CHIP) Workshop, Jaipur, India.
16. Hein Min Tun (2019) School of Life Sciences, Chinese University of Hong Kong, Hong Kong SAR.
17. Hein Min Tun (2019) The Rowett Institute, School of Medicine, University of Aberdeen, United Kingdom.
18. Hein Min Tun (2019) 3rd Alternatives to Antibiotics (ATA) Conference, Bangkok, Thailand.
19. Sophie Valkenburg (2019) Kitasato Institute, Tokyo, Japan.
20. Sophie Valkenburg (2019) The University of Hong Kong, Hong Kong SAR.

5. Annexes

5.1 List of Staff

Name	*Position*
BRUZZONE, Roberto	Co-Director
PEIRIS, Malik	Co-Director
DI SANTO, James	Visiting Research Professor
SANYAL, Sumana	Visiting Assistant Professor
TORDO, Noël	Honorary Professor
LI, Wai Sum Iris	Honorary Research Associate
GAYRAUD-MOREL Barbara	Honorary Research Associate
LI, Anne	Administration Manager
LAI, Jimmy	Laboratory Manager
CHAN, Karen	Executive Assistant
HEIN, Min Tun	Research Assistant Professor
MOK, Chris	Research Assistant Professor
VALKENBURG, Sophie	Research Assistant Professor
KAVIAN-TESSLER, Niloufar	Post-Doctoral Fellow
LAN, Iolanthe	Post-Doctoral Fellow
LI, Mingyuan	Post-Doctoral Fellow (Contract ended 29-Feb-2020)
POONSUK, Kanchana	Post-Doctoral Fellow (Contract ended 31-Mar-2020)
BULL, Maireid	PhD Student
CHAN, Darren	PhD Student
COHEN Carolyn	PhD Student
LI, Athena	PhD Student
LIANG, Suisha	PhD Student
PENG, Ye	PhD Student
TEO, Qi Wen	PhD Student
WONG, Ho Him	PhD Student
HO, Julian	MPhil Student
LIN, Yihan	MPhil Student
LYU, Tomas	MPhil Student
SO, Ray	MPhil Student
YIP, Garrick	MPhil Student
SIU, Lewis	Senior Technician
AKHEE, Sabiha Jahan	Research Assistant I (Contract ended 30-Jun-2019)
CHEN, Lynn	Research Assistant I (Contract ended 30-Jun-2019)
LIANG, Weiwen	Research Assistant I

MAK, Fionn	Research Assistant I
NG, Wilson	Research Assistant I
CHAN, Jodi	Research Assistant II (Contract ended 05-Jul-2019)
CHOW, Gigi	Research Assistant II
FERNANDO, Julia	Research Assistant II
HACHIM, Asmaa	Research Assistant II
LAU, Leslie	Research Assistant II
LI, Hao	Research Assistant II
NAIK, Tripti	Research Assistant II (Contract ended 31-Jul-2019)
ON, Hilda	Research Assistant II
VAN LEUR, Sophie	Research Assistant II
WANG, Yiquan	Research Assistant II
CHEUNG, Wai Sze	Laboratory Assistant
CHUNG, Jordan	Student Intern (Brunel University)
YAN, Bo	Student Intern (Nanjing Medical University)
WANG, Qing	Student Intern (Nanjing Medical University)
Van DIEPEN, Max	Student Intern (Erasmus Medical Center Rotterdam)
Van LEUR, Sophie	Student Intern (Erasmus Medical Center Rotterdam)
STAMM, Margaux	Student Intern (Clermont-Auvergne University)
MAURIN, Morgan	Student Intern (Clermont-Auvergne University)
MATHUR, Vrinda	Student Intern (HKUST)
SIN, Zhen Ye	Student Intern (University of Durham)
LEE, Adrian	Student Intern (Ngee Ann Polytechnic)
LI, Sze Wang	Student Intern (University of Hong Kong)
KWOK, Sun Man	Student Intern (University of Hong Kong)
KWONG, Matthew	Student Intern (University of Hong Kong)
WONG, Wing Kei	Student Intern (HK Institute of Vocational Education)
HUI, Chak Man	Student Intern (HK Institute of Vocational Education)
CHAN, Yin Wing	Student Intern (HK Institute of Vocational Education)
LIAO ,Man Kit	Student Intern (HK Institute of Vocational Education)
DENIS, Elena	Student Intern (French International School)
FESCHET, Geraldine	Student Intern (French International School)
SLAOUI, Gabriel	Student Intern (French International School)
WARD, Caroline	Student Intern (French International School)

