Annual Report 2017

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

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1. 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 of the Li Ka Shing Faculty of Medicine of the University of Hong Kong. As one of the hubs of the Institut Pasteur International Network, HKU-PRP aims to improve global health through research and education by confronting the challenges posed by viral infections and provide solutions to treat infectious diseases.

Research

HKU-PRP supports innovative research programs that promote a "One-Health" approach to understand basic mechanisms of virus biology and mitigate the impact of infectious diseases. We have organized our activity around Group Leaders who are engaged in competitive research projects on respiratory viruses (influenza and coronaviruses) and mosquito borne viruses (dengue and Zika). With respect to influenza research, we have extended our exploration of virus-host interaction and host response to viral infection by combining clinical studies and basic research investigations to gain insight into the mechanistic aspects of disease pathogenesis and adaptive immunity for improved protection. 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. Collaboration with the First Affiliated Hospital of Guangzhou Medical University, where laboratory space has been made available to HKU-PRP, has also led to very significant findings on the viral evolution of H7N9 avian influenza and the newly identified Middle East respiratory syndrome coronavirus. In addition, we have begun to explore the consequences of respiratory virus infections on skeletal muscles and muscle stem cells in vivo. 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 are investigating newly identified host factors that are exploited to facilitate virus replication, biogenesis, trafficking, and egress. As propagation of dengue and Zika viruses appears to involve extensive membrane and lipid remodeling, we have designed a functional screening strategy and a set of proteins in lipid metabolism that are differentially modified upon infection by dengue and Zika viruses. HKU-PRP has published over than 20 papers in 2017 and 10 are currently submitted or in preparation.

Teaching

Our educational program has been further expanded in 2017, drawing an increasing number of highly qualified applications from around the world. We have continued our course series in Immunology and Virology, and have co-organized the second edition of the Croucher Summer School on Advanced Imaging. In collaboration with the C3BI at the Institut Pasteur and the Center for Genomic Sciences at HKU, we have held a hands-on course on Next Generation Sequencing. The 2017 edition of our Public Health Workshop series at the Pasteur Institute of Ho Chi Minh City (Vietnam), which is primarly aimed at public health professionals and academics in the region, has covered for the first time the topic of "Health Economics". HKU-PRP courses have generated a worldwide network of trainees.

Perspectives

We have developed a strong identity to promote the agenda of HKU, IP and the Institut Pasteur International Network, through research, teaching and public health activities. In recognition of our achievements, HKU and IP have signed a10-year extension of their collaborative agreement. Together with the School of Public Health a new Group Leader will join HKU-PRP to develop a research program on anti-microbial resistance. The interdisciplinary nature of our research and teaching will facilitate synergies with the new School of Biomedical Sciences, established by HKU to integrate basic science departments. Dr Sumana Sanyal has received a career development award from the Croucher Foundation that carries a joint affiliation to the School of Biomedical Sciences and Professor James Di Santo's appointment as Visiting Professor from IP for the period 2016-8 will further strengthen collaborations and innovative projects in the field of basic immunology. In summary, the results obtained in 2017 are clearly in line with our strategic objective to position HKU-PRP as a cluster of excellence within the School of Public Health.

2. Overview of the Programs

2.1 Research

The scientific activity of HKU-PRP is organized around three core research questions:

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 by combining clinical studies that span serology, epidemiology and pathogenicity to delineate genetic determinants of virulence and the acquisition of traits that favor crossing of species barriers by zoonotic viruses.
3. *How do pathogens withstand the host immune response?* 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.

Research in the Suki Lee lab focuses on virus-host interaction and host innate immune response to viral infection, with a major objective to investigate the underlining mechanisms of innate immunity relevant to disease pathogenesis. Her lab revealed a novel role of an orphan receptor, TLR10, in viral pathogenesis by showing that influenza virus infection increased TLR10 expression and providing evidence for the involvement of TLR10 in innate immune sensing of viral infection and in cytokine production. The Lee lab has now extended its investigations on TLR10 to identify its ligand and signaling pathways and has demonstrated that TLR10 is a novel nucleotide sensing receptor and that dsRNA is a ligand of TLR10 for its downstream signaling to regulate IFN response. Recognition of dsRNA by TLR10 activates recruitment of MyD88 for signal transduction and suppression of IRF-7 dependent type I IFN production. We have also demonstrated crosstalk between TLR10 and TLR3, as they compete with each other for dsRNA binding. Our results suggest for the first time that dsRNA is a ligand for TLR10 and have proposed novel functions of TLR10 in regulating IFN signaling. The lab is also investigating the neuropathogenicity of avian influenza H7N9 virus. They have demonstrated that avian influenza A H7N9 virus can infect differentiated human astrocytic and neuronal cells, much like pandemic H1N1 virus (pdmH1N1); however only H7N9 produces infectious progeny viruses in human neuronal cells. Neither of these viral strains can generate infectious progeny virus in human astrocytes although replication of viral genome was detected. Furthermore, H7N9 virus triggered high pro-inflammatory cytokine expression, whilst pdmH1N1 virus induced only low cytokine expression in either brain cell type. These experimental findings demonstrate that avian H7N9 virus can infect, replicate, induce cytokine upregulation and cause cytopathic effects in human brain cells, and thus may potentially lead to profound central nervous system injury. Neurological complications due to H7N9 virus infection, therefore, deserves further attention when managing these patients.

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. Through our well-established platform of the "Guangdong-Hong Kong Joint Research Centre for Clinical and Preventive Medicine against Emerging Infectious Diseases" and collaboration with the Princess Margaret Hospital in Hong Kong, the Mok lab has identified two novel avian influenza viruses (H7N9 and H5N1) that showed unusual characteristics and have further investigated their clinical and basic features. Thus the Mok lab has reported one of the first fatal case of human H7N9 in China and described that the infection was due to A/H7N9 virus having a polybasic amino acid sequence at the hemagglutinin cleavage site (PEVPKRKRTAR/GL), which is a hallmark of high pathogenicity in birds. This feature might have contributed to the patient's adverse clinical outcome. The patient had a history of exposure to sick and dying poultry, and his close contacts had no evidence of H7N9 disease, suggesting that human-to-human transmission did not occur. The lab has set up a solid collaboration with the Guangdong Province Center for Disease Control (GDCDC) to monitor the epidemiological data of human H7N9 infections and the prevalence of this subtype in poultry market. This study is of great public health

relevance, as last year the highly pathogenic H7N9 subtype was found to co-circulate with the current low pathogenic subtype in the market. They have now reported the prevalence of the highly pathogenic avian influenza (HPAI) A(H7N9) virus in Guangdong poultry markets through active surveillance and compared the epidemiological characteristics and clinical outcomes between the patients infected with the HPAI and LPAI A(H7N9) viruses in Guangdong province during last season. These investigation have concluded that touching sick or dead poultry was the most important risk factor to HPAI A(H7N9) infections and should be highlighted for the control of future A(H7N9) epidemics. Chris Mok and co-workers have also established a new transcriptomic analysis approach from clinical specimens together with the colleagues at the State Key Laboratory of Respiratory Disease (Guangzhou, PR China) and The Scripps research Institute (USA) to further dissect the pathogenesis of H7N9 infection in humans.

The main objectives of the Sumana Sanyal lab are to combine methods of molecular biology and immunology to address aspects of host-pathogen interactions. Using influenza and dengue as model systems, the lab aims to determine the identity and function of specific host factors that are exploited by these viruses to complete their intracellular life cycle. 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. In this context, 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. The Sanyal lab has 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. These findings with dengue virus are being extended to explore similarities and differences that exist in Zika virus infection. The Sanyal lab also investigates 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, they are particularly interested in 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. The ubiquitylation machinery is frequently exploited by a number of pathogens either to masquerade as host proteins or to inhibit immune signaling cascades. By employing a chemoenzymatic strategy, the lab has identified deubiquitylating enzymes (DUBs) that are specifically expressed upon influenza infection and are currently investigating the role of these DUBs. Ongoing studies involve characterization and pharmacological intervention of these DUBs in order to attenuate influenza infection. Preliminary data in macrophages and dendritic cells 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.

The main objectives of the group of Sophie Valkenburg are to delineate 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, 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 these studies will ultimately help develop. In collaboration with Liyange Perera and Thomas Waldmann at NIH, her group 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, 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 for future vaccine strategies. In a complementary approach, the Valkenburg lab, in collaboration with Ben Cowling, who lead the epidemiology group at the School of Public Health, is assessing the correlation between higher baseline early effector T cell memory responses and protection from influenza infection or reduced symptom severity and viral shedding in a household transmission setting. Whilst T cell responses have been shown to be highly effective in mediating protection in mouse models, corresponding data in human influenza infection is not as robust. All adults have established influenza-specific memory T cell responses; however, we have repeated infections during our lifetime that can range from mild to life threatening. Blood samples are obtained from infected index cases, and uninfected household contacts that are monitored for influenza transmission, at day 0 and day 28. The aim of the study is to find if there is an immunological difference between contacts positive and negative for influenza transmission during sampling. Sample collection has been ongoing since June 2013 due to the limited and specific nature of cases and intensity of monitoring households.

The research activity of HKU-PRP includes work by **Jimmy Lai** (joint appointment in the Department of Pathology), who studies the interactions between viruses with the host receptors, in order to have a better understanding on viral host adaptation and cell/tissue tropism. Main projects include the study of influenza virus-cell receptor interactions at the atomic level by combination of chemical, biochemical and cell biological methods; and the investigation of the interplay between different influenza surface proteins during viral infection. 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, conclusively demonstrate that camels are a significant reservoir for the maintenance of MERS-CoVs, and they are an important source of human infection with MERS. In addition, MERS-CoV is actively circulating in dromedary populations in Africa and the virus in Africa is phylogenetically distinct from that in the Middle East. The Peiris team has also found evidence of reinfection of camels that were previously seropositive, thus suggesting that prior infection does not provide complete immunity from reinfection, an observation that is relevant to camel vaccination strategies as a means to prevent zoonotic transmission. HKU-PRP has welcomed **Barbara Gayraud-Morel** as Visiting Scientist from the Institut Pasteur, who is working in collaboration with teams at HKU and HKUST to explore the consequences of respiratory virus infections on skeletal muscles and muscle stem cells in particular. This work is at the interface between her expertise in skeletal muscle biology and the focus on infectious diseases studied at HKU-PRP. The project involves collaboration between HKU-PRP and several laboratories: Leo Poon (School of Public Health at The University of Hong Kong), Tom Cheung (Hong Kong University of Science and Technology), and the Stem Cell and Development laboratory directed by Shahragim Tajbakhsh (Institut Pasteur, Paris), where Barbara holds a permanent position. Her results show that during influenza viral infection, muscle stem cells are subjected to several modifications at the protein and gene expression levels. We are now investigating whether these molecular changes are the consequences of muscle stem cells sensing circulating cytokines generated by the inflammation-taking place in the lung. We are particularly interested to elucidate whether clearance of adhesion receptors is a cellular strategy of stem cells to limit unwanted leucocyte infiltration to uninjured tissue, preventing unnecessary cell activation which could have detrimental effects on tissue homeostasis. The second area of research aims to establish a human lung epithelium model to study infectious diseases. Until now, most experiments with influenza and other respiratory viruses are performed on cell lines more or less related to human epithelial lung cells. We aim to take advantage of the growing human embryonic stem cell (hESC) and iPSC fields to establish a model of human lung epithelium to investigate respiratory infectious diseases. These past years, few laboratories have succeeded to generate efficient *in vitro* lung and airway epithelial cells from human pluripotent cells for applications in regenerative medicine, modeling lung diseases, or drug screening.

2.2 Teaching and Education

HKU-PRP has pioneered in Hong Kong an advanced teaching program in life sciences that will train a highly selected group of international students who will be at the forefront of biomedical research in their countries. This program is extremely competitive, and significantly contributes to solidifying the reputation of HKU-PRP for training in biomedical research. The **HKU-Pasteur Virology Course** has been held for the 14th consecutive year. The 2017 edition focused on two key questions for influenza research: How does influenza virus cause disease? What are the determinants of influenza virus transmission? The course discussed the different factors that contribute to pathogenicity and transmissibility of influenza virus in humans, in the context of our interactions with animal reservoirs. The lectures emphasized the clinical and practical aspects, basic virology, cell biology, epidemiology and ecology of the influenza viruses. The workshop was built around the preparation of a multidisciplinary grant proposal to address the main challenges that we are facing in influenza research. Students were split into 5 groups focusing on five areas of influenza research: clinical, ecology, epidemiology, immunology and vaccinology. They were required to identify relevant question(s), generate hypothesis and propose experimental approaches to address them. Each group presented their proposed work-package using slide format during the last day of the course. **The HKU-Pasteur Immunology Course** reached the 9th edition. This year the course capitalized on the concepts developed by the multidisciplinary project called Milieu Intérieur to explore the ongoing transition from reductionist studies based on the application of genetic approaches in animal models to a more integrated view of the physiology and pathology of the human immune system that will eventually provide a foundation for defining immune responses of healthy individuals. It highlighted the latest advances in large-scale, quantitative data collection and computational analysis as applied to biochemical aspects of immune cell activation and function, multicellular behavior in tissues and model organisms, and human immune function in health and disease. Lectures were complemented by a hands on practical workshop which spanned the 2 week course. The practical course flowed from cellular isolation, characterization of immune cell subsets by advanced multi-parameter flow cytometry, in vitro stimulation to downstream RNAseq analysis of gene expression. The wet lab experience involved isolation of PBMC from whole blood, freezing and thawing cells, immune cell staining, flow cytometry (LSR Fotressa), in vitro stimulation and RNA isolation. The second week workshop involved a 'dry' laboratory experience, whereby students were given a reference RNAseq dataset of stimulated samples (as derived in the wet lab). The students then worked through the dataset using open source analysis platforms on Galaxy, resulting in interpretation of the effect of immune stimulation on expression profiles. We have co-organized with the Faculty Core Facility of HKU the second edition of the **Croucher Summer Course on Advanced Imaging**. The course showcased the latest advances in the development of single molecule andsuper-resolution microscopy combined with image analysis and applications in biomedical research. We have invited internationally-renowned experts to share their exciting research findings and expertise. Topics included single molecule and organismal imaging,high-content imaging, light-sheetmicroscopy ,super-resolution and high-speedimaging and theirapplications. To take into account the increasing demand for training in *omic* science, we have held a **Hands-on Next Generation Sequencing Course**, in collaboration with the C3BI of the Institut Pasteur and the Center for Genomic Sciences at HKU. There were more than 100 application for the course and we are considering the possibility to hold it on a biennial basis. Overall, our course have received increasing support from extramural funding.

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 2017 edition, organized in close partnership with the Pasteur Institute of Ho Chi Minh City, the School of Public Health at HKU and the International Network of Institut Pasteur, was **"Health Economics"**. The workshop has focused on basic theory of health economics including socio-economic concepts, methods to define, measure and analyse costs of health policies, as well

as comparative analysis of health systems. The course series has been generously supported from its inception by the Regional Health Cooperation Office of the French Ministry of Foreign Affairs.

All Group Leaders are actively engaged in our international courses as well as in the undergraduate and postgraduate curriculum of HKU. We have hosted two international Master students for their laboraotyr placement, from Erasmus Medical Centre (The Netherlands) and the University of Lille (France).

2.3 International Activity

We retain leadership roles in a number of global projects. **Roberto Bruzzone** is a member of the **Executive Committee and Vice-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. **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. This large-scale multidisciplinary project builds on the success of the Area of Excellence scheme on "Control of Pandemic and Inter-pandemic Influenza", which was also initiated and coordinated by **Malik Peiris**. The TRS aims at enhancing global public health by identifying the viral and host determinants of influenza virus transmission and pathogenesis leading to evidence-based interventions. **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.

3. Progress Report

3.1 Suki MY LEE Lab

Main Objectives and Strategy

Acute respiratory viral infections remain a major cause of morbidity worldwide and of mortality in the developing world. Emerging respiratory viruses such as MERS, SARS, avian influenza H5N1 and pandemic H1N1 affected societies and economies in many countries. The innate immune system is the first line of host defense and is central to a patient's effort to combat such emerging infections as well as common respiratory virus diseases. Our lab focuses on virus-host interaction and host innate immune response to viral infection, with a major objective to investigate the underlining mechanisms of innate immunity relevant to disease pathogenesis, and to explore the potential of novel therapeutic targets for the treatment. Our major research projects are listed below.

Involvement of TLR10 in induction of innate immune responses to influenza virus infection

Our lab has uncovered a novel role of an orphan toll-like receptor (TLR), TLR10, in viral pathogenesis. We showed that influenza virus infection increases TLR10 expression and demonstrated the involvement of TLR10 in innate immune sensing of viral infection and the production of cytokine and interferon (IFN). We have extended our study on TLR10 to identify its ligand and signaling pathways and have demonstrated that TLR10 is a novel nucleotide sensing receptor and that dsRNA is a ligand of TLR10 for its downstream signaling to regulate IFN response.

Neuropathogenicity of avian influenza AH7N9 virus

We have demonstrated that avian influenza A H7N9 virus can infect differentiated human astrocytic and neuronal cells, much like pandemic H1N1 virus (pdmH1N1); however only H7N9 produces infectious progeny viruses in human neuronal cells. Neither of these viral strains can generate infectious progeny virus in human astrocytes although replication of viral genome was detected. Furthermore, H7N9 virus triggered high pro-inflammatory cytokine expression, whilst pdmH1N1 virus induced only low cytokine expression in either brain cell type. These experimental findings demonstrate that avian H7N9 virus can infect, replicate, induce cytokine upregulation and cause cytopathic effects in human brain cells, and thus may potentially lead to profound central nervous system injury. Neurological complications due to H7N9 virus infection, therefore, deserves further attention when managing these patients.

Achievements and Ongoing Research

We have revealed that TLR10 predominantly localizes to endosomes and binds dsRNA *in vitro*, suggesting that dsRNA is a ligand of TLR10. Recognition of dsRNA by TLR10 activates recruitment of MyD88 for signal transduction and suppression of IRF-7 dependent type I IFN production. We have also demonstrated crosstalk between TLR10 and TLR3, as they compete with each other for dsRNA binding. Our results suggest for the first time that dsRNA is a ligand for TLR10 and have proposed novel functions of TLR10 in regulating IFN signaling.

In research supervision and teaching, a new MPhil candidate (Aisha SELIM) has joined my team and received the Best Poster Prize at the HKU Research Postgraduate Symposium on 6-7 December 2017. An international exchange student, Myriam Eutamene from the University of Lille (France) trained under my direct supervision for two months and a student from the French International School in Hong Kong, Lison Guyon, joined my lab for

summer internship training.

This year, Suki Lee has received the Milstein Travel Award from the International Cytokine and Interferon Society to attend the 2017 Cytokine Meeting (Japan). Moreover, after receiving the Most Promising Young Researcher Award from Hong Kong Food and Health Bureau in 2014, I was an invited speaker as an outstanding scientist at the 2017 Research Fund Secretariat Grant Skills Training Workshop, City University of Hong Kong.

