HONG KONG SYMPOSIUM ON CHEMICAL BIOLOGY FOR MOLECULAR MEDICINE

18 May 2024 8:45-17:45

ALL ARE WELCOME

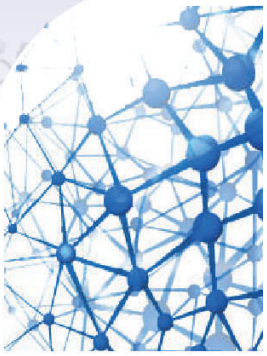
Plenary Speakers

Professor **Motonari Uesugi**

Director of the Institute for Integrated Cell-Material Sciences (iCeMS)
& Professor at Institute for Chemical Research
@ Kyoto University

Professor **Akimitsu Okamoto**

Professor at School of Engineering & Research Center
for Advanced Science and Technology (RCAST)
@ The University of Tokyo



Schedule

- 8:45 ~ 9:00 **Opening**

Morning Session *Venue: LT3, G/F YIA, CUHK*

- 9:00 ~ 9:50 **Motonari Uesugi**
- 9:50 ~ 10:15 **Jiangang Shen**
- 10:15 ~ 10:40 **Xiaoyu Li**
- 10:40 ~ 11:00 **Break**
- 11:00 ~ 11:25 **Yi Wang**
- 11:25 ~ 11:50 **Michael Kenneth Chan**
- 11:50 ~ 12:15 **Quan Hao**

Afternoon Session *Venue: LT3, G/F YIA, CUHK*

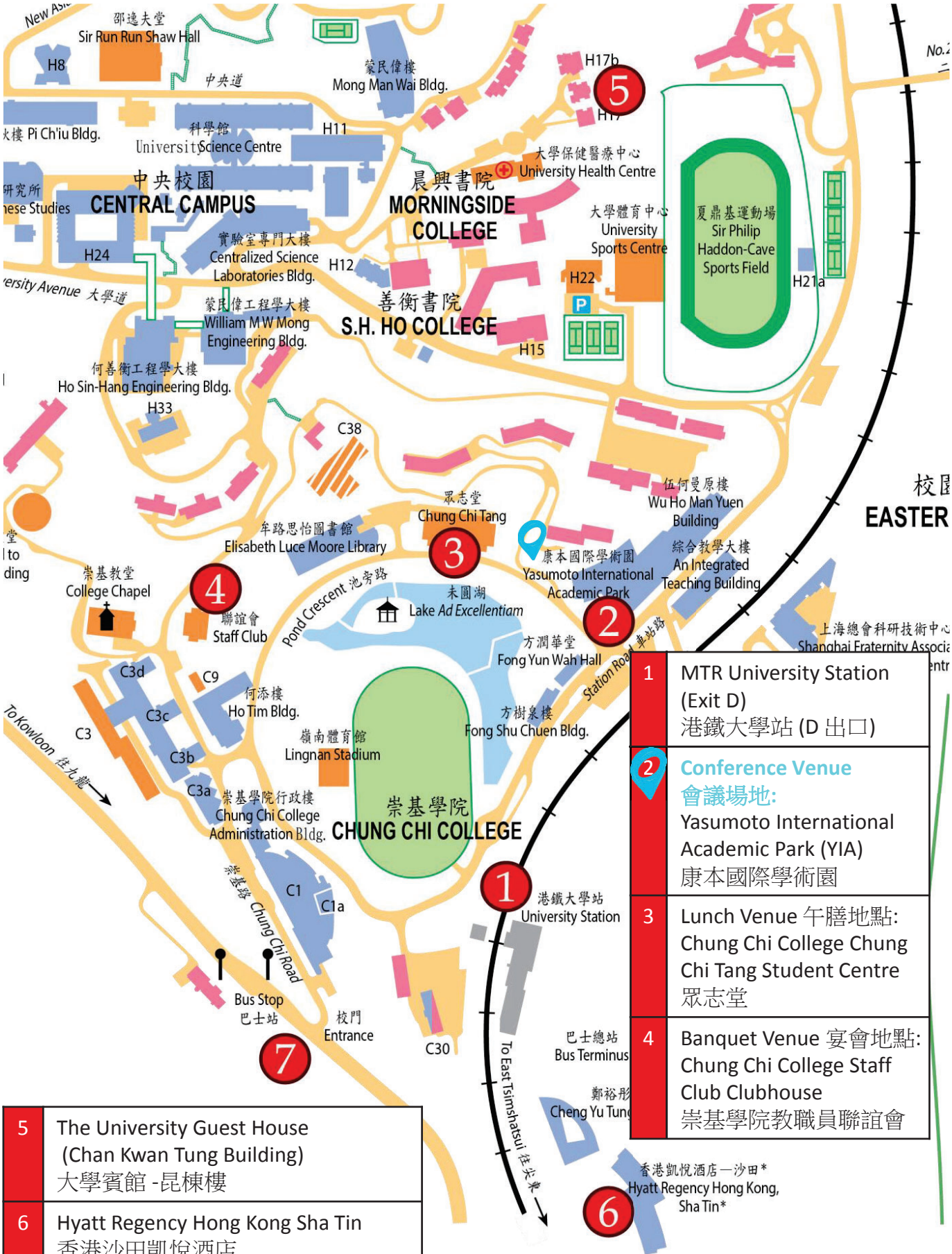
- 14:15 ~ 15:05 **Akimitsu Okamoto**
- 15:05 ~ 15:30 **Xuechen Li**
- 15:30 ~ 15:55 **Xiang David Li**
- 15:55 ~ 16:15 **Break**
- 16:15 ~ 16:40 **Richard Yi Tsun Kao**
- 16:40 ~ 17:05 **Edwin Ho Yin Chan**
- 17:05 ~ 17:30 **Billy Wai Lung Ng**
- 17:30 ~ 17:45 **Discussion & Closing**