5.2 Income & Expenses for the year ending June 2019

INCOME:		
Central Fund		
New Allocation	$ 3,509,107.25	21.8%
Faculty in-kind		
New Allocation	$ 1,375,000.00	8.6%
Institut Pasteur		
New Allocation	$ 2,140,887.22	13.3%
Private Donation		
New Allocation	$ 450,000.00	2.8%
External Grants		
New Allocation	$ 7,359,577.39	45.8%
Teaching/Training		
New Allocation	$ 1,239,467.86	7.7%
TOTAL	**$ 16,074,039.72**	**100.0%**
EXPENSES:		
Staff cost	$ 7,981,536.20	50.9%
Stipend	$ 461,009.86	2.9%
Research	$ 5,744,874.44	36.6%
Administration	$ 65,337.46	0.4%
Teaching/Training	$ 1,377,343.15	8.8%
Refund to fund provider	$ 57,625.48	0.4%
TOTAL	**$ 15,687,726.59**	**100.0%**
BALANCE CARRY FORWARD TO 2019/2020	**$ 386,313.13**	

5.3 Forecast of Income for the year ending June 2020

INCOME:

Central Fund		
New Allocation	$ 3,211,591.00	21.3 %
Faculty in-kind		
New Allocation	$ 1,625,000.00	10.8%
Institut Pasteur		
New Allocation	$ 2,225,283.83	14.8%
Private Donation		
New Allocation	$ 100,000.00	0.7%
External Grants		
New Allocation	$ 6,895,459.74	45.7%
Teaching/Training		
New Allocation	$ 1,040,572.44	6.9%
	$ 15,097,907.01	**100.0%**

5.4 15th HKU-Pasteur Virology Course

15th HKU-Pasteur Virology Course

HKU Med
LKS Faculty of Medicine
HKU-Pasteur Research Pole
香港大學-巴斯德研究中心

Coronaviruses

Open Lectures

			VENUE
July 7, 2019	**13:30 – 15:30**		
	The Biology of Coronaviruses - a general overview		**HRI-S2**
	Peter ROTTIER, Utrecht University, The Netherlands		
July 8, 2019	**08:30 – 10:00**		
	Viral and Host Determinants of MERS-CoV Transmission		**HRI-S1B**
	Bart HAAGMANS, Erasmus MC, The Netherlands		
	10:30 – 12:00		
	Animal Reservoirs of Human Coronaviruses		**HRI-S1B**
	Zhengli SHI, Wuhan Institute of Virology - CAS, PR China		
July 11, 2019	**08:30 – 10:30**		
	Immune Responses in MERS-CoV Infected Mice and Humans		**HRI-S1B**
	Jincun ZHAO, Guangzhou Medical University, PR China		
	11:00 – 12:30		
	Animal Models of Coronavirus Infection		**HRI-S1B**
	Emmie de WIT, National Institute of Allergy and Infectious Diseases, NIH, Hamilton, MT, USA		
July 12, 2019	**08:30 – 10:30**		
	The Search for Coronavirus Prophylactic and Therapeutic Therapies		**HRI-S1B**
	Amy SIMS, University of North Carolina at Chapel Hill, USA		