Publications

1. Ng YP, Yip TF, Peiris JSM, Ip NY, Lee SMY (2018) Neuropathogenesis of avian influenza A H7N9 virus. (*Manuscript in revision)*.
2. Lee SMY, YipTF, Yan S, Jin DY, Wei HL, Guo RT, Peiris JSM (2018) Recognition of double-stranded RNA and regulation of interferon pathway by Toll-like receptor 10. (*Manuscript in revision)*.
3. Zhang N, Bao YJ, Tong A, Bader G, Zuyderduyn S, Peiris JSM, Lok S, Lee SMY (2018) Whole transcriptome analysis reveals differential gene expression profile reflecting macrophage polarization in response to influenza A H5N1 virus infection. (*Manuscript in revision)*

Presentations at Meetings

1. Ng YP, Yip TF, Peiris JSM, Ip NY, Lee SMY (2017) Influenza A H7N9 virus infects human brain astrocytes & neuronal cells and induces inflammatory immune responses. *Cytokines 2017,* Kanazawa, Japan (Poster).

Teaching

1. Suki Lee (2017) Hematology and Immunology System – Problem Based Learning (MBBS Year 2), LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR (*Tutor*).
2. Suki Lee (2017) Institut Pasteur Massive Open Online Courses (MOOC) "Innate immunity and infectious diseases": Toll-like receptors in influenza virus infection (*Lecturer*).

Collaborations (local and international)

1. **Nancy Y Ip** (Division of Life Science, The Hong Kong University of Science and Technology, Hong Kong SAR): Viral neuropathogenesis.
2. **RT Guo** (Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, PR China): Determination of the crystal structure of TLR10.
3. **John Hiscott** (Istituto Pasteur-Fondazione Cenci Bolognetti, Rome, Italy): Effect of RIG-I agonists on TLR10 mediated signaling.
4. **Ben Cowling** (School of Public Health, The University of Hong Kong, Hong Kong SAR): Association between basal leukocyte transcriptome profile and symptom development & disease severity after influenza virus infection in humans.
5. **James Di Santo** (Department of Immunology, Institut Pasteur, Paris, France): Innate lymphoid cell "adaptation" during influenza virus infection.

Funding

1. Determining the involvement of TLR10-a novel innate immune sensor in influenza virus pathogenesis (**Principal Investigator**; RGC Seed Funding for basic research – HK$ 34,490.00, Ends: 02/2017).
2. Association between basal leukocyte transcriptome profile and symptom development & disease severity after influenza virus infection in humans (**Co-Investigator**; Health and Medical Research Fund – Ends: 03/2017).
3. Effect of Volatile Organic Compounds (VOCs) exposure on disease severity in influenza virus infection (**Principal Investigator**; RGC Seed Funding for basic research – HK$ 55,400.00, Ends: 04/2018).
4. Innate lymphoid cell "adaptation" during influenza virus infection (**Principal Investigator**; PROCORE-France/Hong Kong Joint Research Scheme – HK$ 30,600.00, Ends: 12/2018).
5. Pathogenesis and disease severity: Role of TLR10 as an innate immune sensor (**Co-Investigator**; RGC/GRF: Theme-based Research Scheme "Viral, host and environmental determinants of influenza virus transmission and pathogenesis" – HK$1,100,000.00, Ends: 12/2019).

Personnel

Name	Position
Suki LEE	Research Assistant Professor
Selena YAN	Research Associate
Ping Hung LI	Research Technician
Tsz Fung YIP	Research Assistant
Aisha SELIM	MPhil student (started on 1 Jan 2017)
Myriam EUTAMENE	Student Intern (Universite de Lille)

3.2 Chris Ka Pun MOK Lab

Main Objectives and Strategy

The major objective of our group is to understand the pathogenicity of emerging viruses, especially avian influenza viruses, through a combination of clinical, basic and epidemiological studies. In this context, we have set up collaborations with different research partners to identify and investigate viral, host and environmental factors that influence the impact of these viral infection.

Through our well-established platform of the "Guangdong-Hong Kong Joint Research Centre for Clinical and Preventive Medicine against Emerging Infectious Diseases" and collaboration with the Princess Margaret Hospital in Hong Kong, we have identified two novel avian influenza viruses (H7N9 and H5N1) that showed unusual characteristics. The clinical and basic features of these viruses have been investigated further. We have set up a solid collaboration with the Guangdong Province Center for Disease Control (GDCDC) to monitor the epidemiological data of human H7N9 infections and the prevalence of this subtype in poultry market. This study is particularly crucial as last year the highly pathogenic H7N9 subtype was found to co-circulate with the current low pathogenic subtype in the market. We also established a new transcriptomic analysis approach from clinical specimens together with the colleagues at the State Key Laboratory of Respiratory Disease (Guangzhou, PR China) and The Scripps research Institute (USA) to further dissect the pathogenesis of H7N9 infection in humans.

Moreover, we have established a project together with another PI at HKU-PRP, Dr Sumana Sanyal, to understand the functions of ISG15, an antiviral protein induced by interferon (IFN) α/β, during influenza infection.

Achievements and Ongoing Research

The recent increase in zoonotic avian influenza A(H7N9) disease in China is a cause of public health concern. Most of the A/H7N9 viruses previously reported have been of low pathogenicity. We have reported one of the first fatal case of human H7N9 in China and described that the infection was due to A/H7N9 virus having a polybasic amino acid sequence at the hemagglutinin cleavage site (PEVPKRKRTAR/GL), which is a hallmark of high pathogenicity in birds. This feature might have contributed to the patient's adverse clinical outcome. The patient had a history of exposure to sick and dying poultry, and his close contacts had no evidence of H7N9 disease, suggesting that human-to-human transmission did not occur. In collaboration with Guangdong CDC, we further reported the prevalence of the highly pathogenic avian influenza (HPAI) A(H7N9) virus in Guangdong poultry markets through active surveillance and compared the epidemiological characteristics and clinical outcomes between the patients infected with the HPAI and LPAI A(H7N9) viruses in Guangdong province during last season. We described the epidemiology of highly-pathogenic avian influenza (HPAI) A(H7N9) based on poultry market environmental surveillance and laboratory-confirmed human cases in Guangdong, China. We concluded that touching sick or dead poultry was the most important risk factor to HPAI A(H7N9) infections and should be highlighted for the control of future A(H7N9) epidemics.

Highly pathogenic avian influenza H5N1 viruses have affected poultry and other birds all over the world and have transmitted zoonotically to humans with an overall mortality around 60%. Viral encephalitis is a complication reported in patients and other mammals after H5N1 infection. It is currently thought that this complication is a consequence of the inflammation triggered by viral infection and replication in the brain. There is also evidence suggesting that H5N1 viruses acquired an adaptive mutationsat position 627 in the polymerase basic 2 (PB2) protein, from glutamic acid (E) to lysine (K), which allowed dissemination of the virus to the brain. We have identified a 2-year-old boy with highly pathogenic avian influenza A(H5N1) virus infection with minimal respiratory

symptoms who developed encephalitis complicated by obstructive hydrocephalus (**Figure 5**). We have thoroughly investigated the clinical and molecular features of the patient infected with this H5N1 virus. Genetically, this virus belongs to the H5N1 clade 2.3.2.1b and had acquired a mammalian adaptation mutation in PB2, Q591K. We then further focused on understanding the contribution of this PB2 Q591K to pathogenesis in mammalian hosts.

Publications

1) Guan W, Wu NC, Lee HH, Zhong NS, Wilson IA, Peiris JSM, Yang Z, Mok CKP (2017) Clinical correlates of transcriptional signatures in patients with infection of avian influenza (H7N9) virus. *Manuscript in preparation*.

2) Mak GCK, Kwan MY, Mok CKP, Lo JYC, Peiris M, Leung CW (2017) Influenza A(H5N1) virus infection in a child with encephalitis complicated by obstructive hydrocephalus. *Clin Infect Dis*, in press.

3) Chan RWY, Chan LLY, Mok CKP, Lai J, Tao KP, Obadan A, Chan MCW, Perez DR, Peiris JSM, Nicholls JM (2017) Replication of H9 influenza viruses in the human ex vivo respiratory tract, and the influence of neuraminidase on virus release. *Sci Rep* **7**:6208.

4) Kang M, Lau EHY, Guan W, Yang Y, Song T, Cowling BJ, Wu J, Peiris M, He J, Mok CKP (2017) Epidemiology of human infections with highly pathogenic avian influenza A(H7N9) virus in Guangdong, 2016 to 2017. *Eurosurveillance* **22**, pii:30568.

5) Ke C, Mok CKP, Zhu W, Zhou H, He J, Guan W, Wu J, Song W, Wang D, Liu J, Lin Q, Chu DKW, Yang L, Zhong N, Yang Z, Shu Y, Peiris JSM (2017) Human infection with highly pathogenic avian influenza A(H7N9) virus, China. *Emerg Infect Dis* **23**:1332-1340.

6) Li W, Lee HHY, Li RF, Zhu HM, Yi G, Peiris JSM, Yang ZF, Mok CKP (2017) The PB2 mutation with lysine at 627 enhances the pathogenicity of avian influenza (H7N9) virus which belongs to a non-zoonotic lineage. *Sci Rep* **7**:2352.

7) Hui KP, Chan LL, Kuok DI, Mok CK, Yang ZF, Li RF, Luk GS, Lee EF, Lai JC, Yen HL, Zhu H, Guan Y, Nicholls JM, Peiris JS, Chan MC (2017) Tropism and innate host responses of influenza A/H5N6 virus: an analysis of ex vivo and in vitro cultures of the human respiratory tract. *Eur Respir J* **49**, pii:1601710.

8) Bertram S, Thiele S, Dreier C, Resa-Infante P, Preuß A, van Riel D, Mok CK, Schwalm F, Peiris JS, Klenk HD, Gabriel G (2017) H7N9 Influenza A virus exhibits importin-α7-mediated replication in the mammalian respiratory tract. *Am J Pathol* **187**:831-840.

9) Fan Y, Mok CK, Chan MC, Zhang Y, Nal-Rogier B, Kien F, Bruzzone R, Sanyal S (2017) Cell cycle-independent role of cyclin D3 in host restriction of influenza virus infection. *J Biol Chem* **292**:5070-5088.

Seminars and Invited Lectures

1. Chris Mok (2017) International Joint Symposium between Korea and Vietnam "Tropical Diseases & Zoonoses", Iksan, Korea (Invited speaker).
2. Chris Mok (2017) Preparedness for Yellow Fever in Southern China, Institut Pasteur of Shanghai – CAS, Shanghai, PR China (Invited speaker).

Presentations at Meetings

1. Lee HHY, Sanyal S, Peiris JSM, Bruzzone R, Mok CKP (2017) The immune function of ISG15 in macrophages during influenza virus infection. *Transmission of respiratory viruses: from basic science to evidence based options for control*, Hong Kong, Hong Kong SAR (Poster).

Teaching

1. Chris Mok (2017) 14th HKU-Pasteur Virology Course, Hong Kong, Hong Kong SAR (*Co-Director*)
2. Chris Mok (2107) Introduction to the Art and Science of Medicine – Problem Based Learning (MBBS Year 1), The University of Hong Kong, Hong Kong SAR (*Tutor*).

Collaborations (local and international)

1. **Nan-Shan Zhong, 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, Hong Kong SAR) and **Ron Fouchier** (Erasmus Medical Center, The Netherlands): Pathogenicity and transmissibility of H5N6 virus.
3. **Ian Wilson, Nicholas Wu (**The Scripps Research Institute, San Diego, USA): Transcriptomic study on influenza virus infection.

Funding

1. Infection and immunopathogenesis of avian influenza H9N2 virus in tree shrew model (**Co-Principal Investigator**; The Natinal Natural Science Foundation of China – RMB 1,500,000.00, Ends: 04/2018)
2. Guangdong – Hong Kong Joint Research Centre for Clinical and Preventive Medicine against Emerging Infectious Diseases (**Co-Principal Investigator**; Science Research Project of the Guangdong Province – RMB 1,000,000.00, Ends: 09/2018).
3. The pathogenic role of the adaptation in the polymerase basic 2 protein of the new identified duck isolated H7N9 lineage in mammalian hosts (**Principal Investigator**; Health and Medical Research Fund – HK$ 796,778.00, Ends: 06/2017).
4. The Role of ISG15 in macrophages during influenza virus infection/Pathogenesis of H5N1 virus (**Co-Investigator**; RGC/GRF – Theme-based Research Scheme "Viral, host and environmental determinants of influenza virus transmission and pathogenesis" – HK$800,000.00, Ends: 12/2019).
5. Characterization of the new identified human pathogenic avian-origin influenza (H5N6) virus (**Principal Investigator**; RGC Seed funding for basic research – HK$45,980.00, Ends: 05/2017).
6. Importin-alpha protein as the host determinant of influenza B virus replication in human (**Principal Investigator**; RGC Seed funding for basic research – HK$ 44,320.00, Ends: 04/2019).
7. Investigation on a pinanamine derivative as an antiviral agent against influenza A virus infection (**Principal Investigator**; Health and Medical Research Fund – Recommended for support).

Personnel

Name	Position
Chris Ka Pun MOK	Research Assistant Professor
Horace Hok Yeung LEE	PhD student (Graduated October 2017)
Gannon MAK	PhD student (Part-time)
Fion Nok Lam MA	MPhil student
Jane Kong San TSE	Research Technician
Wilson NG	Research Assistant

3.3 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-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.

Characterization of host factors involved in virus infections:

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 DENV to explore similarities and differences that exist in ZIKV infection.

(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 DENV and ZIKV. Deficiency of Lyn through siRNA-mediated suppression as well as pharmacological inhibition had a significant impact on release of both DENV and ZIKV progeny particles. We are in the process of elucidating the mechanism through which

these SFKs activate the signaling cascade that is necessary for transport of flavivirus particles along the host secretory pathway.

Targeting deubiquitylases as therapeutic strategies against viral infections

Influenza virus is responsible not only for annual epidemics, but also for frequent outbreaks of pathogenic avian influenza 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 expressed upon influenza infection and are currently investigating the role of these DUBs. Our ongoing studies involve characterization and pharmacological intervention of these DUBs in order to attenuate influenza infection. Preliminary data in macrophages and dendritic cells 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 current efforts are centered on OtuB1, which appears to interact with influenza PB2. Deficiency of OtuB1 results in a significant drop in release of both pro-inflammatory cytokines and virus particles from infected cells.

Regulation of immune signaling by deubiquitylases

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.

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 and Theme-based Research Scheme as well as Transversal research grants available within the Institut Pasteur International Network. Results obtained in the TCR signaling project were accepted for publication in *Proceedings of the National Academy of Sciences USA*, whereas the function of Cyclin D3 in influenza infection was accepted for publication in the *Journal of Biological Chemistry*. Data generated for the project on host factors involved in dengue infection are currently under consideration at *Cell Host and Microbe* and also summarized in invited review articles in Frontiers. In addition, I have received a Career Development Award from the Croucher Foundation and was promoted to the rank of Assistant Professor (tenure track).

Publications

1. Zhang J, Lan Y, Li MY, Lamers MM, Fusade-Boyer M, Klemm E, Thiele C, Ashour J, Sanyal S (2018) Host cellular ubiquitylation profiling reveals a critical role for lipid droplet metabolism during flavivirus infections. *Cell Host Microbe*, in revision.
2. Pombo JP, Sanyal S (2018) Perturbation of intracellular cholesterol and fatty acid homeostasis during flavivirus infections. *Front Immunol* (under review).
3. Zhang J, Lan Y, Sanyal S (2017) Modulation of Lipid Droplet Metabolism – A potential target for therapeutic intervention in *Flaviviridae* infections. *Front Microbiol* **8**:2286.
4. Fan Y, Mok CK, Chan MCW, Zhang Y, Nal B, Kien F, Bruzzone R, Sanyal S (2017) Cell-cycle independent role of CyclinD3 in host restriction of influenza infection. *J Biol Chem* **292**:5070-5088.

Seminars and Invited Lectures

1. Sumana Sanyal (2017) Department of Immunology Annual Retreat, Institut Pasteur, France.
2. Sumana Sanyal (2017) The University of Oxford, UK.
3. Sumana Sanyal (2017) Whitehead Institute for Biomedical Research/Massachusetts Institute of Technology, USA.

Presentations at Meetings

1. Sanyal S (2018) *Keystone Conference: Ubiquitin Signaling.* Tahoe City, California, USA (Oral).
2. Sanyal S (2017) *EBI-Wellcome Trust Scientific conference and advances course: Protein interactions and network.* Hinxton, UK (Oral).
3. Jahan AS, Sanyal S (2017) *EMBO Conference: Hijacking host signalling and epigenetic mimicry during infections,* Paris, France (Poster).
4. Jahan AS, Sanyal S (2017) *EMBO Practical Course: Current Methods in Cell Biology,* Heidelberg, Germany (Oral/Poster).
5. Li MY, Siu L, Bruzzone R and Sanyal S (2017) *EMBO Conference: Hijacking host signalling and epigenetic mimicry during infections,* Paris, France (Poster).
6. Li MY, Siu L, Bruzzone R and Sanyal S (2017) *EMBO Conference: Hijacking host signalling and epigenetic mimicry during infections,* Paris, France (Poster).
7. Lan Y, Zhang JT, Sanyal S (2017) Role of lipid droplets in flavivirus infection. *EMBO Conference: Hijacking host signalling and epigenetic mimicry during infections,* Paris, France (Poster).
8. Lan Y, Zhang JT, Sanyal S (2017) Modulation of host lipid metabolism during Zika virus infection. *Microbes, Immunity and Metabolism international conference,* Institut Pasteur, Paris, France (Oral).
9. Zhang JS, Biquand E, Lamers MM, Karim M, Fan Y, Demeret C, Sanyal S (2017) *Microbes, Immunity and Metabolism international conference*. Institut Pasteur, Paris, France (Poster).
10. Zhang JS, Biquand E, Lamers MM, Karim M, Fan Y, Demeret C, Sanyal S (2017) *Transmission of respiratory viruses: from basic science to evidence based options for control*, The University of Hong Kong, Hong Kong SAR (Poster).
11. Zhang JS, Biquand E, Lamers MM, Karim M, Fan Y, Sanyal S, Demeret C (2017) *EMBO conference: Hijacking host signaling and epigenetic mimicry during infections*, Paris, France (Poster).

Teaching

1. Sumana Sanyal (2017) Basic Metabolism (BSc Biochemistry Year 3), The University of Hong Kong, Hong Kong SAR.
2. Sumana Sanyal (2017) Cancer Screening – Problem Based Learning (MBBS Year 4), The University of Hong Kong, Hong Kong SAR.
3. Sumana Sanyal (2017) Introduction to the art and science of medicine – Problem Based Learning (MBBS Year 1), The University of Hong Kong, Hong Kong SAR (*Tutor*).
4. Sumana Sanyal (2017) Molecular Biology of the Cell Course, Institut Pasteur, Paris, France (*Lecturer* and *Tutor*).