生命科學學院
School of Life Sciences
The Chinese University of Hong Kong

The University of Hong Kong
Department of Chemistry
香港大學化學系

Areas of Excellence Scheme
AoE/P-705/16

Campus Map



1	MTR University Station (Exit D) 港鐵大學站 (D 出口)
2	**Conference Venue** **會議場地:** Yasumoto International Academic Park (YIA) 康本國際學術園
3	Lunch Venue 午膳地點: Chung Chi College Chung Chi Tang Student Centre 眾志堂
4	Banquet Venue 宴會地點: Chung Chi College Staff Club Clubhouse 崇基學院教職員聯誼會

5	The University Guest House (Chan Kwan Tung Building) 大學賓館 -昆棟樓
6	Hyatt Regency Hong Kong Sha Tin 香港沙田凱悅酒店
7	Tai Po Road Entrance 大埔道入口

Chemical Biology of Self-Assembly

Motonari Uesugi

Institute for Chemical Research and Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Japan

Self-assembly, the spontaneous organization of molecules into non-covalent structures, is a fundamental concept in material sciences. However, its significance extends far beyond this domain, as cells exploit self-assembly structures to sustain life, including membrane-separated or membrane-less organelles. Our research explores the potential of entirely synthetic self-assembling small organic molecules to mimic, control, or detect these cellular assemblies.

While soluble small molecules typically exhibit mono-functionality, self-assembled small molecules offer a platform for achieving complex properties and functions. This presentation showcases our discoveries in the realm of self-assembling bioactive molecules. I will also discuss the discovery and mechanistic insights of a novel self-assembling organic molecule capable of mitigating endoplasmic reticulum (ER) stress and proteotoxicity.

This unique molecule mitigates proteotoxicity by co-assembling with denatured proteins and subsequently facilitating their elimination through p62-dependent autophagy, offering a unique mechanism distinct from conventional drugs. The molecule is effective in ameliorating ER stress-related conditions in *C. elegans* and preventing lens-induced myopia in mice. This finding uncovers a promising avenue for self-assembling molecules as an unprecedented modality in managing diseases associated with protein denaturation and proteotoxicity.

New Functions of Next-Generation Synthetic Nucleic Acids

Akimitsu Okamoto

School of Engineering and Research Centre for Advanced Science and Technology (RCAST), The University of Tokyo, Japan

Oligonucleotides can be easily chemically synthesized. In addition, the method of chemically introducing arbitrary chain lengths and chemical modifications to oligonucleotides has already been established. Using this method, we have developed new anti-cancer oligonucleotides. Several oligonucleotides were synthesized that specifically change conformation in target cancers triggered by characteristic molecules and environments. These oligonucleotides acquire anticancer properties by undergoing a conformational change and kill cells that have taken up the oligonucleotides. In this seminar, we will introduce two types of anticancer oligonucleotides: (1) oligonucleotides that exhibit anticancer properties by degradation in a hypoxic environment and (2) oligonucleotides that manifest anticancer properties by forming aggregates in the presence of overexpressed cancer-related miRNAs. If time remains, I would also like to discuss our chemical protein synthesis.