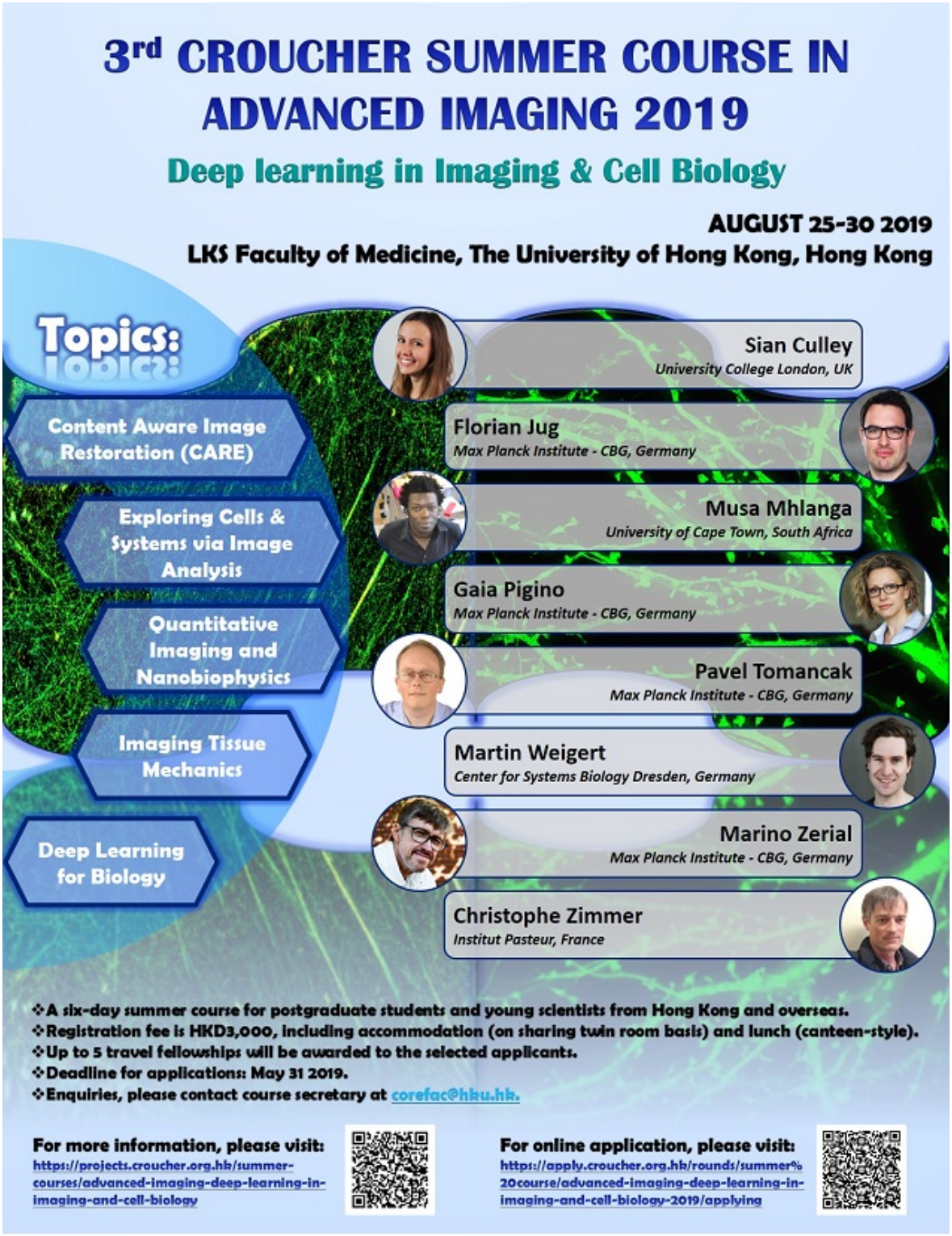
Venue
Seminar Room, Ground Floor
HK Jockey Club Building for Interdisciplinary Research
5 Sassoon Road, Pokfulam, Hong Kong