Collaborations

1. **Caroline Demeret** (Institut Pasteur, Paris): Role of deubiquitylases in influenza virus infections.
2. **Lee Kim Swee** (BiomedX Innovation Center, Heidelberg, Germany): Ubiquitin-mediated regulation of the T-cell receptor-signaling pathway
3. **Joseph Ashour** (Mount Sinai School of Medicine, New York, NY, USA): Manipulation of host factors in influenza and dengue infections
4. **Adolfo Garcia-Sastre** (Mount Sinai School of Medicine, New York, NY, USA): Studying the function of Isg15 and its mode of restricting influenza virus trafficking, specifically, the efficacy of influenza NS1 in preventing ISG15 activity.
5. **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 Tsg101.

Funding

1. Role of Tsg101 in influenza virus infection (**Principal Investigator**; Research Grants Council/General Research Fund – HK$769,020.00, Ends: 10/2017).
2. Development of therapeutic strategies against viral infections by targeting the ubiquitylation machinery and its modulation of the host innate immune response (**Principal Investigator**; Health and Medical Research Fund – HK$ 981,120.00, Ends: 06/2017).
3. Deciphering influenza viral polymerase interplay with host ubiquitin proteasome system in correlation with pathogenesis (**Co-principal Investigator**; Institut Pasteur – Programme Transversaux de Recherche – EUR143,000.00, Ends: 12/2017)
4. Elucidating the role of Tsg101 in influenza virus assembly and release (**Co-Investigator**; GRC/GRF: Theme-based Research Scheme – HK$850,000.00, Ends: 12/2019).
5. Role of Usp4 in T Cell Receptor-signaling (**Principal Investigator**; RGC Seed Funding for basic research – HK$80,470.00, Ends: 05/2018).
6. Targeting lipid droplet metabolism as therapeutic intervention during dengue virus infections (**Principal Investigator**; Health and Medical Research Fund – HK$1,200,000.00, Ends: 06/2019).
7. Regulation of dengue virus life cycle by KDEL receptor-dependent signaling pathway: a new target to interfere with viral infection and pathogenesis (**Co-Investigator**; Health and Medical Research Fund – HK$ 1,130,112.00, Ends: 08/2019)
8. Mechanism of OtuB1 mediated regulation of influenza virus infection (**Principal Investigator**; Research Grants Council/General Research Fund – HK$ 829,393.00, Ends: 12/2019).

9. A chemical proteomics-based strategy for target discovery in flavivirus infections (**Principal Investigator**; Health and Medical Research Fund – recommended for support).
10. Regulation of the intracellular life cycle of influenza A virus by E3 ubiquitin ligase Mgrn1 (**Co-Investigator**; Health and Medical Research Fund – recommended for support).
11. Host lipid metabolism as a potential target for Zika antiviral therapy (**Co-Investigator**; Health and Medical Research Fund – recommended for support).

Personnel

Name	Position
Sumana SANYAL	Assistant Professor
Ming Yuan LI	Postdoctoral Fellow
Tami ZHANG	Postdoctoral Fellow
Yun LAN	Technical Officer
Lewis SIU	Research Technician
Akhee Sabiha JAHAN	PhD Student
Joao POMBO	MPhil Student
Qiwen TEO	MPhil Student
Trupti Shivaprasad NAIK	Research Assistant
Wai Yuet CHAN	Student Intern (IVE)
Man Tak FONG	Student Intern (IVE)
Wing Ki LEE	Student Intern (IVE)
Hoi Yan SUEN	Student Intern (IVE)
Ka Lok WONG	Student Intern (IVE)
Mike Zi Xi Mike DAI	Student Intern (HKUST)

3.4 Sophie VALKENBURG Lab

Main Objectives and Strategy

The main objectives of the lab are to delineate 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.

Broadly reactive influenza vaccines in mouse models

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 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 for future vaccine strategies.

(b) *An HA-stem based vaccine:* The HA protein contains a stem region with conserved conformational epitopes that are relatively conserved between different influenza strains, leading to the induction of broadly neutralizing antibodies that recognize influenza viruses of different subtypes, in some cases groups (group 1 or 2) or even both influenza A and B viruses. Using a protein minimization technique, the Varadarajan lab at the Indian Institute of Science developed an HA-mini stem recombinant protein vaccine that mimics the pre-fusion native form of the HA protein by utilizing a trimerization motif, Foldon.

Human correlates of protection from influenza

(a) *Protective pre-existing T cell responses*: Whilst T cell responses have been shown to be highly effective in mediating protection in mouse models, corresponding data in human influenza infection is not as robust. All adults have established influenza-specific memory T cell responses; however, we have repeated infections during our lifetime that can range from mild to life threatening. The half-life of T cell memory and cross reactivity may explain the variability in protection from repeated infection. In collaboration with Benjamin Cowling (School of Public Health at HKU), we aim to determine the correlation between higher baseline early effector T cell memory responses and protection from influenza infection or reduced symptom severity and viral shedding in a household

transmission setting. Blood samples are obtained from infected index cases, and uninfected household contacts that are monitored for influenza transmission, at day 0 and day 28. The aim of the study is to find if there is an immunological difference between contacts positive and negative for influenza transmission during sampling. Sample collection has been ongoing since June 2013 due to the limited and specific nature of cases and intensity of monitoring households.

(b) *ADCC avian cross-reactivity:* H7N9-specific ADCC antibodies have been found from the blood of healthy unexposed adults, and therefore ADCC antibodies must target conserved epitopes of the HA protein. In collaboration with Joe Wu (School of Public Health at HKU), the level of H1 and H7-specific ADCC antibodies is being probed in a large community cohort study, using archived serum from Red Cross blood collection.

(c) *Enhanced influenza vaccines for the susceptible elderly:* The 2015 Northern hemisphere winter influenza season had excess mortality in over 65 year olds 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 Yat Hang Tam (School of Public Health at HKU), the benefit of re-vaccinating the elderly in establishing H3N2-Switzerland specific T and B cell and ADCC responses is being assessed by comparing subjects who received one dose of the updated vaccine versus two doses of vaccine.

Achievements and Ongoing Research

Since joining HKU-Pasteur PRP in April 2016, my research, team, teaching and grants have significantly consolidated during 2017. My team has further grown with the recruitment and training of a Post-doctoral research fellow (Niloufar Kavian), PhD student (Athena Li), and research assistant (Jodi Chan). I joined the international network of the NIH Centres of Excellence for Influenza Research and Surveillance (CEIRS), attending meetings in Atlanta and Washington, and was awarded 2-year funding for a collaborative project with St Jude's Children's hospital (Memphis, USA).

We have been successful in 3 research grants from the NIH CEIRS USA, and HMRF and GRF of Hon Kong, which will support my research for the next 3 years. Two of these projects build on the epidemiology aspect of influenza infection with Professor Ben Cowling (School of Public Health), and will provide important information on the immunological impact of vaccination in the Hong Kong children and elderly . My teaching expanded to include problem based learning (PBL) tutorial of medical students, and lectures for the Pasteur Virology course and Masters of Public Health.

Publications

1. Tam YH, Valkenburg SA, Perera RAPM, Wong JHF, Fang VJ, Ng TWY, Kwong ASK, Tsui WWS, Ip DKM, Poon LLM, Chau CKV, Barr IG, Peiris JSM, Cowling BJ (2017) Immune responses to twice-annual influenza vaccination in older adults in Hong Kong. *Clin Infect Dis*, in press.
2. Nguyen THO, Sant S, Bird NL, Grant EJ, Clemens EB, Koutsakos M, Valkenburg SA, Gras S, Lappas M, Jaworowski A, Crowe J, Loh L, Kedzierska K (2017) Perturbed $CD8_+$ T cell immunity across universal influenza epitopes in the elderly. *J Leukoc Biol*, in press.
3. Valkenburg SA, Li OTW, Li A, Bull M, Waldmann TA, Perera LP, Peiris JSM, Poon LLM (2018) Protection by universal influenza vaccine is mediated by memory CD4 T cells. *Submitted*.

Seminars and Invited Lectures

1. Sophie Valkenburg (2017) Korean Society for Molecular and Cellular Biology, Seoul, Korea.
2. Sophie Valkenburg (2017) Café Scientifique, Hong Kong SAR.

Presentations at Meetings

1. Valkenburg SA, Fan R, Choy KT, Sia SF, Nicholls JM, Perera LP, Peiris JSM, Yen HL, Poon LLM (2107) Broadly reactive T cell activating vaccine does not provide sterilizing immunity enabling secondary transmission of influenza in ferrets. *TRS Transmission meeting*, The University of Hong Kong, Hong Kong SAR (Oral).
2. Valkenburg SA, Zhang Y, Leung K, Wu JT, Poon LLM (2017) Pre-existing ADCC antibody responses are stable longitudinally and are not boosted by recent influenza exposure. *CEIRS Annual meeting*, Atlanta, USA (Poster).
3. Valkenburg SA, Li OTW, Peiris JSM, Perera LP, Poon LLM (2017) Protection by universal influenza vaccine mediated by CD4 T cells, bringing our cornerstone defense to the forefront of protection. *KSMCB*, Seoul, Korea (Invited Oral).
4. Valkenburg SA, Zhang Y, Leung K, Wu JT, Poon LLM (2017) Pre-existing ADCC antibody responses are stable longitudinally and are not boosted by recent influenza exposure. *Global virus network*, Melbourne, Australia (Poster).
5. Valkenburg SA (2017) CEIRS Strategic Universal Vaccine meeting, Rockville, USA (Oral).

Teaching

1. Sophie Valkenburg (2017) 9th HKU-Pasteur Immunology Course, The University of Hong Kong, Hong Kong SAR (*Tutor*).
2. Sophie Valkenburg (2017) 14th HKU-Pasteur Virology Course, The University of Hong Kong, Hong Kong SAR (*Lecturer*).
3. Sophie Valkenburg (2017) "Biological Basis of Disease" (Master of Public Health), School of Public Health, The University of Hong Kong, Hong Kong SAR (*Lecturer*).
4. Sophie Valkenburg (2017) Muscoskeletal system block – Problem Based Learning (MBBS Year 2), The University of Hong Kong, Hong Kong SAR (*Tutor*).

Collaborations

1. **Leo LM Poon** (School of Public Health, The University of Hong Kong, Hong Kong SAR): Broadly reactive influenza vaccines in mouse models.
2. **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.
3. **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.
4. **Joseph Wu** (School of Public Health, The University of Hong Kong, Hong Kong SAR): Probing ADCC antibody responses towards avian influenza viruses in the community.
5. **Yat Hang Tam** (School of Public Health, The University of Hong Kong, Hong Kong SAR): Two-dose vaccine immune effect in elderly for the H3N2-mismatch.

6. **Liyange Perera and Thomas Waldmann** (NIH, NAID, USA): Vaccinia vector H5N1 vaccine for broad T cell responses, with an emphasis on CD4 mediated heterologous protection.
7. **Katherine Kedzierska** (The University of Melbourne, Australia): Mutation rates in T cell epitopes during infection and human T cell responses towards influenza.

Funding

1. Understanding alternate immune correlates of protection in household transmission of influenza (**Principal Investigator**; Health and Medical Research Fund – HK$ 999,828.00, Ends: 12/2017).
2. Vaccination scheme development to stimulate both B and T cell dependent heterosubtypic protection against influenza A viruses in mice (**Co-Investigator**; Health and Medical Research Fund – Ends: 06/2017).
3. Influenza virus escape is the double-edged sword of effective T cell immunity (**Principal Investigator**; RGC Seed Funding for basic research – HK$ 150,000.00, Ends: 10/2018).
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. Detection and characterization of antibody-dependent cell-mediated cytotoxicity (ADCC) responses against human H7N9 virus in humans and mice (**Co-Investigator**; Health and Medical Research Fund – Ends: 04/2018).
6. Influenza viruses adapt to escape T cell responses (**Principal Investigator**; General Research Fund/Research Grants Council – HK$ 1,200,839.00, 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 – Recommended for support).
8. Repeated elderly influenza vaccination and establishing cellular immune responses (**Co-Investigator**; CEIRS NIH – Ends: 08/2019).
9. The protective role of antibody effector functions for influenza in mice and humans (Principal Investigator; General Research Fund/Research Grants Council – Pending).

Personnel

Name	Position
Sophie Valkenburg DOAK	Research Assistant Professor
Niloufar KAVIAN	Post-doctoral fellow
Athena LI	PhD Student
Maireid BULL	MPhil student
Yizhuo WANG	Research Assistant
Jodi CHAN	Research Assistant
Emily MIAO	Student Intern (Erasmus MC Rotterdam)
Matthew WONG	Student Intern (HKU)

3.5 Jimmy Chun Cheong LAI GROUP

Main Objectives and Strategy

Our group aims to study the interactions between viruses with the host receptors, in order to have a better understanding on viral host adaptation and cell/tissue tropism. Main projects include the study of influenza virus-cell receptor interactions at the atomic level by combination of chemical, biochemical and cell biological methods; the investigation of the interplay between different influenza surface proteins during viral infection; and the role of Sd^a/Cad carbohydrate antigen in the inhibition of influenza infections. In addition, in collaboration with the department of clinical oncology of HKU and QIMR Berghofer Medical Research Institute in Australia, we are performing a clinical trial to evaluate effectiveness of adoptive immunotherapy as treatment of nasopharyngeal carcinoma (NPC), which is caused by a combination of environmental, genetic and viral factors, being often linked to Epstein–Barr virus (EBV) infection.

Study of influenza virus-host receptor

The objective of the study is to obtain a better understanding of the influenza viral tropism. Sialic acids are known to be the receptor molecules of influenza viruses, but the diversity of sialylated glycans is not equivalent in different animal species and organs. Therefore, it is likely that the interactions between influenza viral proteins and different sialylated glycans are involved in the viral adaptation to the host and one possible mechanism underlying species jump, e.g. from avian to human. In our study, we have produced influenza virions or virus-like particles (VLP) of different influenza subtypes and/or different viral origin. The interactions between hemagglutinin (HA), neuraminidase (NA) and a variety of sialylated glycans are being investigated using chemical methods. Functional studies of the virions are also carried out on cell/tissue cultures.

Interplays between influenza surface proteins in cell receptor interactions

Influenza HA and NA are two major glycoproteins both interacting with sialic acids receptor on cell surface. It has been long recognized that a balance between HA receptor-binding and NA receptor-destroying functions is important for the influenza virulence and transmission. However, interplays between the two viral proteins were not clearly studied. In this project we aim to investigate the role of HA-receptor binding properties on the NA functions. The effect of HA inactivation on NA enzymatic activity will be tested in native virions. VLPs containing NA with or without corresponding HA will also be produced for the comparison of their NA activities.

Effect of human B4GALNT2 gene expression on influenza virus infection

B4GALNT2 is involved in the biosynthesis of human Sd^a/Cad carbohydrate antigen by adding a terminal GalNAc side chain to glycoprotein containing NeuAc2,3-Gal1,4-GlcNAc moiety. Published data suggested that Sd^a glycotope is expressed in both N- and O-linked glycans and the present of Sd^a in animal tissue is a potential protective mechanism in against avian influenza viruses. Our objective is to over-express B4GALNT2 gene in different cell lines and test for their susceptibility against avian and human influenza viruses.

Immunotherapy against nasopharyngeal carcinoma

The aim of the project is to develop an effective immunotherapy treatment against Epstein-Barr virus (EBV)-associated nasopharyngeal carcinoma (NPC), which, differently from Western countries, is endemic in southern China, including Hong Kong. EBV is present in virtually all poorly differentiated and undifferentiated nonkeratinizing NPC (type II and III, according to the WHO classification), making the viral antigens expressed by tumor cells attractive targets for immunotherapy. Our strategy is to generate LMP/EBNA1-specific T cells from PBMC isolated from NPC patients using an adenoviral vector. The safety and efficacy of expanded T cells can be assessed upon adoptive CTL infusion as immunotherapy.

Achievements and Ongoing Research

In 2017, we have continued our exploration of the basis of influenza receptor specificity and the role O-linked sialylated glycans in influenza viral infection. Our data shown that O-glycans are important receptors for some influenza strains, which overturn the dogma that N-glycans are the predominant cell receptor for influenza viruses. Using our VLPs system together with the HA inactivation methodology we developed, we further characterized the role of HA-receptor bindings on the level of NA activity and the NA-substrate specificity. We also found that an increase in Sd^a/Cad antigen expression inhibit the *in-vitro* influenza infections by reducing the virus attachment.

Publications

1. Chan RW, Chan LL, Mok CK, Lai JC, Tao KP, Chan MC, Perez DR, Peiris JS, Nicholls JN (2017) Replication of H9 influenza viruses in the human ex vivo respiratory tract, and the influence of neuraminidase on virus release. *Sci Rep* **7**:6208.
2. Hui KP, Chan LL, Kuok DI, Mok CK, Yang ZF, Luk GS, Lee, EF, Lai JC, Yen HL, Zhu HC, Guan Y, Nicholls JN, Peiris JS, Chan MC (2017) Tropism and innate host responses of influenza A/H5N6 virus: an analysis of *ex-vivo* and *in-vitro* cultures of the human respiratory tract. *Eur Resp J* **49**:1601710.
3. Mayr J, Lau K, Lai JC, Gagarinov I, Chan RW, von Itzstein M, Nicholls JN, Haselhorst T (2017) Unraveling the role of O-glycans in influenza virus infections. *Sci Rep* (under revision).
4. Lai JC, Herath MT, Wong HH, Peiris JS, Nicholls JN (2017) Neuraminidase activity and specificity of Influenza A virus is influenced by Hemagglutinin-receptor binding. *Submitted*.

Seminars and Invited Lectures

1. Lai JC (2017) Interplay between influenza hemagglutinin and neuraminidase. Department of Pathology, The University of Hong Kong, Hong Kong SAR.

Collaborations

1. **Xuechen Li** (Department of Chemistry, The University of Hong Kong): Molecular determinants of influenza virus tropism and binding; expertise in glycan synthesis, to produce glycans of interest as influenza receptor analogues.
2. **Guang Zhu** (Division of Life Science, The University of Hong Kong Science and Technology): Access to equipment and technical support regarding NMR spectroscopy.
3. **Mark von Itzstein and Thomas Haselhorst** (Institute for Glycomics, Griffith University, Australia): Study of O-linked sialylated glycans and synthesis of O-glycans analogue.

4. **Michael Chan** (School of Public Health, The University of Hong Kong): Comparison of native influenza virus and virus-like-particles in their receptor-binding properties using the *ex vivo* human culture model.
5. **Dora Kwong** (Department of Clinical Oncology, The University of Hong Kong ong): Clinical trials of immunotherapy against EBV-associated NPC.
6. **Rajiv Khanna** (Department of Immunology, Queensland Institute of Medical Research, Australia): Immunotherapy against EBV and technology transfer to develop methods of T cells expansion.

Funding

1. Viral, Host and Environmental Determinants of Influenza Virus Transmission and Pathogenesis (**Co-Investigator**; RGC/GRF – Theme-based Research Scheme "Viral, host and environmental determinants of influenza virus transmission and pathogenesis" – Ends: 12/2019).
2. Structural insights of virus-glycan interactions. (**Collaborator**, ARC Future Fellowships FT120100419, Australian Research Council – Ends: 2017).
3. Immunotherapy against nasopharyngeal carcinoma (**Co-Investigator**; Ester Lee and Chew Pik Foundation, Croucher Foundation and other donors – Ends: open).