Hypochlorous acid derived from microglial myeloperoxidase could mediate high-mobility group box 1 release from neurons to amplify brain damage in cerebral ischemia-reperfusion injury

Jiangang Shen

School of Chinese Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, Hong Kong SAR China

Myeloperoxidase (MPO) plays critical role in the pathology of cerebral ischemia-reperfusion (I/R) injury via producing hypochlorous acid (HOCl) and inducing oxidative modification of proteins. High-mobility group box 1 (HMGB1) oxidation, particularly disulfide HMGB1 formation, facilitates the secretion and release of HMGB1 and activates neuroinflammation, aggravating cerebral I/R injury. However, the cellular sources of MPO/HOCl in ischemic brain injury are unclear yet. Whether HOCl could promote HMGB1 secretion and release remains unknown. In the present study, we investigated the roles of microglia-derived MPO/HOCl in mediating HMGB1 translocation and secretion, and aggravating the brain damage and blood-brain barrier (BBB) disruption in cerebral I/R injury. In vitro, under the co-culture conditions with microglia BV cells but not the single culture conditions, oxygen-glucose deprivation/reoxygenation (OGD/R) significantly increased MPO/HOCl expression in PC12 cells. After the cells were exposed to OGD/R, MPO-containing exosomes derived from BV2 cells were released and transferred to PC12 cells, increasing MPO/HOCl in the PC12 cells. The HOCl promoted disulfide HMGB1 translocation and secretion and aggravated OGD/R-induced apoptosis. In vivo, SD rats were subjected to 2 h of middle cerebral artery occlusion (MCAO) plus different periods of reperfusion. Increased MPO/HOCl production was observed at the reperfusion stage, accomplished with enlarged infarct volume, aggravated BBB disruption and neurological dysfunctions. Treatment of MPO inhibitor 4-aminobenzoic acid hydrazide (4-ABAH) and HOCl scavenger taurine reversed those changes. HOCl was colocalized with cytoplasm transferred HMGB1, which was blocked by taurine in rat I/R-injured brain. We finally performed a clinical investigation and found that plasma HOCl concentration was positively correlated with infarct volume and neurological deficit scores in ischemic stroke patients. Taken together, we conclude that ischemia/hypoxia could activate microglia to release MPO-containing exosomes that transfer MPO to adjacent cells for HOCl production; Subsequently, the production of HOCl could mediate the translocation and secretion of disulfide HMGB1 that aggravates cerebral I/R injury. Furthermore, plasma HOCl level could be a novel biomarker for indexing brain damage in ischemic stroke patients.

Two New Modalities in the Selection of DNA-encoded Chemical Libraries (DELs)

Xiaoyu Li

Department of Chemistry, Faculty of Science, HKU, Hong Kong, China

We describe our recent efforts on developing new methods to enable DEL selections against cancer cells without predefined targets to discover cell-targeting ligands and cancer biomarkers. In addition, we also present a protein-templated DEL selection method for fragment-based drug discovery.

From membrane partition of fluorescent probes to single base-pair recognition of transcription factors

Yi Wang

Department of Physics, The Chinese University of Hong Kong

Molecular dynamics (MD) simulations have been known as the computational microscope that complements experimental approaches in various research of chemical biology. In this talk, I will showcase two aspects of MD studies from our group: 1) The plasma membranes constitute the first barrier against the cellular entrance of fluorescent probes designed to act as transmembrane or intracellular sensors. I will present our MD simulations and free energy calculations designed to understand how physico-chemical properties of these fluorescent probes may control their membrane partition and/or permeation. 2) The NF-κB family of transcription factors regulate the expression of hundreds of target genes by recognizing cognate sequences of approximately 10 base-pairs. In the second part of this talk I will present our work on two NF-κB transcription factors, namely, the RelA:RelA and p52:p52 homodimers. Combining MD simulations and machine learning algorithms, I will discuss how distinct dynamics of key amino acids underlies differential specificities of these transcription factors towards DNA sequences that differ by only a single base-pair.