Pasteur Foundation Asia 巴斯德亞洲基金

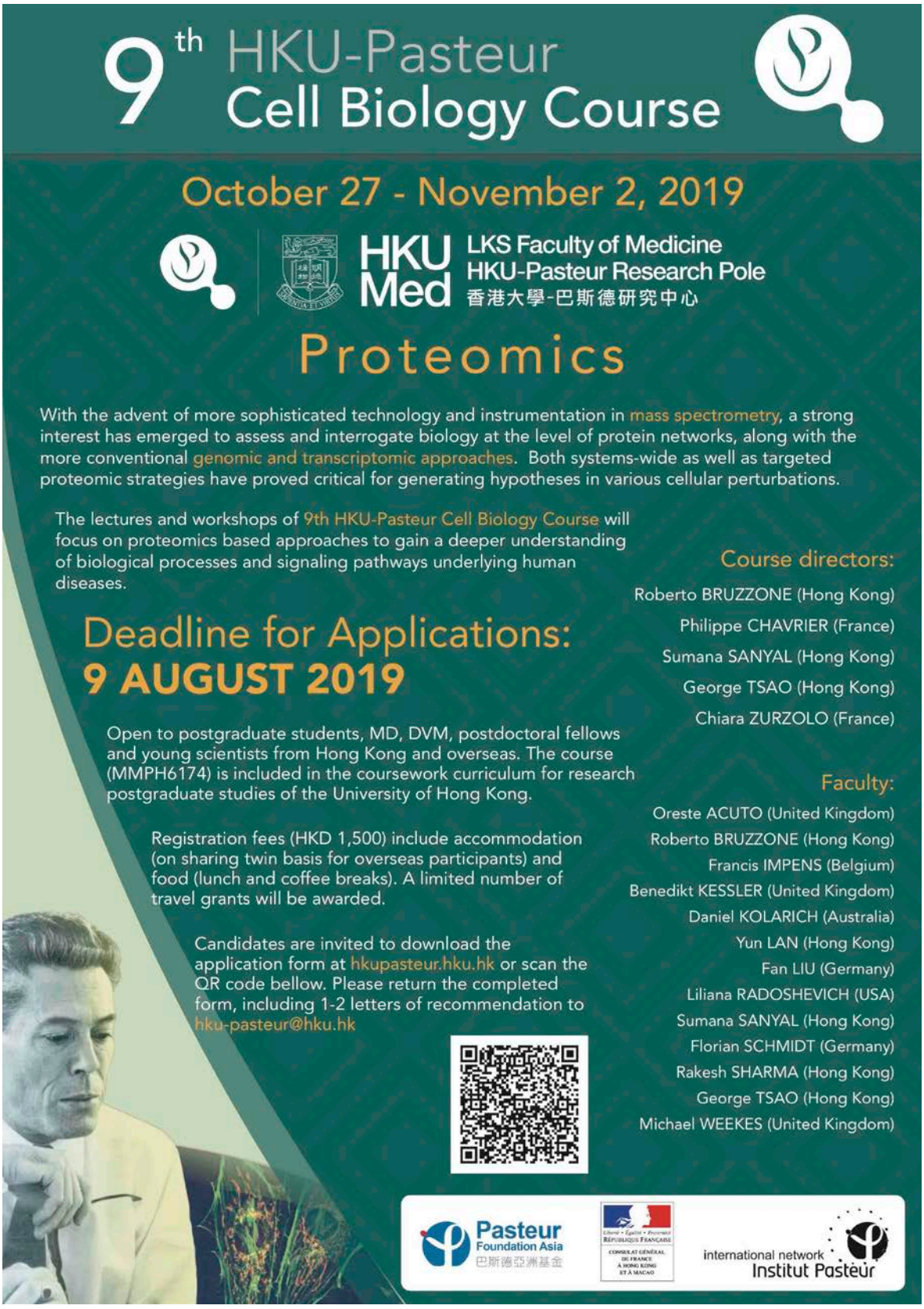
Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
CONSULAT GÉNÉRAL DE FRANCE À HONG KONG ET À MACAO

international network Institut Pasteur

5.5 3rd Croucher Summer Course in Advanced Imaging



5.6 9th HKU-Pasteur Cell Biology Course



9th HKU-Pasteur Cell Biology Course

HKU Med LKS Faculty of Medicine
HKU-Pasteur Research Pole
香港大學-巴斯德研究中心

Proteomics
Open Lectures

Monday, 28 October 2019

L2: Exploring the ubiquitin landscape in cancer with advanced proteomics **09:00 – 11:00**
Benedikt Kessler, University of Oxford, UK

L3: Cross-linking mass spectrometry in complex biological systems – Part 1 **11:30 – 12:30**
Fan Liu, Leibniz Institute of Molecular Pharmacology, Germany

L3: Cross-linking mass spectrometry in complex biological systems – Part 2 **14:00 – 15:00**
Fan Liu, Leibniz Institute of Molecular Pharmacology, Germany