Personnel

Name	Position
Jimmy CHUN CHEONG LAI	Postdoctoral Fellow (Joint Appointment with the Department of Pathology in the Nicholls Lab)
Herath M. THUSITHA KUMARA K.	MPhil student (Graduated February 2017)
Ho Him WONG	MPhil student (Graduated December 2017)

3.6 Barbara GAYRAUD-MOREL (Visiting Scientist from the Institut Pasteur, Paris)

Main Objectives and Strategy

Consequences of influenza infection on skeletal muscle

This project aims to explore the consequences of respiratory virus infections on skeletal muscles and muscle stem cells in particular. This work is at the interface between my expertise in skeletal muscle biology and the focus on infectious diseases studied at HKU-PRP. The project involves collaboration between HKU-PRP and several laboratories: Leo Poon (School of Public Health at The University of Hong Kong), Tom Cheung (Hong Kong University of Science and Technology), and the Stem Cell and Development laboratory directed by Shahragim Tajbakhsh (Institut Pasteur, Paris), where I hold a permanent position.

Respiratory virus infections are primarily damaging the respiratory tract, but also induce several other symptoms, like fever, headache, cough, nasal congestion and skeletal muscle pain, referred as myalgia, which are not life threatening but remain highly uncomfortable for patients. Most respiratory viruses (with the notable exception of highly pathogenic avian influenza H5N1) infecting the lung do not reach the systemic circulation and are therefore unlikely to affect directly other organs. However, pro-inflammatory molecules released during viral pulmonary infection into the bloodstream are considered to induce myalgia by stimulating the peripheral nervous system. Several cytokines, such as Interleukin 6 (IL6), IL1β and TNFα, generate E2 prostaglandins, which trigger dorsal root ganglion (DRG) stimulation and pain. Cytokines acting on skeletal muscles are called myokines. Among the numerous cytokines released in the body several of them are known to have certain biological effects on muscle and muscle stem cells, particularly during muscle regeneration. Most of these cytokines have a dose-dependent effect and can have a beneficial or detrimental effect on muscle cells. For example, IFNγ has a positive effect on myoblast proliferation and regeneration at low doses but interferes with regeneration if present in high concentration. Similarly, a low level of IL6 improves regeneration but high levels are linked to muscle wasting, chronic inflammation in mdx mice (muscle dystrophic mice).

Skeletal muscle cells, named myofibers, are elongated and multinucleated. Satellite cells are the principal cell type ensuring muscle growth and regeneration and are therefore identified as the stem cell of the skeletal muscle. They are located to the periphery of myofibers, between the sarcolemma and the basement membrane surrounding the fiber (**Figure 1**). The precise composition of their niche is still poorly defined, but involves multiple other cell types. For example, capillaries running along the fibers are found in proximity to satellite cells. Mesoangioblasts, or pericytes, surrounding the capillaries and small vessels establish some cross talk with satellite cells trough signaling molecules. Fibroblasts, adipocytes and resident macrophages are also present in the vicinity of satellite cells and could contribute to their homeostasis. A previous study has shown that, in culture, influenza virus can directly infect muscle cells, which are not able to sustain infection, however, as they lack proteases needed to cleave hemagglutinin at the virus surface, a required step for influenza virus to become infectious. Consequently, very few viral particles have been identified in skeletal muscle of infected mice. Nevertheless, myalgia occurring during influenza infection suggests that cytokines reach the skeletal muscle and the consequences of this high amount of inflammatory molecules on the skeletal muscle have not been addressed. We are particularly interested in potential damages that could occur on muscle stem cells, which are essential for homeostasis and regeneration of skeletal muscles. In addition, it has not been explored whether the skeletal muscle itself contributes to inducing or sustaining muscle pain, for example via resident macrophages. We chose to address these questions *in vivo* with a mouse model of viral infection, during resting state and regeneration after muscle injury.

Establishment of a human lung epithelium derived from hESCs to study infectious diseases

The second area of research aims to establish a human lung epithelium model to study infectious diseases. Until now, most experiments with influenza and other respiratory viruses are performed

on cell lines more or less related to human epithelial lung cells. We aim to take advantage of the growing human embryonic stem cell (hESC) and iPSC fields to establish a model of human lung epithelium to investigate respiratory infectious diseases. These past years, few laboratories have succeeded to generate efficient *in vitro* lung and airway epithelial cells from human pluripotent cells for applications in regenerative medicine, modeling lung diseases, or drug screening.

To differentiate hESCs into pulmonary cells the Snoeck lab developed a protocol which consist in recapitulating embryonic stages of lung development by providing key signaling molecules (Activin A, BMP, FGF, Wnt...) in a sequential and controlled timing. Briefly, hESCs are induced into Definitive Endoderm (DE), and then specified to a more anterior foregut endoderm (AFE) fate. They are further directed to produce lung progenitors before being finally differentiated into mature epithelial cells (mostly distal type II alveolar epithelial cells). To monitor differentiation, expression of several genetic markers, like transcription factors or cell surface receptors, is used to validate the sequential cell types generated. Once differentiated epithelial cell cultures are established in the laboratory, we will validate our model by performing viral infection. Several respiratory viruses (influenza, coronaviruses) will be tested in this in vitro system to evaluate their infectiousness. This paradigm should be very useful to translate experiments from cell lines to a more physiological human lung model, which presents several advantages, including an unlimited and homogeneous source of hESC, contrary to primary explant cultures, which rely on availability of human lung biopsies. hESCs are also easily manipulated to perform editing (mutation, deletion, tagging) of genes relevant to biological questions concerning host-virus mechanisms of infection. The first attempts will be performed with hESCs, which are considered to be more homogeneous in their ability to proceed through differentiation. However, we aim to apply such protocol to hiPSC lines that could be generated in the lab from patients more resistant or susceptible to influenza infection.

Achievements and ongoing research

We are studying the consequences of viral infection on skeletal muscles in mice to model an organismal response to infection. Mice are infected by intra nasal inoculation with a high dose of a mouse-adapted PR8 influenza A strain, which causes acute lung infection, rapid weight loss within 5 days and severe sickness. We performed our analysis between day 5 and 7 post-infection before animals reached the critical end point of 30% weight loss after which ethical regulations impose that they be euthanized. The first analysis aimed to quantify the different cell populations present in infected and control muscles. Briefly, hind limb muscles were dissected and subsequently digested enzymatically by collagenase and dispase into a single cell suspension prior to FACS analysis. A specific set of antibodies for cell surface receptors was used to identify distinct cell populations, i.e., fibroblast, endothelial, hematopoietic, inflammatory, and muscle stem cells (MuSCs). Non-muscle cells were discarded with a set of antibodies (CD45-CD31-Sca1) and muscle stem cells were labeled with Vcam+ cell surface receptor. Interestingly, muscles from PR8 infected mice showed around 50% loss of their Vcam+ muscle stem cells compared to PBS-treated control mice. Our preliminary data analysis of total muscle cell suspension showed an increase of inflammatory cells, monocytes and macrophages, labeled by CD11b or Ly6G/C, in infected muscles compared to controls. However, further experiments are required to determine if this higher number of inflammatory cells is present in blood vessels or in the muscle interstitium. Nevertheless, following infection, gene expression of pro-inflammatory signaling molecules, such as IL6, SDF1, CXCL2, was increased in MuSCs and suggested a contribution from the skeletal muscle to the overall inflammation triggered by influenza. Overall, these results show that during influenza viral infection, MuSCs are subjected to several modifications at the protein and gene expression levels. We will investigate whether these molecular changes are the consequences of MuSCs sensing circulating cytokines generated by the inflammation-taking place in the lung. We are particularly interested to elucidate whether clearance of adhesion receptors such as Vcam is a cellular strategy of stem cells to limit unwanted leucocyte infiltration to uninjured tissue, preventing unnecessary cell activation which could have detrimental effects on tissue homeostasis. Finally, we are particularly interested to study whether these molecular changes are altering muscle regenerating capacity, during or after a viral infection, in wild type adult mice but also in *mdx* mice, the mouse model mimicking Duchenne muscular dystrophy.

Publications

1. **Gayraud-Morel B**, Pala F, Sakai H, Tajbakhsh S (2017) Isolation of muscle stem cells from mouse skeletal muscle. In: Muscle Stem Cells – Methods Mol Biol (**Perdiguero** E and **Cornelison** D, Eds.), pp. 23-39.

Collaborations (local and international)

2. **Leo Poon** (School of Public Health, The University of Hong Kong, Hong Kong SAR)
3. **Thomas Cheung** (Division of Life Sciences, Hong Kong University of Science and Technology, Hong Kong SAR)
4. **Shahragim Tajbakhsh** (Department of Developmental Biology, Institut Pasteur, Paris, France)

Teaching

1. 5th Advances in Stem Cell BiologyCourse, Institut Pasteur, Paris, France (*Tutor*).

3.7 Teaching and Education

HKU-Pasteur Courses

The main objective of our educational pillar is to further develop an advanced teaching program in life sciences that will train a highly selected group of students who will be at the forefront of biomedical research in their countries. 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. In 2017 we have organized and co-organized five international courses, 4 in Hong Kong (Immunology, Virology, Advanced Imaging, NGS) and 1 in Ho Chi Minh City ,Vietnam (Health Economics). We received more than 300 applications from 37 countries; 177 students with global geographic representation were selected for participation.

The **HKU-Pasteur Virology Course** has been held for the 14th consecutive year. Influenza virus is one of the most common infectious diseases, which is highly contagious; influenza occurs in seasonal outbreaks and has caused recurrent pandemics that have been well documented since the Spanish flu struck almost a century ago. The significance of the virus not only reflects the public concern for the threat it poses to health, but also the massive efforts of the scientific community, which has studied the virus as an excellent model to understand the mechanisms of respiratory infection and transmission. Thus, our knowledge on this pathogen has been dramatically changed since the time of the first documented pandemic, as technological breakthroughs have brought about a deeper understanding of the virus and its interactions with the natural hosts. The 2017 edition focused on two key questions for influenza research: a) How does influenza virus cause disease? b) What are the determinants of influenza virus transmission? The course discussed the different factors that contribute to pathogenicity and transmissibility of influenza virus in humans, in the context of our interactions with animal reservoirs. These different aspects and our knowledge gaps were reviewed with a holistic "One-Health" approach spanning experimental medicine, virology, immunology, cell biology, epidemiology and ecology. The lectures emphasized the clinical and practical aspects, basic virology, cell biology, epidemiology and ecology of the influenza viruses. The workshop was built around the preparation of a multidisciplinary grant proposal to address the main challenges that we are facing in influenza research. Students were split into 5 groups focusing on five areas of influenza research: clinical, ecology, epidemiology, immunology and vaccinology. They were required to identify relevant question(s), generate hypothesis and propose experimental approaches to address them. Each group presented their proposed work-package using slide format during the last day 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.

The HKU-Pasteur Immunology Course reached the 9th edition. This year the course capitalized on the concepts developed by the multidisciplinary project called Milieu Intérieur to explore the ongoing transition from reductionist studies based on the application of genetic approaches in animal models to a more integrated view of the physiology and pathology of the human immune system that will eventually provide a foundation for defining immune responses of healthy individuals. It highlighted the latest advances in large-scale, quantitative data collection and computational analysis as applied to biochemical aspects of immune cell activation and function, multicellular behavior in

tissues and model organisms, and human immune function in health and disease. Lectures were complemented by a hands-on practical workshop which spanned the 2 week course. The practical course flowed from cellular isolation, characterization of immune cell subsets by advanced multi-parameter flow cytometry, in vitro stimulation to downstream RNAseq analysis of gene expression. The wet lab experience involved isolation of PBMC from whole blood, freezing and thawing cells, immune cell staining, flow cytometry (LSR Fotressa), in vitro stimulation and RNA isolation. The second week workshop involved a 'dry' laboratory experience, whereby students were given a reference RNAseq dataset of stimulated samples (as derived in the wet lab). The students then worked through the dataset using open source analysis platforms on Galaxy, resulting in interpretation of the effect of immune stimulation on expression profiles. Results from the practical highlighted the inherent variability in the human population, and by using methods directly from the Milieu Intérieur project students were able to compare their dataset with a larger cohort study. Ultimately the results from the laboratory workshop were presented to the Faculty in a students'-led presentation. This formed the basis for the student assement in combination with their active participation during lectures and workshop series. The HKU-Pasteur Immunology course has been approved by the Research Postgraduate Committee of HKU for inclusion in the coursework curriculum of MPhil/PhD students.

HKU-PRP has pioneered a unique method in Hong Kong and in the region as we provide state of the art lectures and practical workshops in a "Master class" setting to outstanding students at the postgraduate and early postdoctoral level 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 that are received, on a competitive basis, from Institut Pasteur International Network, the Li Ka Shing Faculty of Medicine at HKU, the French Consulate in Hong Kong and Macau and other private donations. Our budget cover advertising costs, travel and accommodation for all lecturers (except from industry). Selected students are expected to pay for their travel costs. Registration fees (HKD 1,000) include tuition, all course materials, accommodation (on sharing twin basis for overseas participants) and food (lunch and coffee breaks). Full reports of all events have been separately provided to the members of the HKU-PRP Advisory Committee.

Additional teaching and training

We have co-organized with the Faculty Core Facility of HKU the second edition of the **Croucher Summer Course on Advanced Imaging**. This Croucher Summer Course is intended to provide a conceptual and hands-on training in super-resolution and advanced microscopy. It will highlight the power of optical imaging tools, microanalysis and their applications in biomedical research. The course showcased the latest advances in the development of single molecule andsuper-resolution microscopy combined with image analysis and applications in biomedical research. Eight leading experts and scientists in imaging microscopy, coming from USA, France, Germany, Brazil, Singapore and South Africa, have been invited to share their exciting research findings and expertise. Topics included single molecule and organismal imaging,high-content imaging, light-sheetmicroscopy ,super-resolution and high-speedimaging and theirapplications. There were five parallel practical workshops (including Spinning Disc confocal, TIRF, Light-sheet, STORM microscopy and imaging analysis) run on afternoons and evenings. Students were thus exposed to a week of exciting learning experiences through lectures, hands-on experiments and, most important of all, close interactions among the participants and

course instructors and their assistants. We are confident that these interactions will continue after the course.

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 2017 edition, organized in close partnership with the Pasteur Institute of Ho Chi Minh City, the School of Public Health at HKU and the International Network of Institut Pasteur, was **"Health Economics",** the branch of Public Health that is concerned with the resources needed to provide and promote health. Resources should be intended as not limited to money but also including people, materials, education, communication, time, that might be used in different ways to achieve the principal goal of improving health. The demands of policy makers for information on the cost-effectiveness of health interventions have become more extensive and complex. Economic assessment is also increasingly used to support decisions in public health such as vaccination programs. Health professionals involved in the mitigation of infectious diseases need, therefore, a common knowledge of health economics to communicate about their action, and advise health authorities and decision makers to implement cost-efficient response programs with relevant allocation of the available resources. The workshop focused on basic theory of health economics including socio-economic concepts, methods to define, measure and analyse costs of health policies, as well as comparative analysis of health systems. Participants were trained in the planning of public health responses, based on the interactive teaching carried out by expert faculty. Training sessions will cover cost effectiveness analysis of vaccination programs and other interventions, design of surveys, resource allocation strategy. The workshop also addressed how the implementation of these different types of measures is translated into the everyday life of target populations. An important objective of this program is to build the foundation of a series of events that will ultimately empower participants to conduct similar training in their own institutions. The course series has been generously supported from its inception by the Regional Health Cooperation Office of the French Ministry of Foreign Affairs. We also thank Sanofi Pasteur for being our sponsor for a second year, and the Pasteur Foundation Asia for its generous contribution.

To contribute to, and to fully benefit from, the opportunities in the emerging era of big data intensive and global biomedical research, an additional targeted action around big data utilization has been initiated, **the** Institut Pasteur International Network for Data Analysis (INDA). We have taken into account the increasing demand for training in *omic* science and held a **Hands-on Next Generation Sequencing INDA Course**, in collaboration with the Center of Bioinformatics, Biostatistics and Integrative Biology (C3BI) of the Institut Pasteur and the Center for Genomic Sciences at HKU. This theoretical and practical course was aimed at researchers who would like to get the most out of their Next Generation Sequencing datasets. We tackled several topics, encompassing theoretical NGS approaches and statistical analysis of NGS data. Ultimately, we wanted this course to be of immediate value to the students. Thus, the first week was devoted to theory and practical examples for a broad audience, whereas the second week was dedicated to practical analysis and hands-on for a selected group of participants. There were more than 100 application for the course and we are considering the possibility to hold it on a biennial basis.

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 s. HKU-PRP regularly hosts undergraduate/postgraduate students from overseas institutions for internships. In 2017 we welcomed two international trainees for an internship period:

- **Myriam EUTAMENE** from the **University of Lille, France**;
- **Emily MIAO** from **Erasmus University Medical Center, The Netherlands**.

We continue our educational program for high school students from the French International School in Hong Kong and have hosted four of them for the week-long work experience laboratory placement. Moreover, five 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 joined HKU-PRP for MPhil research work.

Complete list of taught courses

1. Roberto Bruzzone (2017) Course Director, Molecular Biology of the Cell Course, Institut Pasteur, Paris, France.
2. Roberto Bruzzone (2017) Course Director, 9th HKU-Pasteur Immunology Course, The University of Hong Kong, Hong Kong SAR.
3. Roberto Bruzzone (2017) Course Director, 14th HKU-Pasteur Virology Course, The University of Hong Kong, Hong Kong SAR.
4. Roberto Bruzzone (2017) Course Director, 2nd Croucher Summer School on Advanced Imaging, The University of Hong Kong, Hong Kong SAR.
5. Roberto Bruzzone (2017) CMED6227 – Biological Basis of Disease (Master of Public Health), The University of Hong Kong, Hong Kong SAR.
6. Roberto Bruzzone (2017) Introduction to the Art and Science of Medicine, Problem Based Learning (MBBS Year 1), The University of Hong Kong, Hong Kong SAR (*Tutor*).
7. Roberto Bruzzone (2017) Course Co-Organizer, Hands-on NGS course, The University of Hong Kong, Hong Kong SAR.
8. Roberto Bruzzone (2017) Course Director, Health Economics, Pasteur Institute of Ho Chi Minh City, Vietnam.
9. Barbara Gayraud-Morel (2017) 5th Advances in Stem Cell BiologyCourse, Institut Pasteur, Paris, France (*Tutor*).
10. Suki Lee (2017) Hematology and Immunology System – Problem Based Learning (MBBS Year 2), LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR (*Tutor*).
11. Suki Lee (2017) Institut Pasteur Massive Open Online Courses (MOOC) "Innate immunity and infectious diseases": Toll-like receptors in influenza virus infection (*Lecturer*).
12. Chris Mok (2017) Course Director, 14th HKU-Pasteur Virology Course, Hong Kong, Hong Kong SAR.
13. Chris Mok (2107) Introduction to the Art and Science of Medicine – Problem Based Learning (MBBS Year 1), The University of Hong Kong, Hong Kong SAR (*Tutor*).
14. Mailik Peiris (2017) Course Director, 14th HKU-Pasteur Virology Course, The University of Hong Kong, Hong Kong SAR.
15. Malik Peiris (2017) CMED6104 – Emerging infectious diseases: the "One Health" concept (Master of Public Health), The University of Hong Kong, Hong Kong SAR.
16. Sumana Sanyal (2017) Basic Metabolism (BSc Biochemistry Year 3), The University of Hong Kong, Hong Kong SAR
17. Sumana Sanyal (2017) Cancer Screening – Problem Based Learning (MBBS Year 4), The University of Hong Kong, Hong Kong SAR
18. Sumana Sanyal (2017) Introduction to the art and science of medicine – Problem Based Learning (MBBS Year 1), The University of Hong Kong, Hong Kong SAR (*Tutor*).
19. Sumana Sanyal (2017) Molecular Biology of the Cell Course, Institut Pasteur, Paris, France (*Lecturer* and *Tutor*).

20. Sophie Valkenburg (2017) 9th HKU-Pasteur Immunology Course, The University of Hong Kong, Hong Kong SAR (*Tutor*).
21. Sophie Valkenburg (2017) 14th HKU-Pasteur Virology Course, The University of Hong Kong, Hong Kong SAR (*Lecturer*).
22. Sophie Valkenburg (2017) "Biological Basis of Disease" (Master of Public Health), School of Public Health, The University of Hong Kong, Hong Kong SAR (*Lecturer*).
23. Sophie Valkenburg (2017) Muscoskeletal system block – Problem Based Learning (MBBS Year 2), The University of Hong Kong, Hong Kong SAR (*Tutor*).

Complete list of student interns

CHAN, Wai Yuet	Student at the Institute of Vocational Education, Hong Kong
FONG, Man Tak	Student at the Institute of Vocational Education, Hong Kong
LEE, Wing Ki	Student at the Institute of Vocational Education, Hong Kong
SUEN, Hoi Yan	Student at the Institute of Vocational Education, Hong Kong
WONG, Ka Lok	Student at the Institute of Vocational Education, Hong Kong
COHEN, Celeste	High School Student (French International School)
GUYON, Lison	High School Student (French International School)
SIDNEY, Jones	High School Student (French International School)
VITALE, Lorenzo	High School Student (French International School)
MIAO, Emily	Master Student (Erasmus MC Rotterdam)
EUTAMENE, Myriam	Master Student (Universite de Lille)
WONG, Matthew	Medical Student (MBBS Year 1, HKU)
DAI, Zi Xi Mike	MPhil Student (HKUST)

3.8 International Activity

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 has been on the Executive Committee of ISARIC since its official launching in 2012 and has been Vice-Chair since 2014. ISARIC is a global consortium of over 50 clinical research networks with representatives in 111 countries, who are committed to working together to conduct world-class research on emerging infections to generate new knowledge to save lives. It exists because we all recognize the need for a rapid, coordinated and high quality clinical research response to epidemics. Over this period ISARIC has made a notable impact on the clinical research response to infectious diseases such as MERS-CoV and Ebola and has established itself as a well-known and key contributor to international outbreak research preparedness and response. ISARIC's mission is both to conduct world class clinical research in the inter pandemic period and to provide a collaborative platform through which clinical studies could be undertaken rapidly in response to the emergence of a novel respiratory pathogen or other new or reemerging infectious disease outbreak. The consortium mission is to ensure that clinical research is fully integrated and complementary to the 'public health' response in order to understand the causes of such infections and, how they develop and progress in patients, to identify the best treatment for individuals and prevent further transmission and hence save lives. In 2014 ISARIC has laid down the foundations for more challenging co-ordinated studies, including clinical trials of pathogen-specific therapies with pragmatic endpoints. 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.

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.

The TRS will promote the implementation of the "One Health" concept to manage influenza risks, with a strong educational component embedded in the program.

Visiting Research Professors Scheme

Professor James Di Santo from the Institut Pasteur has been appointed as Visiting Professor for the period 2016-8 through the "Visiting Research Professors" scheme of the University Research Committee of HKU. It is expected that having Professor James Di Santo as a Visiting Research Professor will stimulate research efforts and exchanges at several different levels within the LKS Faculty of Medicine. A discussion concerning establishing the Institut Pasteur Human Healthy Global Project (HHGP; http://www.milieuinterieur.fr/en) in Hong Kong, where cohorts have been established for many years by the School of Public Health, has been initiated; HHGP aims to understand the genetic and environmental determinants of immune responsiveness in normal individuals and provides a framework for future disease-related investigations that involve the immune system. Professor Di Santo will have an active role in mentoring postgraduate students and early stage investigators involved in the projects.

We have obtained additional funds through the PROCORE – France/Hong Kong Joint Research Scheme supported by the RGC to further explore the functions of human ILCs during the course of infection by respiratory pathogens. Several questions will be addressed: How are ILC numbers and effector functions modified during influenza infection? Does this result from changes in ILC subset structure? How is ILC functional heterogeneity influenced? Are ILCs targets for influenza infection? The complementary expertise of Professor Di Santo and research scientists at HKU should create the perfect conditions to address these and other questions. The influenza research team in HKU has established a robust cell infection system to study the responses of virus-infected cells. We will investigate whether these human ILCs can be infected by influenza A virus, including the highly pathogenic influenza virus H5N1 as well as the lately emerging H7N9 virus and compared to low pathogenic viruses, including seasonal H3N2 and H1N1 viruses. We will then characterize whether ILC effector functions are modified by influenza infection and the underlying mechanisms for these changes. These studies will provide a new view of how different types of influenza virus infection might alter host immune response. Results in this area could help explain mechanisms of virus pathogenesis. These projects also complement well the recently approved Theme-based Research Scheme entitle "Viral, host and environmental determinants of influenza virus transmission and pathogenesis" under the "Promoting Good Health" theme, which is coordinated by Malik Peiris. The appointment of James Di Santo will be an invaluable asset in building an even stronger program in human immunology, a strategic area of research that will reinforce the partnership between LKS Faculty of Medicine of HKU and Institut Pasteur.

Visiting Researchers

Dr. Stephanie Lebreton, a tenured scientis from the Institut Pasteur joined HKU-PRP as Visitng Researcher in July-August, as part of the new exchange scheme implemented to encourage mobility of researchers in Paris within the Institut Pasteur International Network. Dr. Lebreton is a cell biologist currently working in the understanding of epithelial polarity establishment and maintenance. She is particularly focused on understanding the mechanism of apical sorting of glycosylphosphatidylinositol-anchored proteins in polarized epithelial cells in correlation with their biological activities. As influenza firstly infect polarized cells, she started a project aimed at investigating the role of polarity during influenza infection. Dr. Lebreton has compared the lifetime of epithelium integrity following apical and basolateral infections by confocal microscopy using both low cytokine (H1N1 pdm A/HK/41512/2009) and a high cytokine (H9N2 A/quail/HK/G1/97) inducing viruses. In addition, the same set of analysis have been performed in polarized epithelial cells where the content of cholesterol and/or calcium were pharmacologically manipulated.

This project will be pursued to improve our general understanding of influenza infection in fully polarized epithelial cells and decipher the putative role of cholesterol and calcium during infection.

Professor Juan Carlos Saez, Deputy Director of the Neuroscience Institute of Valparaiso (Chile) and the Department of Physiology, Pontificia Universidad Catolica de Chile (Santiago, Chile), was appointed as Honorary Professor in the School of Public Health and spent the month of Novelmber 2017 in the lab. Professor Saez is a renowned cell physiologist who has given seminal contributions to the understanding of two classes of membrane channels, pannexins and connexins, in health and disease for the past three decades. Both pannexins and connexins are expressed in cells of the immune system and the epithelium of the respiratory tract, which are the focus of our studies here. His appointment and on-site visit allowed to jumpstart experiments aiming at defining the role of these druggable targets (pannexins and connexins) in the immune response to viral infections, intercellular signaling, the activation of inflammasome and apoptosis. Professor Saez obtained a competitive fellowship ((Santander UC Top China) to set up collaborations with HKU and other local universities and promote the exchange of students and ideas with Chile. It is expected that this program will reveal novel aspects of viral pathogenesis and related immunological mechanism that may open new research avenues for the lab in collaboration with Professor Saez.

Other key actions

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. He co-organised with WHO informal meeting to discuss environmental contamination studies of MERS-CoV (Hong Kong, 13-14 March 2017), the WHO GOARN MERS-CoV development workshop (15 -16 March 2017, The University of Hong Kong) and the international meeting "Transmission of Respiratory Viruses: from basic science to evidence based options for control" (Hong Kong, June 19-21, 2017). Malik Peiris was a session co-chairma at the FAO-OIE-WHO Global Technical Meeting on MERS-CoV (Geneva, 25-27 Sept 2017) and particioated in WHO Teleconferences on the clinical management of human infections caused by influenza A (H7N9)during the 5th seasonal epidemic in China, (16th Feb 2017).

Malik Peiris was awarded the title of Officier de la Legion d'Honneur, France (2017) and elected as Foreign Associate to the National Academy of Sciences USA.

4. Scientific Output

4.1 Publications

1. Bertram S, Thiele S, Dreier C, Resa-Infante P, Preuss A, van Riel D, Mok CK, Schwalm F, Peiris JS, Klenk HD, Gabriel G (2017) H7N9 influenza A virus exhibits importin-α7 mediated replication in the mammalian respiratory tract. *Am J Pathol* **187**:831-840.
2. Chan RWY, Chan LLY, Mok CKP, Lai J, Tao KP, Obadan A, Chan MCW, Perez DR, Peiris JSM, Nicholls JM (2017) Replication of H9 influenza viruses in the human ex vivo respiratory tract, and the influence of neuraminidase on virus release. *Sci Rep* **7**:6208.
3. Choe PG, Perera RAPM, Park WB, Song KH, Bang JH, Kim ES, Kim HB, Ko LWR, Park SW, Kim NJ, Lau EHY, Poon LLM, Peiris M, Oh MD (2017) MERS-CoV antibody responses 1 year after symptom onset, South Korea, 2015. *Emerg Infect Dis* **23**:1079-1084.
4. Chu DKW, Chan SMS, Perera RAPM, Miguel E, Roger F, Chevalier V, Poon LLM, **Peiris** M (2017) MERS-CoV in Arabian camels in Africa and Central Asia. *Virus Evol* **3**(Suppl 1), pii:vew036.045.
5. Fan Y, Mok CK, Zhang Y, Nal B, Kien F, Bruzzone R, Sanyal S (2017) Cell cycle independent role of cyclin D3 in host restriction of influenza virus infection. *J Biol Chem*, **292**:5070-5088.
6. Gayraud-Morel B, Pala F, Sakai H, Tajbakhsh S (2017) Isolation of muscle stem cells from mouse skeletal muscle. In: Muscle Stem Cells – Methods and Protocols (Perdiguero E and Cornelison D, eds.), pp. 23-39.
7. Guan W, Wu NC, Lee HH, Zhong NS, Wilson IA, Peiris JSM, Yang Z, Mok CKP (2017) Clinical correlates of transcriptional signatures in patients with infection of avian influenza (H7N9) virus. *In preparation*.
8. Hemida MG, Alnaeem A, Chu DK, Perera RA, Chan SM, Almathen F, Yau E, Ng BC, Webby RJ, Poon LL, Peiris M (2017) Longitudinal study of Middle East Respiratory Syndrome coronavirus infection in dromedary camel herds in Saudi Arabia, 2014-2015. *Emerg Microbes Infect* **6**:e56.
9. Hemida MG, Chu DKW, Perera RAPM, Ko RLW, So RTY, Ng BCY, Chan SMS, Chu S, Alnaeem AA, Alhammadi MA, Webby RJ, Poon LLM, Balasuriya UBR, Peiris M (2017) Coronavirus infections in horses in Saudi Arabia and Oman. *Transbound Emerg Dis* **64**:2093-2103.
10. Hemida MG, Elmoslemany A, Al-Hizab F, Alnaeem A, Almathen F, Faye B, Chu DK, Perera RA, Peiris M (2017) Dromedary camels and the transmission of Middle East Respiratory Syndrome Coronavirus (MERS-CoV). *Transbound Emerg Dis* **64**:344-353.
11. Hui KP, Chan LL, Kuok DI, Mok CK, Yang ZF, Li RF, Luk GS, Lee EF, Lai JC, Yen HL, Zhu H, Guan Y, Nicholls JM, Peiris JS, Chan MC (2017) Tropism and innate host responses of influenza A/H5N6 virus: an analysis of ex vivo and in vitro cultures of the human respiratory tract. *Eur Respir J* **49**:pii:1601710.
12. Ip DK, Lau LL, Leung NH, Fang VJ, Chan KH, Chu DK, Leung GM, Peiris JS, Uyeki TM, Cowling BJ (2017) Viral Shedding and Transmission Potential of Asymptomatic and Paucisymptomatic Influenza Virus Infections in the Community. Clin Infect Dis. 64(6):736-742.
13. Kang M, Lau EHY, Guan W, Yang Y, Song T, Cowling BJ, Wu J, Peiris M, He J, Mok CKP (2017) Epidemiology of human infections with highly pathogenic avian influenza A(H7N9) virus in Guangdong, 2016 to 2017. *Eurosurveillance* **22**, pii:30568.
14. Kasem S, Qasim I, Al-Hufofi A, Hashim O, Alkarar A, Abu-Obeida A, Gaafer A, Elfadil A, Zaki A, Al-Romaihi A, Babekr N, El-Harby N, Hussien R, Al-Sahaf A, Al-Doweriej A, Bayoumi F, Poon LLM, Chu DKW, Peiris M (2017) Cross-sectional study of MERS-CoV-specific RNA and antibodies in animals that have had contact with MERS patients in Saudi Arabia. *J Infect Public Health*, in press.
15. Ke C, Mok CKP, Zhu W, Zhou H, He J, Guan W, Wu J, Song W, Wang D, Liu J, Lin Q, Chu DKW, Yang L, Zhong N, Yang Z, Shu Y, Peiris JSM (2017) Human infection with highly pathogenic avian influenza A(H7N9) virus, China. *Emerg Infect Dis* **23**:1332-1340.

16. Lai JC, Herath MT, Wong HH, Peiris JS, Nicholls JN (2017) Neuraminidase activity and specificity of Influenza A virus is influenced by Hemagglutinin-receptor binding. *Submitted*.

17. Lee SM, Yan S, Yip TF, Peiris JS (2017) Toll-like receptor 10 is a novel nucleotide sensing receptor. *Submitted*.

18. Lee SMY, YipTF, Yan S, Jin DY, Wei HL, Guo RT, Peiris JSM (2108) Recognition of double-stranded RNA and regulation of interferon pathway by Toll-like receptor 10. *In revision*.

19. Li W, Lee HHY, Li RF, Zhu HM, Yi G, Peiris JSM, Yang ZF, Mok CKP (2017) The PB2 mutation with lysine at 627 enhances the pathogenicity of avian influenza (H7N9) virus which belongs to a non-zoonotic lineage. *Sci Rep* **7**:2352.

20. Mak GCK, Kwan MY, Mok CKP, Lo JYC, Peiris M, Leung CW (2017) Influenza A(H5N1) virus infection in a child with encephalitis complicated by obstructive hydrocephalus. *Clin Infect Dis*, in press.

21. Mayr J, Lau K, Lai JC, Gagarinov I, Chan RW, von Itzstein M, Nicholls JN, Haselhorst T (2017). Unraveling the role of O-glycans in influenza virus infections. *Sci Rep*, in revision.

22. Miguel E, Chevalier V, Ayelet G, Ben Bencheikh MN, Boussini H, Chu DK, El Berbri I, Fassi-Fihri O, Faye B, Fekadu G, Grosbois V, Ng BC, Perera RA, So TY, Traore A, Roger F, Peiris M (2017) Risk factors for MERS coronavirus infection in dromedary camels in Burkina Faso, Ethiopia, and Morocco, 2015. *Euro Surveill* **22**, pii:30498.

23. Ng YP, Yip TF, Peiris JSM, Ip NY, Lee SMY (2018) Neuropathogenesis of avian influenza A H7N9 virus. *In revision*.

24. Nguyen THO, Sant S, Bird NL, Grant EJ, Clemens EB, Koutsakos M, Valkenburg SA, Gras S, Lappas M, Jaworowski A, Crowe J, Loh L, Kedzierska K (2017) Perturbed $CD8_+$ T cell immunity across universal influenza epitopes in the elderly. *J Leukoc Biol*, in press.

25. Pombo JP, Sanyal S (2018) Perturbation of intracellular cholesterol and fatty acid homeostasis during flavivirus infections. *Front Immunol*, submitted.

26. Tam YH, Valkenburg SA, Perera RAPM, Wong JHF, Fang VJ, Ng TWY, Kwong ASK, Tsui WWS, Ip DKM, Poon LLM, Chau CKV, Barr IG, Peiris JSM, Cowling BJ (2017) Immune responses to twice-annual influenza vaccination in older adults in Hong Kong. *Clin Infect Dis*, in press.

27. Teng O, Chen ST, Hsu TL, Sia SF, Cole S, Valkenburg SA, Hsu TY, Zheng JT, Tu W, Bruzzone R, Peiris JS, Hsieh SL, Yen HL (2017) CLEC5A-mediated enhancement of the inflammatory response in myeloid cells contributes to influenza pathogenicity in vivo. *J Virol* **91**: e01813-16.

28. Valkenburg SA, Li OTW, Li A, Bull M, Waldmann TA, Perera LP, Peiris JSM, Poon LLM (2018) Protection by universal influenza vaccine is mediated by memory CD4 T cells. *Submitted*.

29. Yan S, Ip KK, Lee SM (2017) TLR10 modulates poly(I:C) induced pro-inflammatory response. *In preparation*.

30. Zhang N, Bao YJ, Tong A, Bader G, Zuyderduyn S, Peiris JSM, Lok S, Lee SMY (2018) Whole transcriptome analysis reveals differential gene expression profile reflecting macrophage polarization in response to influenza A H5N1 virus infection. *In revision*.

31. Zhang J, Lan Y, Li MY, Lamers MM, Fusade-Boyer M, Klemm E, Thiele C, Ashour J, Sanyal S (2018) Host cellular ubiquitylation profiling reveals a critical role for lipid droplet metabolism during flavivirus infections. *Cell Host Microbe*, in revision.

32. Zhang J, Lan Y, Sanyal S (2017) Modulation of Lipid Droplet Metabolism – A potential target for therapeutic intervention in *Flaviviridae* infections. *Front Microbiol* **8**:2286.