Tuesday, 29 October 2019

L4: How proteomics can help understanding immunity **09:00 – 11:00**
Oreste Acuto, University of Oxford, UK

L5: Functional strategies to isolate ubiquitylated proteins during flavivirus infections - Part 1 **11:30 – 12:30**
Sumana Sanyal, HKU-Pasteur Research Pole, Hong Kong SAR

L5: Functional strategies to isolate ubiquitylated proteins during flavivirus infections - Part 2 **14:00 – 15:00**
Sumana Sanyal, HKU-Pasteur Research Pole, Hong Kong SAR

Thursday, 31 October 2019

L7: Interrogating the Cell Biology of Infection and Immunity with Camelid Nanobodies **09:00 – 11:00**
Florian Schmidt, University of Bonn, Germany

L8: Quantitative label-free proteomics to investigate host-pathogen interactions – Part 1 **11:30 – 12:30**
Francis Impens, Ghent University, Belgium

L8: Quantitative label-free proteomics to investigate host-pathogen interactions – Part 2 **14:00 – 15:00**
Francis Impens, Ghent University, Belgium

Venue: HKJC Building for Interdisciplinary Research HRI-S2

Pasteur Foundation Asia 巴斯德亞洲基金

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
CONSULAT GÉNÉRAL DE FRANCE À HONG KONG ET À MACAO

international network Institut Pasteur

5.8 8th Epidemiology Workshop "Measles and Rubella Elimination: Options for Public Health Interventions" in Ho Chi Minh City, Vietnam

5.7 List of Public Lectures organized by HKU-PRP

03/07/2019
Erik Karlsson, Virology Unit Institut Pasteur - Cambodia
Nutrition and Endemic/Emerging Infectious Diseases in Cambodia

07/07/2019
Peter Rottier, Utrecht University, The Netherlands
The Biology of Coronaviruses - a general overview

08/07/2019
Bart Haagmans, Erasmus MC, The Netherlands
Viral and Host Determinants of MERS-CoV Transmission

08/07/2019
Zhengli Shi, Wuhan Institute of Virology - CAS, PR China
Animal Reservoirs of Human Coronaviruses

09/07/2019
Manon Ragonnet, MRC Fellow, Imperial College London
Cryptic transmission risk factors in HIV transmission networks

11/07/2019
Jincun Zhao, Guangzhou Medical University, PR China
Immune Responses in MERS-CoV Infected Mice and Humans

11/07/2019
Emmie De Wit, National Institute of Allergy and Infectious Diseases, NIH, Hamilton, USA
Animal Models of Coronavirus Infection

12/07/2019
Amy Sims, University of North Carolina at Chapel Hill, USA
The Search for Coronavirus Prophylactic and Therapeutic Therapies

09/09/2019
Shashank Tripathi, Center for Infectious Disease Research, Indian Institute of Science, Bengaluru, India
Host interactions and pathogenesis of emerging human viruses: Zika and Influenza in focus

25/10/2019
James Di Santo, Institut Pasteur, France
Innate Lymphoid Cell Differentiation - From a T Cell Perspective

28/10/2019
Benedikt Kessler, University of Oxford, United Kingdom
Exploring the ubiquitin landscape in cancer with advanced proteomics

28/10/2019
Fan Liu, Leibniz Institute of Molecular Pharmacology, Germany
Cross-linking mass spectrometry in complex biological systems

29/10/2019
Oreste Acuto, University of Oxford, United Kingdom
How proteomics can help understanding immunity

29/10/2019
Sumana Sanyal, HKU-Pasteur Research Pole, Hong Kong SAR
Functional strategies to isolate ubiquitylated proteins during flavivirus infections

31/10/2019
Florian Schmidt, University of Bonn, Germany
Interrogating the Cell Biology of Infection and Immunity with Camelid Nanobodies

31/10/2019
Francis Impens, Ghent University, Belgium
Quantitative label-free proteomics to investigate host-pathogen interactions