4.2 Presentations at Meetings

1. Jahan AS, Sanyal S (2017) *EMBO Conference: Hijacking host signalling and epigenetic mimicry during infections,* Paris, France (Poster).
2. Jahan AS, Sanyal S (2017) *EMBO Practical Course: Current Methods in Cell Biology,* Heidelberg, Germany (Oral/Poster).
3. Lan Y, Zhang JT, Sanyal S (2017) Role of lipid droplets in flavivirus infection. *EMBO Conference: Hijacking host signalling and epigenetic mimicry during infections,* Paris, France (Poster).
4. Lan Y, Zhang JT, Sanyal S (2017) Modulation of host lipid metabolism during Zika virus infection. *Microbes, Immunity and Metabolism international conference,* Institut Pasteur, Paris, France (Oral).
5. Lee HHY, Sanyal S, Peiris JSM, Bruzzone R, Mok CKP (2017) The immune function of ISG15 in macrophages during influenza virus infection. *Transmission of respiratory viruses: from basic science to evidence based options for control*, Hong Kong, Hong Kong SAR (Poster).
6. Li MY, Siu L, Bruzzone R and Sanyal S (2017) *EMBO Conference: Hijacking host signalling and epigenetic mimicry during infections,* Paris, France (Poster).
7. Ng YP, Yip TF, Peiris JSM, Ip NY, Lee SMY (2017) Influenza A H7N9 virus infects human brain astrocytes & neuronal cells and induces inflammatory immune responses. *Cytokines 2017,* Kanazawa, Japan (Poster).
8. Sanyal S (2017) *EBI-Wellcome Trust Scientific conference and advances course: Protein interactions and network.* Hinxton, UK (Oral).
9. Yan S, Lee SMY (2016) TLR10 is involved in regulation of dsRNA-induced proinflammatory response. *Scientific Symposium of the Institut Pasteur International Network*, Paris, France (Poster).
10. Zhang JS, Biquand E, Lamers MM, Karim M, Fan Y, Demeret C, Sanyal S (2017) *Microbes, Immunity and Metabolism international conference*. Institut Pasteur, Paris, France (Poster).
11. Zhang JS, Biquand E, Lamers MM, Karim M, Fan Y, Demeret C, Sanyal S (2017) *Transmission of respiratory viruses: from basic science to evidence based options for control*, The University of Hong Kong, Hong Kong SAR (Poster).
12. Zhang JS, Biquand E, Lamers MM, Karim M, Fan Y, Sanyal S, Demeret C (2017) *EMBO conference: Hijacking host signaling and epigenetic mimicry during infections*, Paris, France (Poster).
13. Sophie Valkenburg (2017) TRS Transmission meeting: *Broadly reactive T cell activating vaccine does not provide sterilizing immunity enabling secondary transmission of influenza in ferrets*, The University of Hong Kong, Hong Kong SAR (Oral).
14. Sophie Valkenburg (2017) CEIRS Annual meeting: *Pre-existing ADCC antibody responses are stable longitudinally and are not boosted by recent influenza exposure*, Atlanta, USA (Poster).
15. Sophie Valkenburg (2017) Global Virus Network: *Pre-existing ADCC antibody responses are stable longitudinally and are not boosted by recent influenza exposure*, Melbourne, Australia (Poster).
16. Sophie Valkenburg (2017) CEIRS Strategic Universal Vaccine meeting, Rockville, USA (Oral).
17. Sophie Valkenburg (2017) KSMCB: *Protection by universal influenza vaccine mediated by CD4 T cells, bringing our cornerstone defense to the forefront of protection*, Seoul, Korea (Invited Oral).

4.3 Seminars, Invited Lectures and Other Oral Presentations

1. Roberto Bruzzone (2017) Scientific Conference of Research for Public Health, Pasteur Institute of Ho Chi Min City, Vietnam
2. Akhee Jahan (2017) *EMBO Practical Course: Current Methods in Cell Biology,* Heidelberg, Germany
3. Jimmy Lai (2017) Interplay between influenza hemagglutinin and neuraminidase. Department of Pathology, The University of Hong Kong, Hong Kong SAR.
4. Yun Lan (2017) Modulation of host lipid metabolism during Zika virus infection. *Microbes, Immunity and Metabolism international conference,* Institut Pasteur, Paris, France.
5. Chris Mok (2017) International Joint Symposium between Korea and Vietnam "Tropical Diseases & Zoonoses", Iksan, Korea.
6. Chris Mok (2017) Preparedness for Yellow Fever in Southern China, Institut Pasteur of Shanghai – CAS, Shanghai, PR China.
7. Malik Peiris (2017) King Faisal University, Conference on MERS-CoV: The Current Challenges and The Future Perspective, Plenary Lectures: "SARS, MERS and other coronaviruses: emergence and reducing risks" and Influenza: A "One Health" approach, Saudi Arabia.
8. Malik Peiris (2017) Institut Pasteur of Shanghai Chinese Academy of Sciences. Institut Pasteur International Network Course 2017 "Infectious diseases pathogenesis in Asia/pacific". Session "Viral pathogenesis" Lecture "Orthomyxovirus, coronaviruses and other respiratory", Shanghai, China.
9. Malik Peiris (2017) University of Sri Jayewardenepura. Scientific Sessions 2017 "Building Bridges for Better Health", plenary speaker: "A lifetime in Bio-medical Research: the excitement and challenge", Sri Lanka.
10. Malik Peiris (2017) Sri Lankan Society for Microbiology and National Science Foundation. Seminiar on "Virology Day", lecture entitled "Need for virology in development countries", Sri Lanka.
11. Malik Peiris (2017) University of Sydney. Conference title: Viral outbreaks, such as influenza: what more can we learn from ecology, anthropology, and history, Sydney.
12. Malik Peiris (2017) ISIRV. Conference on Prevention and Treatment of RVIs: Antivirals, Traditional Therapies and Host-Directed Interventions; keynote lecture: Zoonotic Respiratory Viral Threats at the Animal-Human Interface and Chair the session: Symposium on Novel Coronaviruses, Shanghai.
13. Malik Peiris (2017) HKU, Croucher Foundation and ISIRV. Transmission Conference 2017. Chair of Conference Scientific Committee and Lecture entitled: Differences in genetic and phenotypic characteristics of MERS coronaviruses may explain the lact of zoonotic MERS in West Africa, Hong Kong.
14. Malik Peiris (2017) NIAID. 10th Annual CEIRS Network Meeting. Session: Outbreak response: lecture: Human H7N9 disease, Atlanta, USA.
15. Malik Peiris (2017) General Sir John Kotelawala Defence Unviersity. Changing dynamics in the global environment; Challenges and Opportunities in Medicine. Plenary session: Emerging Infectious Diseases: The neglected dimension of Global Security, Sri Lanka.
16. Malik Peiris (2017) Agriculture, Fisheries and Conservation Department, Hong Kong Government. International Conference on One Health, Connect and Proact; Topic: Zoonotic respiratory viral threats and the One Health Response, Hong Kong.
17. Malik Peiris (2017) ESWI. The Sixth ESWI Influenza Conference. Keynote lecture, titled 'The One Health perspective of H5, H7 influenza viruses: where do we go" and to chair a session "Influenza Prevention in Development Countries "A Global Responsibility", Riga.
18. Malik Peiris (2017) Ministry of Health, Italy. G7 Meeting "Avian Influenza A Global Threat". Invited speaker: The emergence and threats posed by influenza A H7N9 viruses and how understanding the drivers of emergence and spread of these viruses can provide options for risk reduction, Rome, Italy.

19. Malik Peiris (2017) University of Melbourne (The Peter Doherty Institute for Infection and Immunity). 12th Australian Influenza Symposium. Plenary speaker for 2 lectures: "Pandemic risk assessment of influenza viruses" and "MERS", Melbourne, Australia.
20. Malik Peiris (2017) Ministry of Science, Technology & Research, Sri Lanka. Brainstorming and Planning Meetings on ICGEB Regional Research Centre (RRC), Colombo, Sri Lanka.
21. Malik Peiris (2017) WSPID. 10th Congress of the World Society for Pediatric Infectious Diseases (WSPID), Invited speaker for Special Lecture: "Responding to emerging viral disease threats" Shenzhen, China.
22. Malik Peiris (2017) CRTM & University of Peradeniya, Sri Lanka. 2nd International Conference on Tropical Medicine. Invited speaker: Chief Guest speaker on "Emerging Respiratory Viral Infections", Colombo, Sri Lanka.
23. Malik Peiris (2017) Medical Association of Thailand. Speaker Session: Inaugural Session Topic: "One Health approach: Influenza and MERS and Speaker Panel Discussion Topic: One Health: How can we collaborate, Bankgok, Thailand.
24. Sumana Sanyal (2017) Department of Immunology Annual Retreat, Institut Pasteur, France.
25. Sumana Sanyal (2017) The University of Oxford, UK.
26. Sumana Sanyal (2017) *EBI-Wellcome Trust Scientific conference and advances course: Protein interactions and network.* Hinxton, UK.
27. Sumana Sanyal (2017) Whitehead Institute for Biomedical Research/Massachusetts Institute of Technology, USA.
28. Sophie Valkenburg (2017) Korean Society for Molecular and Cellular Biology, Seoul, Korea.
29. Sophie Valkenburg (2017) Café Scientifique, Hong Kong SAR.

4.4 Active Grants

Australian Research Council

Principal Investigator:	Dr Thomas Haselhorst (Institute for Glycomics, Australia)
Collaborator :	Dr Jimmy Lai
Amount:	AU$ 696,000.00
Period:	24/Aug/2015 to 22/Aug/2017 **(Closed)**

CEIRS NIH

Co-Investigator:	Dr Sophie Valkenburg
Period:	30/Aug/2017 to 29/Aug/2019

Center for Disease Control

Principal Investigator:	Prof Ben Cowling
Co-Investigator:	Dr Sophie Valkenburg
Period:	ending 31/Jul/2021

Ester Lee and Chew Pik Foundation, Croucher Foundation and other donors

Principal Investigator:	Prof Rajiv Khanna (QIMR Berghofer Medical Research Institute, Australia);
Co-Investigatorss:	Prof John Nicholls; Prof Dora Kwong (HKU)

Health and Medical Research Fund (HMRF)

Principal Investigator:	Dr Sophie Valkenburg
Amount:	HK$999,828.00
Period:	01/Jul/2015 to 31/Dec/2017 **(Closed)**

Health and Medical Research Fund (HMRF)

Principal Investigator:	Prof Leo Poon
Co-Investigator:	Dr Sophie Valkenburg
Period:	01/May/2016 to 30/Apr/2018

Health and Medical Research Fund (HMRF)

Co-Investigator:	Dr Suki Lee
Amount:	HK$796,778.00
Period:	01/Apr/2015 to 30/Mar/2017 **(Closed)**

Health and Medical Research Fund (HMRF)

Principal Investigator:	Dr Chris Mok
Amount:	HK$638,340.00
Period:	01/Jul/2015 to 30/Jun/2017 **(Closed)**

Health and Medical Research Fund (HMRF)

Principal Investigator:	Dr Sumana Sanyal
Amount:	HK$981,120.00
Period:	01/Jul/2015 to 30/Jun/2017 **(Closed)**

Health and Medical Research Fund (HMRF)

Principal Investigator:	Dr Sumana Sanyal
Amount:	HK$1,200,000.00
Period:	01/Jul/2017 to 30/Jun/2019

Health and Medical Research Fund (HMRF)

Principal Investigator:	Dr Roberto Bruzzone/Dr Mingyuan Li
Amount:	HK$1,170,000.00

Period: 01/Sep/2017 to 31/Aug/2019

Health and Medical Research Fund (HMRF)

Principal Investigator: Dr Roberto Bruzzone/Dr Yun Lan
Amount: HK$1,184,712.00 (*Recommended for Support)*

Health and Medical Research Fund (HMRF)

Principal Investigator: Dr Chris Mok
Amount: HK$996,376.00) *Recommended for Support*

Health and Medical Research Fund (HMRF)

Principal Investigator: Dr Sumana Sanyal
Amount: HK$1,200,000.00 (*Recommended for Support)*

Health and Medical Research Fund (HMRF)

Principal Investigator: Dr Sophie Valkenburg
Amount: HK$1,187,554.00 (*Recommended for Support)*

Health and Medical Research Fund (HMRF)

Principal Investigator: Dr Tami Zhang
Amount: HK$1,179,424.00 (*Recommended for Support)*

IPP-PTR

Principal Investigator: Dr Sumana Sanyal
Amount: EUR143,000.00
Period: 01/Jul/2015 to 31/Dec/2017 **(Closed)**

National Natural Science Foundation of China

Principal Investigator: Dr Zi Feng Yang
Co-Investigator: Dr Chris Mok
Amount: RMB1,500,000.00
Period: ending 30/Apr/2018

Research Grants Council

Principal Investigator: Dr Sumana Sanyal
Amount: HK$769,020.00
Period: 01/Nov/2015 to 31/Oct/2017 **(Closed)**

Research Grants Council (2017/18)

Principal Investigator: Dr Sophie Valkenburg
Amount: HK$ 1,200,839.00
Period: 01/Jan/2018 to 31/Dec/2020

Research Grants Council (2017/18)

Principal Investigator: Dr Sumana Sanyal
Amount: HK$829,393.00
Period: 01/Jan/2018 to 31/Dec/2019

Research Grants Council/Consulate General of France – PROCORE – France/Hong Kong Joint Research Scheme

Principal Investigator: Dr Suki Lee
Amount: HK$30,600.00
Period: 01/Jan/2017 to 31/Dec/2018

RGC Seed Funding for Basic research

Principal Investigator:	Dr Suki Lee
Amount:	HK$34,490.00
Period:	01/Mar/2016 to 28/Feb/2017 **(Closed)**

RGC Seed Funding for Basic research

Principal Investigator:	Dr Suki Lee
Amount:	HK$55,400.00
Period:	01/May/2017 to 30/Apr/2018

RGC Seed Funding for Basic research

Principal Investigator:	Dr Chris Mok
Amount:	HK$45,980.00
Period:	01/Jun/2016 to 31/May/2017 **(Closed)**

RGC Seed Funding for Basic research

Principal Investigator:	Dr Chris Mok
Amount:	HK$44,320.00
Period:	01/May/2017 to 30/Apr/2019

RGC Seed Funding for Basic research

Principal Investigator:	Dr Sumana Sanyal
Amount:	HK$80,470.00
Period:	01/Jun/2016 to 31/May/2018

Science research project of the Guangdong Province

Principal Investigator:	Dr Zi Feng Yang
Co-Investigator:	Dr Chris Mok
Amount:	RMB1,000,000.00
Period:	01/Jul/2016 to 30/Jun/2018

Seed Funding for Basic research

Principal Investigator:	Dr Sophie Valkenburg
Amount:	HK$150,000.00
Period:	14/Oct/2016 to 13/Oct/2018

Viral, Host and Environmental Determinants of Influenza Virus Transmission and Pathogenesis

Principal Investigator:	Dr Suki Lee
Amount:	HK$1,100,000.00
Period:	01/Jan/2015 to 31/Dec/2019

Viral, Host and Environmental Determinants of Influenza Virus Transmission and Pathogenesis

Principal Investigator:	Dr Chris Mok
Amount:	HK$800,000.00
Period:	01/Jan/2015 to 31/Dec/2019

Viral, Host and Environmental Determinants of Influenza Virus Transmission and Pathogenesis

Principal Investigator:	Dr Sumana Sanyal
Amount:	HK$950,000.00
Period:	01/Jan/2015 to 31/Dec/2019

Viral, Host and Environmental Determinants of Influenza Virus Transmission and Pathogenesis

Principal Investigator:	Prof Malik Peiris
Co-Investigator:	Prof John Nicholls/Dr Jimmy Lai
Period:	01/Jan/2015 to 31/Dec/2019

WHO

Principal Investigator:	Prof Malik Peiris
Amount:	US$19,444.99
Period:	01/Nov/2016 to 30/Sep/2017 **(Closed)**

4.5 Pending Grant Applications

Research Grants Council (2018/19)

Principal Investigator: Dr Suki Lee
Amount: HK$ 1,164,664.00

Research Grants Council (2018/19)

Principal Investigator: Dr Chris Mok
Amount: HK$

Research Grants Council (2018/19)

Principal Investigator: Dr Sumana Sanyal
Amount: HK$ 1,200,000.00

Research Grants Council (2018/19)

Principal Investigator: Dr Sophie Valkenburg
Amount: HK$ 1,193,552.00

5. Annexes

5.1 List of Staff

Name	***Position***
BRUZZONE, Roberto	Co-Director
PEIRIS, Malik	Co-Director
DI-SANTO, James	Visiting Research Professor
SAEZ, Juan Carlos	Honorary Professor
SANYAL, Sumana	Assistant Professor (non-Clinical)
LEE, Man Yan Suki	Research Assistant Professor
MOK, Ka Pun Chris	Research Assistant Professor
VALKENBURG, Sophie	Research Assistant Professor
KAVIAN-TESSLER, Niloufar	Post-Doctoral Fellow
LAI, Chun Cheong Jimmy	Post-Doctoral Fellow (Joint Appointment with Department of Pathology)
ZHANG, Jingshu Tami	Post-Doctoral Fellow
LI, Mingyuan	Post-Doctoral Fellow
LAN, Yun	Technical Officer
YAN, Sheng Selena	Research Associate
GAYRAUD-MOREL Barbara	Honorary Research Associate
LEBRETON, Stephanie	Visting Scientist
LI, Ping Hung	Research Technician
SIU, Yu Lam Lewis	Research Technician
TSE, Kong San Jane	Research Technician
CHAN, Jodi	Research Assistant
TRUPTI, Naik	Research Assistant
WANG, Yizhuo	Research Assistant
YIP, Tsz Fung	Research Assistant
LI, Pui Yee Athena	PhD Student
AKHEE, Sabiha Jahan	PhD Student
LEE, Hok Yeung Horace	PhD Student

BULL, Máiréid	MPhil Student		
HERATH M Thusitha Kumara K	MPhil Student	Graduated:	28-Feb-2017
MA, Nok Lam Fion	MPhil Student		
POMBO, Joao	MPhil Student		
SELIM Asisha	MPhil Student		
TEO, Qi Wen	Mphil Student		
WONG, Ho Him	MPhil Student	Graduated:	31-Dec-2017
MAK, Ganon	PhD Student (Part-time)		
CHAN, Wai Yuet	Student Intern (IVE)		
FONG, Man Tak	Student Intern (IVE)		
LEE, Wing Ki	Student Intern (IVE)		
SUEN, Hoi Yan	Student Intern (IVE)		
WONG, Ka Lok	Student Intern (IVE)		
COHEN, Celeste	Student Intern (French International School)		
GUYON, Lison	Student Intern (French International School)		
SIDNEY, Jones	Student Intern (French International School)		
VITALE, Lorenzo	Student Intern (French International School)		
MIAO, Emily	Student Intern (Erasmus MC Rotterdam)		
EUTAMENE, Myriam	Student Intern (Universite de Lille)		
WONG, Matthew	Student Intern (HKU)		
DAI, Zi Xi Mike	Student Intern (HKUST)		
LI, Suk Yin Anne	Administrative Assistant		
BENET, Gabriel	Scientific Officer (International Volunteer of the French Ministry of Foreiogn Affairs)	Until:	30-Nov-2017
MULLER, Simon	Executive Officer (International Volunteer of the French Ministry of Foreiogn Affairs)		
CHEUNG, Wai Sze	Laboratory Attendant		
NG, Tsz Wai	Laboratory Attendant		