HKU Med LKS Faculty of Medicine
HKU-Pasteur Research Pole
香港大學-巴斯德研究中心

Seminar

Nutrition and Endemic/Emerging Infectious Diseases in Cambodia

by
Erik Karlsson, PhD
Virology Unit
Institut Pasteur – Cambodia

Date: Wednesday, 3rd July 2019
Time: 11:00 am
Venue: Seminar Room 2 (HRI-S2), Ground Floor,
HKJC Building for Interdisciplinary Research
5 Sassoon Road, Pokfulam, Hong Kong

Abstract

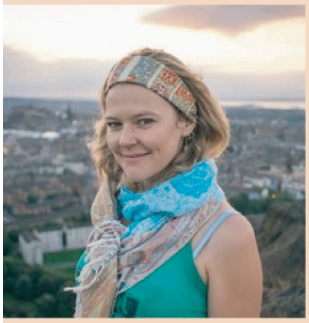
Cambodia is a hotspot of emerging and endemic infectious disease. In addition, after facing numerous years of rampant undernutrition, Cambodia is now facing a "triple burden" of malnutrition where obesity and underweight exist side-by-side with other dietary concerns, such as micronutrient deficienc y. This talk will explore the current status of both infectious disease and nutrition in Cambodia and discuss some of the work done on understanding the interplay between nutrition and several pathogens (avian and seasonal influenza, dengue, rabies) in the context of disease severity, transmission, vaccination, and viral evolution itself.

Biosketch

Dr. Karlsson obtained his doctoral degree in Nutrition from the University of North Carolina at Chapel Hill, Gilling's School of Global Public Health and was a postdoc at St. Jude Children's Research Hospital where his work focused on nutritional influences on influenza virus pathogenesis and global influenza sur veillance. He currently ser ves as the Senior Research Fellow in the Virology Unit at Institut Pasteur du Cambodge (IPC) in Phnom Penh, Cambodia. His work covers several aspects of virus research in Cambodia including surveillance and vaccination, with a special interest in the interplay between malnutrition and infection.

LKS Faculty of Medicine
HKU-Pasteur Research Pole
香港大學-巴斯德研究中心

Seminar



Cryptic transmission risk factors in HIV transmission networks

by
Manon Ragonnet
MRC Fellow, Imperial College London

Date: 9 July 2019
Time: 16:00 - 17:30
Venue: HRI-1B, Ground Floor
HKJC Building for Interdisciplinary Research
5 Sassoon Road, Pokfulam, Hong Kong

Abstract

HIV combination antiretroviral therapy prolongs the lives of people living with HIV and significantly reduces onward transmission. Yet, HIV continues to spread through increasingly concentrated populations and poorly understood contact networks. The UK and the USA have accumulated large datasets of HIV sequences from patients and anonymised genetic analysis of these sequences can elucidate transmission patterns within and between key risk groups.

In the UK, these analyses have highlighted the existence of a group of men who self-report as heterosexual but whose viruses link only to men who have sex with men. Further inquiry into the position of these men in reconstructed networks suggests that their behaviour may differ from that of both heterosexual men and men who have sex with men.

In Los Angeles County, California, we specifically looked at the position of transgender women (individuals assigned the male sex at birth, but who identify as women) in HIV transmission networks and developed a framework for increasing diagnosis rates among transgender women based on network structure.

Our results provide a more thorough understanding of local HIV transmission dynamics with the aim of improving targeted HIV intervention strategies.

Biosketch

Manon Ragonnet is a Research Fellow at Imperial College London. She studies the evolution and spread of RNA viruses (mostly HIV with a little hepatis C) using phylodynamic analysis. Her research interests stem from both the challenge presented by HIV's formidable adaptive capacity and its public health implications. She has previously worked on HIV transmission in Canada, the US, Uganda, and South Africa and currently works in the UK and Botswana. Her current research focuses on estimating meaningful epidemic parameters during HIV outbreaks (such as the recent HIV outbreak among people who inject drugs in Glasgow) and on quantifying the impact of imports into regional epidemics.

ALL ARE WELCOME

HKU Med LKS Faculty of Medicine School of Public Health 香港大學公共衞生學院

Host interactions and pathogenesis of emerging human viruses: Zika and Influenza in focus

by

Dr Shashank Tripathi

Assistant Professor
Wellcome-Trust India Alliance Intermediate Fellow
Center for Infectious Disease Research
Indian Institute of Science, Bengaluru, India

Date : 9 September 2019 (Monday)
Time : 11:30 a.m.
Venue : Room S1A, G/F Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road

Abstract:

With increasing globalization, urbanization, deforestation and climate change there has been alarming increase in emergence of new human viral pathogens and reemergence of old ones. Zika virus is the latest example which caused global emergency in 2016. Influenza on the other hand is constantly remerging and continues to be a grave concern for public health across the globe. In this talk speaker will discuss his published research on Zika virus, which will include antagonism of host cellular innate immunity by ZIKV NS5 mediated targeting of STAT2, development of *Stat2-/-* mouse as a model to study Zika virus pathogenesis, ZIKV strain specific differences in the virulence and role of preexisting anti-flavivirus immunity in antibody dependent enhancement of Zika virus infection. Further, speaker will discuss his work on systems level analysis of Influenza A virus RNAi and Proteomics datasets to chart the functional landscape of IAV-Host interaction network, which led to identification of multiple host directed therapy targets. Speaker will conclude with discussing new research on regulation of intracellular trafficking of IAV structural proteins.

Bio-sketch:

Dr. Shashank Tripathi is currently an Assistant Professor in the Microbiology & Cell Biology Department of Indian Institute of Science, which is India's no.1 research and education Institute. He was awarded Wellcome Trust India Alliance Intermediate fellowship in 2018 and Infosys young investigator award in 2019. Earlier, he worked as Research Assistant Professor (2017-2018) and as Post-Doctoral Researcher (2012-2016) in Microbiology Department of Icahn School of Medicine at Mount Sinai in New York. There he worked in world renowned virologist Prof. Adolfo Garcia-Sastre's lab, studying influenza A virus-host interactions at systems level and immune evasion and pathogenesis of Zika viruses. Dr. Tripathi did his PhD (2012) in supervision of Dr. Sunil Lal in the Virology Group of International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi in collaboration with Influenza Division, Centers for Disease Control, Atlanta.

HKU Med LKS Faculty of Medicine
HKU-Pasteur Research Pole
香港大學-巴斯德研究中心

Seminar

Innate Lymphoid Cell Differentiation From a T Cell Perspective

by James Di Santo
Director of Research Exceptional Class, Inserm
Professor, Institut Pasteur, France

Date: Friday, 25th of October, 2019
Time: 11:00 am
Venue: HRI-S1B, Ground Floor
HKJC Building for Interdisciplinary Research
5 Sassoon Road, Pokfulam, Hong Kong

Abstract

Innate lymphoid cells (ILCs) and natural killer (NK) cells have garnered considerable interest due to their functional properties in immune defense and tissue homeostasis. Our current understanding of how these develop has been greatly facilitated by knowledge of T cell biology.

Established models of T cell differentiation have provided the conceptual basis for a classification of ILCs and NK cells as innate homologues of adaptive T helper cells and cytotoxic T cells, respectively. Furthermore, NK cell and ILC activation finds parallels with known regulatory mechanisms within the T cell system.

Here, I will examine the process of NK cell and ILC biology from a 'T cell perspective' in an attempt to extend the analogy between adaptive T cells and their innate ILC and NK cell counterparts.

Biosketch

James Di Santo received a combined MD/PhD from Cornell Medical College and the Sloan Kettering Institute in NYC, pursued postdoctoral training with Pr Alain Fisher (Necker Hospital, Paris) and Pr Klaus Rajewsky (Institute for Genetics, Cologne) and have more than 30 years of experience in fundamental and translational immunology.

The main interests of his laboratory at the Institut Pasteur (Paris) are in the areas of lymphocyte biology, cytokines, transcription factors and signaling pathways in the development and function of both adaptive (T and B cell) and innate lymphoid cells (ILC, NK cells) in mice and man.

In parallel, over the last 20 years, his team has developed a series of humanized mouse models for the immune system that allows us to probe fundamental questions in human immunology especially in relation to infectious diseases. While largely fundamental in nature, his projects have a translational aim to impact in the clinics.

ALL ARE WELCOME