5.2 Income & Expenses for the year ending 30 June 2017

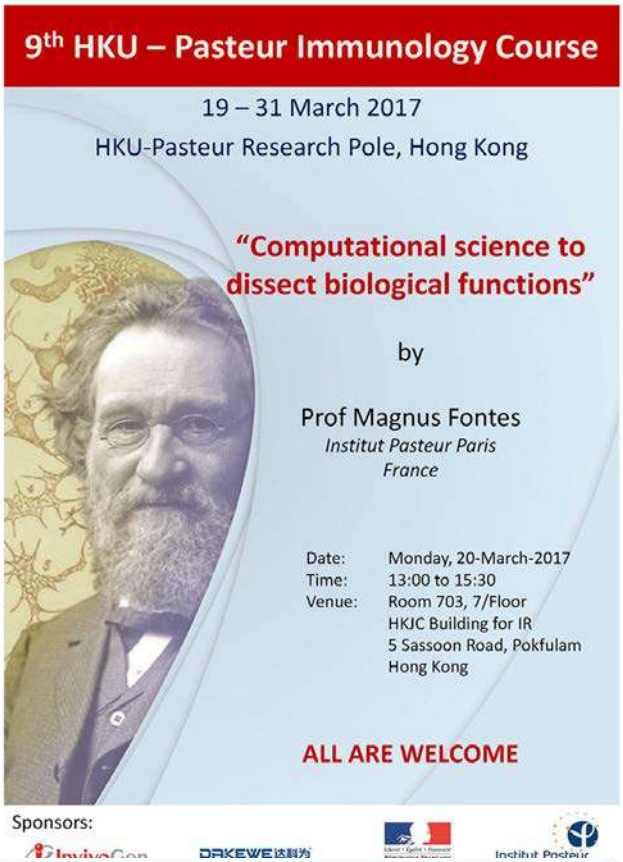
INCOME:

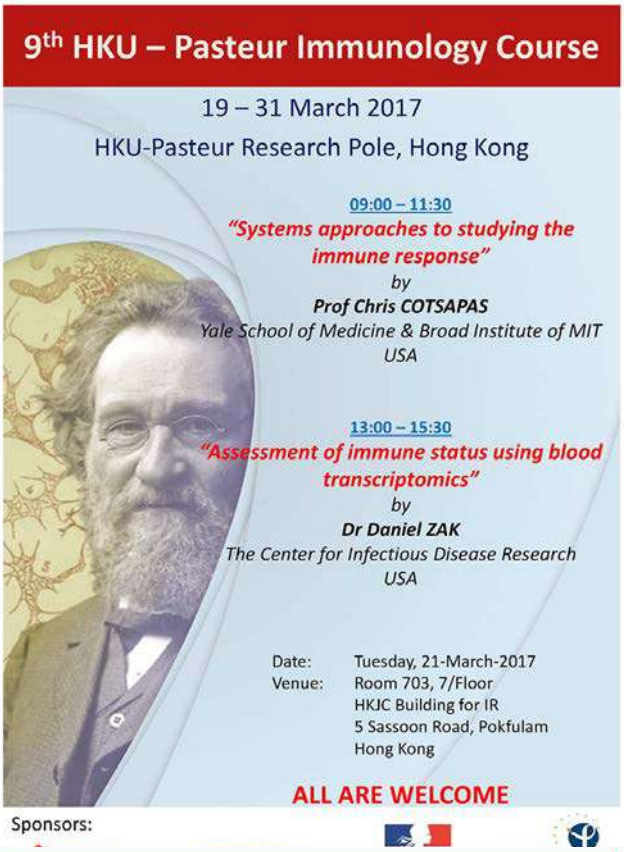
Central Funds	2,653,686.42
	538,000.00
	5,414,325.39
	3,114,741.02
Private Donation	1,214,199.00
External Grants	4,709,507.08
Teaching/Training	388,155.65
TOTAL	**18,032,614.56**

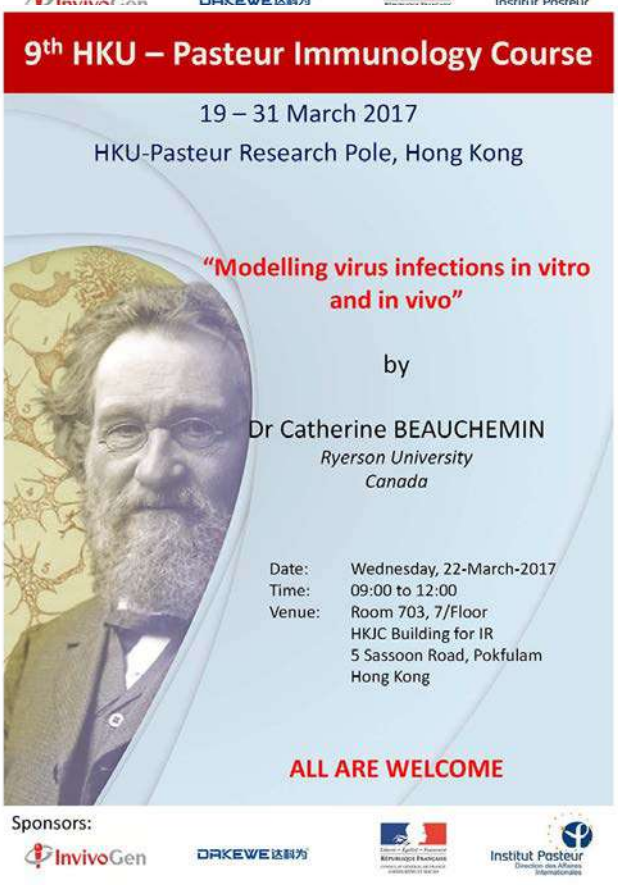
EXPENSES:

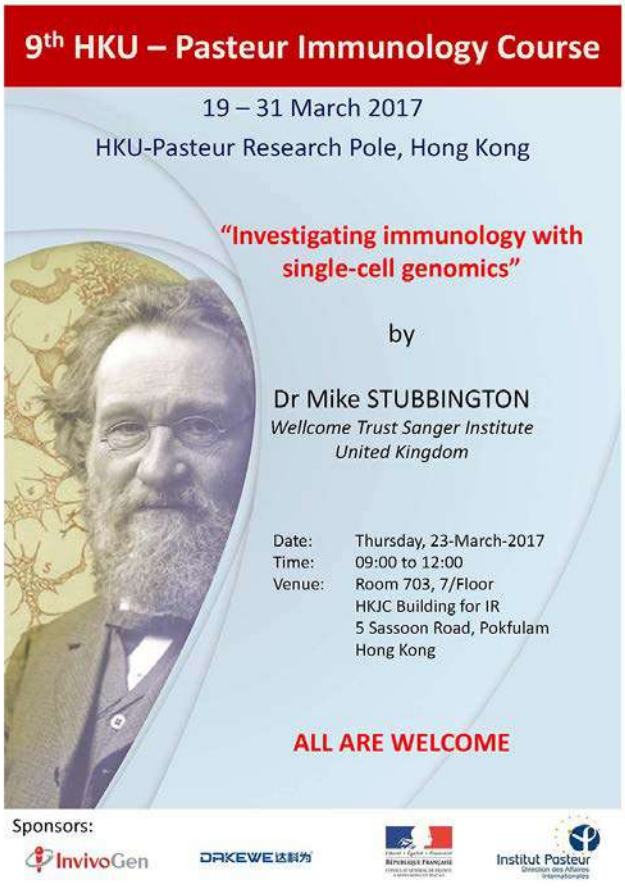
Staff Cost	7,331,244.92
Research	3,028,848.55
Administration	194,480.52
Teaching/Training	501,083.49
TOTAL	**11,055,657.48**

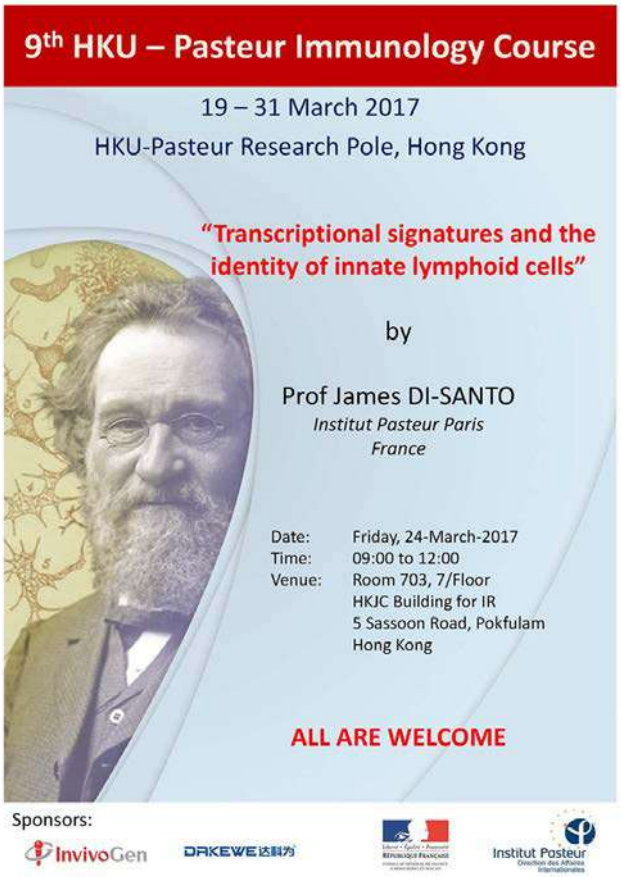
5.3 9th HKU-Pasteur Immunology Course 2017

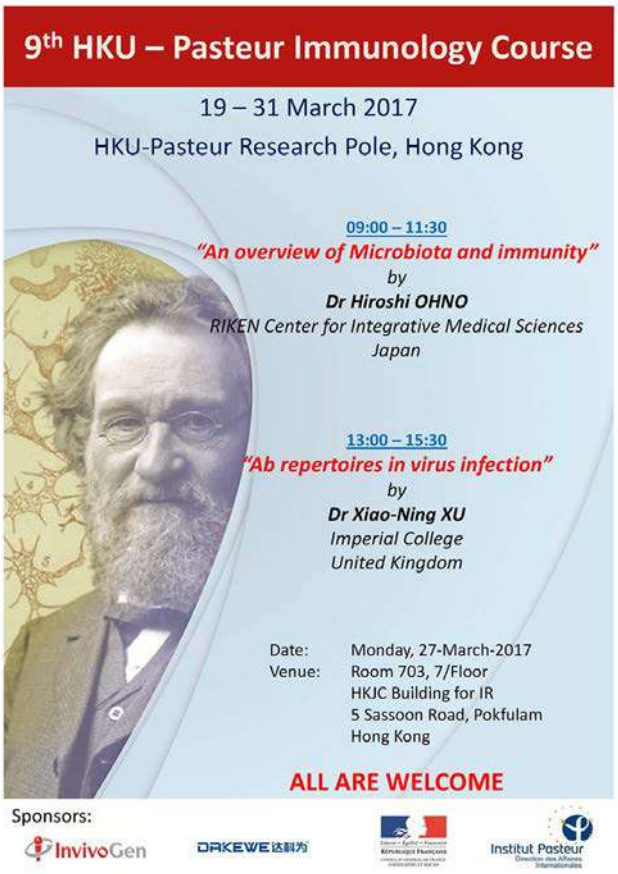

9th HKU – Pasteur Immunology Course
19 – 31 March 2017
HKU-Pasteur Research Pole, Hong Kong
"Computational science to dissect biological functions"
by
Prof Magnus Fontes
Institut Pasteur Paris
France
Date: Monday, 20-March-2017
Time: 13:00 to 15:30
Venue: Room 703, 7/Floor
HKJC Building for IR
5 Sassoon Road, Pokfulam
Hong Kong
ALL ARE WELCOME
Sponsors:

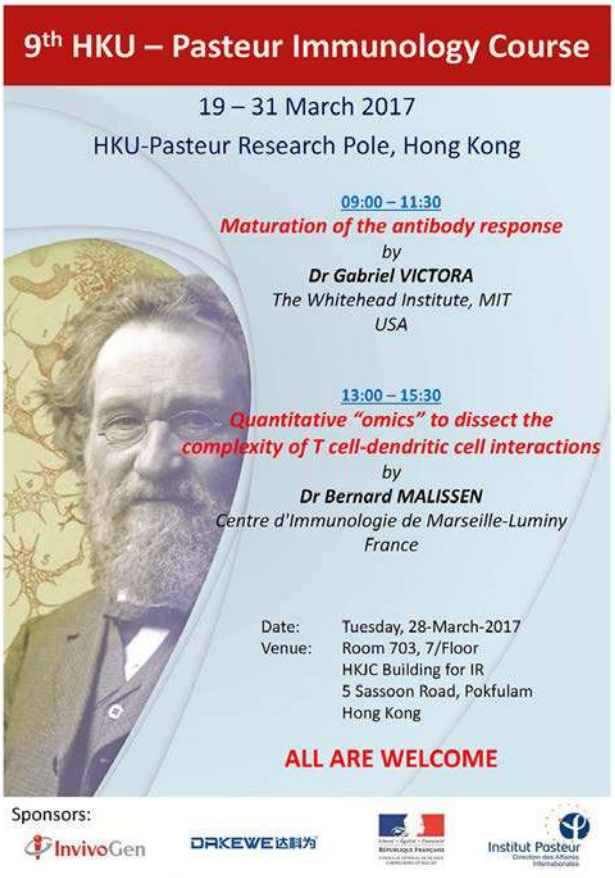

9th HKU – Pasteur Immunology Course
19 – 31 March 2017
HKU-Pasteur Research Pole, Hong Kong
09:00 – 11:30
"Systems approaches to studying the immune response"
by
Prof Chris COTSAPAS
Yale School of Medicine & Broad Institute of MIT
USA
13:00 – 15:30
"Assessment of immune status using blood transcriptomics"
by
Dr Daniel ZAK
The Center for Infectious Disease Research
USA
Date: Tuesday, 21-March-2017
Venue: Room 703, 7/Floor
HKJC Building for IR
5 Sassoon Road, Pokfulam
Hong Kong
ALL ARE WELCOME
Sponsors:

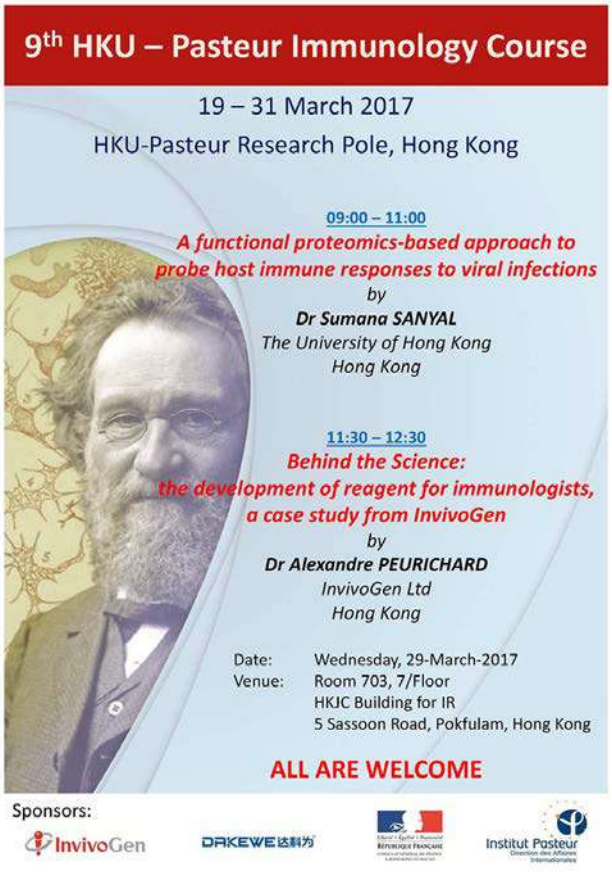

9th HKU – Pasteur Immunology Course
19 – 31 March 2017
HKU-Pasteur Research Pole, Hong Kong
"Modelling virus infections in vitro and in vivo"
by
Dr Catherine BEAUCHEMIN
Ryerson University
Canada
Date: Wednesday, 22-March-2017
Time: 09:00 to 12:00
Venue: Room 703, 7/Floor
HKJC Building for IR
5 Sassoon Road, Pokfulam
Hong Kong
ALL ARE WELCOME
Sponsors:
InvivoGen
DAKEWE达科为
Institut Pasteur


9th HKU – Pasteur Immunology Course
19 – 31 March 2017
HKU-Pasteur Research Pole, Hong Kong
"Investigating immunology with single-cell genomics"
by
Dr Mike STUBBINGTON
Wellcome Trust Sanger Institute
United Kingdom
Date: Thursday, 23-March-2017
Time: 09:00 to 12:00
Venue: Room 703, 7/Floor
HKJC Building for IR
5 Sassoon Road, Pokfulam
Hong Kong
ALL ARE WELCOME
Sponsors:
InvivoGen
DAKEWE达科为
Institut Pasteur

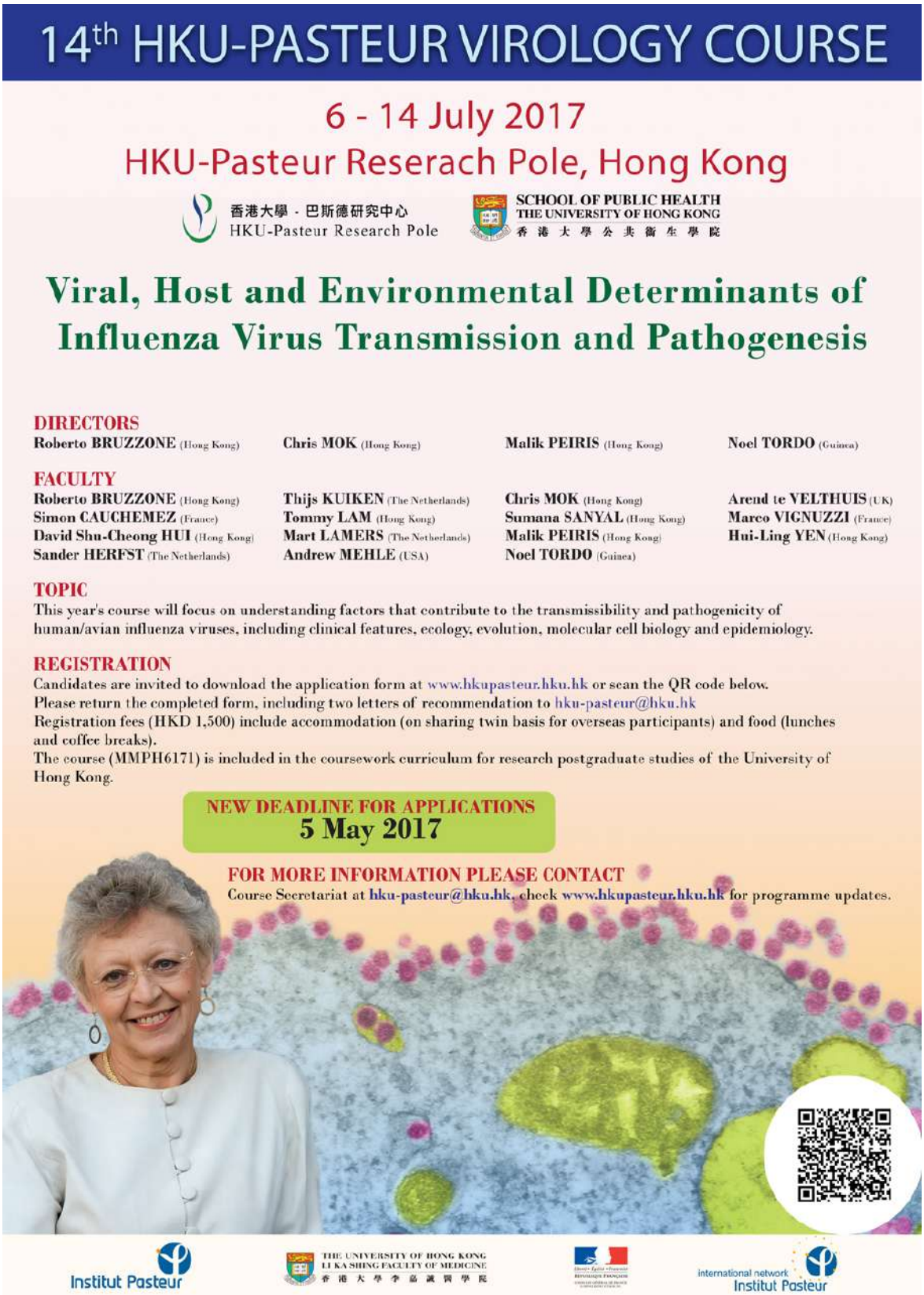

9th HKU – Pasteur Immunology Course
19 – 31 March 2017
HKU-Pasteur Research Pole, Hong Kong
"Transcriptional signatures and the identity of innate lymphoid cells"
by
Prof James DI-SANTO
Institut Pasteur Paris
France
Date: Friday, 24-March-2017
Time: 09:00 to 12:00
Venue: Room 703, 7/Floor
HKJC Building for IR
5 Sassoon Road, Pokfulam
Hong Kong
ALL ARE WELCOME
Sponsors:
InvivoGen
DAKEWE达科为
Institut Pasteur


9th HKU – Pasteur Immunology Course
19 – 31 March 2017
HKU-Pasteur Research Pole, Hong Kong
09:00 – 11:30
"An overview of Microbiota and immunity"
by
Dr Hiroshi OHNO
RIKEN Center for Integrative Medical Sciences
Japan
13:00 – 15:30
"Ab repertoires in virus infection"
by
Dr Xiao-Ning XU
Imperial College
United Kingdom
Date: Monday, 27-March-2017
Venue: Room 703, 7/Floor
HKJC Building for IR
5 Sassoon Road, Pokfulam
Hong Kong
ALL ARE WELCOME
Sponsors:
InvivoGen
DAKEWE达科为
Institut Pasteur


9th HKU – Pasteur Immunology Course
19 – 31 March 2017
HKU-Pasteur Research Pole, Hong Kong
09:00 – 11:30
Maturation of the antibody response
by
Dr Gabriel VICTORA
The Whitehead Institute, MIT
USA
13:00 – 15:30
Quantitative "omics" to dissect the complexity of T cell-dendritic cell interactions
by
Dr Bernard MALISSEN
Centre d'Immunologie de Marseille-Luminy
France
Date: Tuesday, 28-March-2017
Venue: Room 703, 7/Floor
HKJC Building for IR
5 Sassoon Road, Pokfulam
Hong Kong
ALL ARE WELCOME
Sponsors:
InvivoGen
DAKEWE达科为
Institut Pasteur


9th HKU – Pasteur Immunology Course
19 – 31 March 2017
HKU-Pasteur Research Pole, Hong Kong
09:00 – 11:00
A functional proteomics-based approach to probe host immune responses to viral infections
by
Dr Sumana SANYAL
The University of Hong Kong
Hong Kong
11:30 – 12:30
Behind the Science:
the development of reagent for immunologists, a case study from InvivoGen
by
Dr Alexandre PEURICHARD
InvivoGen Ltd
Hong Kong
Date: Wednesday, 29-March-2017
Venue: Room 703, 7/Floor
HKJC Building for IR
5 Sassoon Road, Pokfulam, Hong Kong
ALL ARE WELCOME
Sponsors:
InvivoGen
DAKEWE达科为
Institut Pasteur

5.4 14th HKU-Pasteur Virology Course 2017



HKU-PASTEUR VIROLOGY COURSE

FOR RESEARCH POSTGRADUATE STUDENTS

Institut Pasteur

香港大學・巴斯德研究中心
HKU-Pasteur Research Pole

THE UNIVERSITY OF HONG KONG
LI KA SHING FACULTY OF MEDICINE
香港大學李嘉誠醫學院

14th HKU – PASTEUR VIROLOGY COURSE

OPEN LECTURE

07-Jul-2017

09:00 - 11:00 "Ecology and evolution of influenza virus"
by ***Dr Thijs Kuiken***, Erasmus University, The Netherlands

11:30 - 13:30 "The molecular biology of influenza virus replication"
by ***Dr Aartijan te Velthuis***, Oxford University, United Kingdom

11-Jul-2017

09:00 - 11:00 "Genetic diversity and quasispecies"
by ***Dr Marco Vignuzzi***, Institut Pasteur, France

11:30 - 13:00 "Modes of influenza transmission"
by ***Dr Hui-Ling Yen***, The University of Hong Kong, Hong Kong

12-Jul-2017

09:00 - 11:00 "Host regulators of the influenza virus replication machinery"
by ***Dr Andrew Mehle***, University of Wisconsin, USA

11:30 - 13:00 "Host cellular reprogramming induced by flavivirus infections"
by ***Dr Sumana Sanyal***, HKU-Pasteur Research Pole, Hong Kong

13-Jul-2017

09:30 - 12:00 "Analysis and modelling during infectious disease epidemics"
by Dr Simon Cauchemez, Institut Pasteur,France

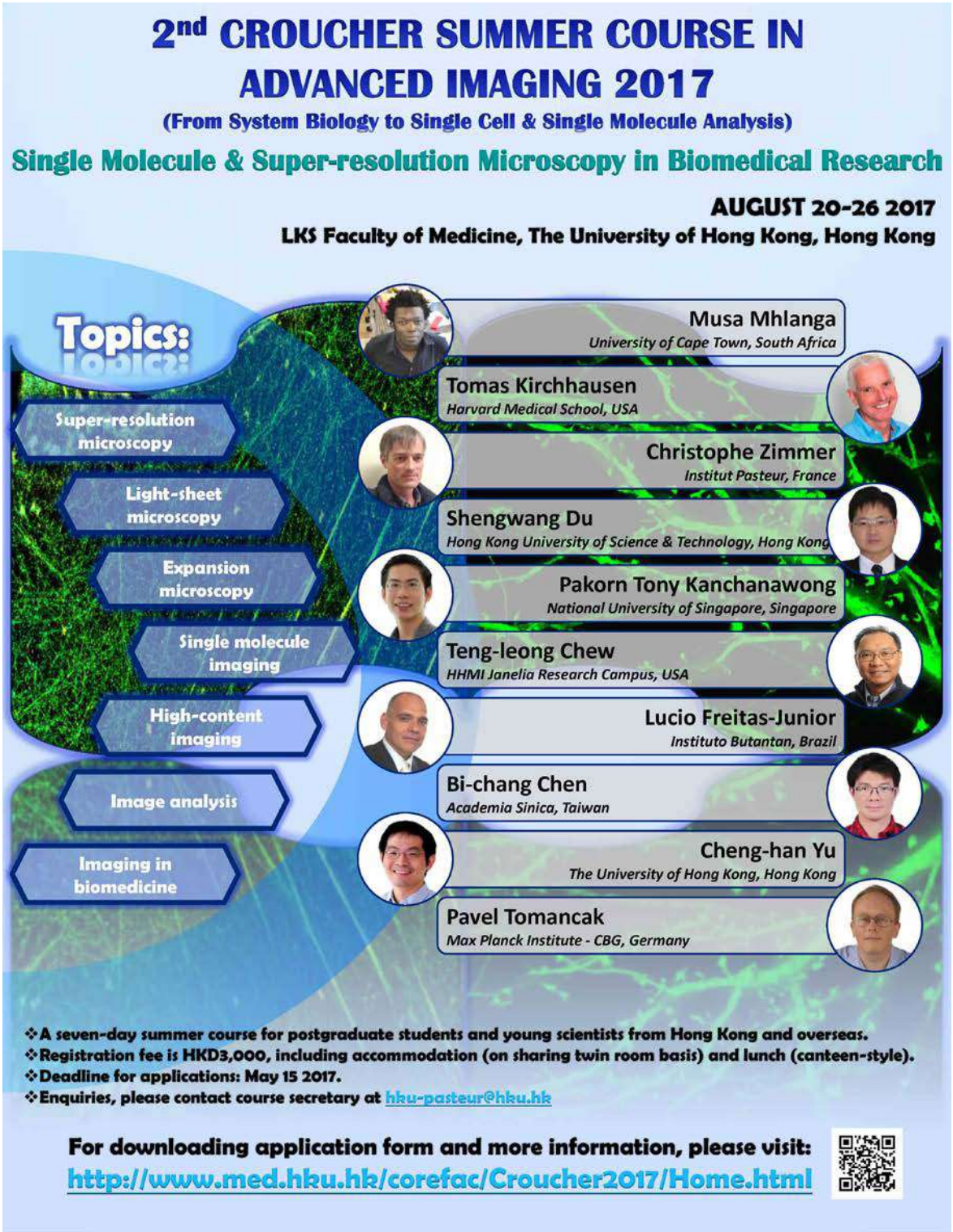
Françoise Barré-Sinoussi (b. 1947) co-recipient of the 2008 Nobel Prize in Medicine for the "discovery of human immunodeficiency virus"

VENUE:
Seminar Room 7, 7th Floor
HKJC Building for IR
5 Sassoon Road
Pokfulam, Hong Kong

ALL ARE WELCOME

SARS-CoV virions budding from infected cells (Departments of Pathology and Microbiology, HKU)

5.5 2nd Croucher Summer Course in Advanced Imaging




CROUCHER SYMPOSIUM IN ADVANCED IMAGING 2017
(From Systems Biology to Single Cell & Single Molecule Analysis)
Single Molecule & Super-resolution Microscopy in Biomedical Research
AUGUST 25 2017 (Friday)
Cheung Kung Hai Lecture Theatre 1
William MW Mong Building, Li Ka Shing Faculty of Medicine, The University of Hong Kong
Invited Speakers
Cellular imaging from molecules to organisms
Tomas Kirchhausen
Harvard Medical School, USA
Transcription factor dynamics during Drosophila development
Pavel Tomancak
Max Planck Institute of Molecular Cell Biology and Genetics, Germany
Optical single-cell imaging – How much faster and deeper can we go?
Kelvin Tsia
The University of Hong Kong, Hong Kong
Phenotypic screening for accelerating drug discovery for infectious diseases
Lucio Freitas-Junior
Instituto Butantan, Brazil
Computationally enhancing localization microscopy in 3D and time
Christophe Zimmer
Institut Pasteur, France
Higher-order genome architecture and lncRNAs permit robust transcription of immune genes
Musa Mhlanga
University of Cape Town, South Africa
Beyond the diffraction limit by light-sheet microsocpy
Bi-Chang Chen
Academia Sinica, Taiwan
Understanding synapses through imaging
Kwok-On Lai
The University of Hong Kong, Hong Kong
Imaging life with the emerging microscopy frontiers at HHMI Janelia Research Campus
Teng-Leong Chew
HHMI Janelia Research Campus, USA
Nanoscale architecture of cadherin-based cell adhesions
Pakorn Tony Kanchanawong
National University of Singapore, Singapore
Registration: https://hkuems1.hku.hk/hkuems/ec_hdetail.aspx?guest=Y&ueid=51185
Free Registration. Sandwich lunch will be provided to registered participants. Enquiries, please contact corefac@hku.hk
Jointly Organized by:
Faculty Core Facility
香港大學 - 巴斯德研究中心
HKU-Pasteur Research Pole
School of Biomedical Sciences The University of Hong Kong
Sponsored by:
ZEISS
BD
GRIFFIN BIOTECH
Gene Company Limited
ThermoFisher SCIENTIFIC
ptc
Molecular Devices
BECKMAN COULTER Life Sciences
CTS

5.6 C3BI Hands-on NGS Course

5.7 International Workshop: Health Economics

International Workshop

HEALTH ECONOMICS

December 4-7, 2017 Ho Chi Minh City, Vietnam

NO REGISTRATION FEES - FREE
ACCOMMODATION WILL BE PROVIDED
DEADLINE FOR APPLICATIONS: SEPTEMBER 22, 2017

Course's Objectives

The workshop will provide basic theory of health economics including socio-economic concepts, methods to define, measure and analyse costs of health policies, as well as comparative analysis of health systems. Participants will be trained to the planning of public health responses, based on the interactive teaching carried out by expert faculty. Training sessions will cover cost effectiveness analysis of vaccination programs and other interventions, design of surveys, resource allocation strategy. The workshop will also address how the implementation of these different types of measures is translated into the everyday life of target populations.

Faculty

J.T. WU The University of Hong Kong, **P. CLARKE, P. ANNEAR** The University of Melbourne, **M. JIT, M. LIVERANI** London School of Hygiene & Tropical Medicine, **M. HAENSSGEN** University of Oxford, **H. VAN MINH** Hanoi School of Public Health, **R. BRUZZONE** HKU-Pasteur Research Pole, **H. CLAPHAM, H. TURNER** Oxford University Clinical Research Unit, Vietnam, **C. HOANG QUOC, Q. PHAM DUY** Pasteur Institute - Ho Chi Minh City.

Participants' Profile

The course is specifically designed for health personnel, mainly but not exclusively from countries in South East Asia, including medical and health professionals, policy makers, disease researchers interested in expanding their critical understanding of the complex economic issues in health sector administration.

Applications

Candidates are invited to download application forms at www.hkupasteur.hku.hk. Please return the completed form, including 1-2 letters of recommendation, to hku-pasteur@hku.hk. The course teaching committee will review applications and select participants.

Taught in English. Limited to 24 participants.

香港大學 · 巴斯德研究中心 HKU-Pasteur Research Pole
Pasteur Institute Ho Chi Minh City Training Center
Pasteur Foundation Asia
SANOFI PASTEUR
international network Institut Pasteur

5.8 List of Public Lectures organized by HKU-PRP

08/12/2017
"Growing role of economic evaluation within health technology assessment to inform vaccination policy" by Mark JIT, London School of Hygiene & Tropical Medicine, London, UK

16/11/2017
"PhenoCARE: single cell drug response profiling" by Pamela Dobay, Former Coordinator for Bioinformatics, University Children's Hospital Zurich- Eleonore Foundation

14/11/2017
"Connexin- and pannexin-based channels at the cell surface of immune system cells" by Juan Carlos Sáez, Ph.D.,Physiology Department, Pontificia Universidad Católica de Chile-Santiago and Interdisciplinary Neuroscience Institute of Valparaiso University, Valparaiso-Chile

06/11/2017
"The Mechanobiology of Ion Channels: May the Force Be with You!" by Eric Honoré, Institute of Molecular and Cellular Pharmacology, Centre National de la Recherche Scientifique (CNRS), Valbonne, Sophia Antipolis, France

24/10/2017
"Milieu Intérieur: defining the boundaries of a healthy immune response for a better understanding of disease" by Dr Darragh Duffy, The Milieu Interieur Consortium, Institut Pasteur, France

23/10/2017
"Imaging and modeling dynamic 3D chromosome architecture" by Christophe ZIMMER, Institut Pasteur, France

13/07/2017
"Analysis and modelling during infectious disease epidemics" by Simon Cauchemez, Institut Pasteur, France

12/07/2017
"Host regulators of the influenza virus replication machinery" by Andrew Mehle, University of Wisconsin, USA

12/07/2017
"Host cellular reprogramming induced by flavivirus infections" by Sumana Sanyal, HKU-Pasteur Research Pole, Hong Kong

11/07/2017
"Genetic diversity and quasispecies" by Marco Vignuzzi, Institut Pasteur, France

11/07/2017
"Modes of influenza transmission" by Hui-Ling Yen, The University of Hong Kong, Hong Kong

07/07/2017
"Ecology and evolution of influenza virus" by Thijs Kuiken, Erasmus University, The Netherlands

07/07/2017
"The molecular biology of influenza virus replication" by Aartijan te Velthuis, Oxford University, United Kingdom

03/07/2017
"Disruptive technologies enabling patient based drug discovery" by Ulf Nehrbass, Chief Executive Officer, Ksilink, France

29/03/2017
"A functional proteomics-based approach to probe host immune responses to viral infections" by Sumana Sanyal, HKU-Pasteur Research Pole, Hong Kong

29/03/2017
"Behind the Science: the development of reagent for immunologists, a case study from InvivoGen" by Alexandre Peurichard, InvivoGen Ltd, Hong Kong

28/03/2017
"Maturation of the antibody response" by Gabriel Victora, The Whitehead Institute, MIT, USA

28/03/2017
"Quantitative "omics" to dissect the complexity of T cell-dendritic cell interaction" by Bernard Malissen, Centre d'Immunologie de Marseille-Luminy, France

27/03/2017
"An overview of Microbiota and immunity" by Hiroshi Ohno, RIKEN Center for Integrative Medical Sciences, Japan

27/03/2017
"Ab repertoires in virus infection" by Xiao-Ning Xu, Imperial College, United Kingdom

24/03/2017
"Transcriptional signatures and the identity of innate lymphoid cells" by James Di Santo, Institut Pasteur, France

23/03/2017
"Investigating immunology with single-cell genomics" by Mike Stubbington, Wellcome Trust Sanger Institute, United Kingdom

22/03/2017
"Modelling virus infections in vitro and in vivo" by Catherine Beauchemin, Department of Physics, Ryerson University, Canada

21/03/2017
"Systems approaches to studying the immune response" by Chris Cotsapas, Yale School of Medicine, USA

21/03/2017
"Assessment of immune status using blood transcriptomics" by Daniel Zak, The Center for Infectious Disease Research, USA

20/03/2017
"Computational science to dissect biological functions" by Magnus Fontes, Institut Pasteur, France

06/03/2017
"Understand cell entry process of Hepatitis C Virus and neutralization by antibodies to develop new antiviral strategies" by Dimitri Lavillette, Institut Pasteur Shanghai-CAS, PR China

16/02/2017
"Epigenetic Mechanisms Regulating Cardiac Function" by Gianluigi Condorelli, Department of Cardiovascular Medicine, Humanitas University, Italy