Development of SUMO-derived inhibitors for treating synucleinopathies

Michael Kenneth Chan

Previous studies had demonstrated that SUMOylation of α-synuclein inhibits its aggregation and toxicity in vitro. In our attempts to produce site-specifically sumoylated α-synuclein, we discovered that a truncated SUMO1(15-55) peptide is able to suppress α-synuclein aggregation even in the absence of a direct covalent interaction as demonstrated in vitro and in cellular and Drosophilia models. Computational modeling and mutagenesis studies implicate the interaction of these SUMO-derived peptides with the SIM-motifs of α-synuclein. Subsequent studies have led to the development of advanced variants of SUMO1(15-55) with nanomolar binding to α-synuclein. The effectiveness of this peptide in alleviating the disease symptoms in a transgenic mouse model is demonstrated.

Structural Study of Enzymatic Reaction Intermediates

Quan Hao

The catalytic ability of an enzyme depends on the structure of the intermediate state of the enzyme reaction, which is a transient state during the conversion of substrate into product. I will use human CD38 and Sirtuins as examples to illustrate how to use crystallography and biochemistry methods to capture and determine the structure of reaction intermediate states. Human CD38 can catalyze NAD+ to produce two calcium regulatory molecules. We determined the high-resolution crystal structures of CD38 complexes with substrates, reaction intermediates and products. By analyzing the structures of these complexes, we can better understand the catalytic mechanism of CD38, consisting of three basic processes of nicotinamide removal, intermediate state stabilization, and product production. Sirtuins are NAD+ dependent deacylases. Sirtuins can regulate many important biological processes. We used structural and mass spectrometry studies to reveal multiple catalytic intermediates, and understanding the detailed reaction mechanism may help develop sirtuin inhibitors or activators.

Chemical Glycobiology Studies on Bacterial Pseudaminic Acid

Xuechen Li

Department of Chemistry, the University of Hong Kong, Hong Kong, P.R.China

Pseudaminic acid (Pse), first discovered in 1984, has been identified in a variety of pathogenic bacteria as important surface glycans. Belonging to the nonulosonic acid carbohydrate family, Pse is structurally related to its well-known congener, sialic acid. Pse exists with both α and β configuration in native glycoconjugates with variable substitution patterns at *N*5 and *N*7. Such structural diversity makes the structure-function relationship of Pse-containing glycans both intriguing but also challenging to study. The biological and evolutional significances of bacterial pseudaminic acid and its glycoconjugates remain largely unexplored, mainly due to the lack of synthetic access to pseudaminic acid and the structurally defined pseudaminylated glycoconjuates. Over the past years, we have been working on the chemical synthesis, biochemistry, biosynthesis, biology studies, and vaccine development on the bacterial pseudaminic acid. In this presentation, I will present our updated progress.

Keywords: pseudaminic acid, chemical glycobiology, chemical synthesis, vaccine development

Reference：

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6. X. Guo, Y. C. Cheung, C. Li, H. Liu, S. Chen. X. Li. (2024) Chem. Sci. (15) 5950

7. Y. C. Cheung, X. Guo, X. Yang, R. Wei, E. W. Chan, X. Li, S. (2024) Chem. Eur. J. e202400703

Chemical Approaches to Decode Histone Epigenetics

Xiang David Li

Histone posttranslational modifications (PTMs), such as phosphorylation, methylation and acetylation, play crucial roles in regulating many fundamental cellular processes, such as gene transcription, DNA replication, DNA damage repair, chromosome segregation, and cell differentiation. Increasing evidence has indicated that PTMs of histones can serve as a heritable 'code' (so-called 'histone code'), which provides epigenetic information that a mother cell can pass to its daughters. Histone code is 'written' or 'erased' by enzymes that generate or remove the modifications of histones. Meanwhile, 'readers' of histone code recognize specific histone modifications and 'translate' the code by executing distinct cellular programs necessary to establish the diverse cell phenotypes.

While a large number of PTMs have been identified on histones, the biological significance of vast majority of them remains poorly understood. This is particularly the case for those newly discovered histone modifications such as lysine crotonylation, succinylation, fatty-acid acylation, and the modifications present at histone cores such as methylation at H3 lysine 79. Studies of these new PTMs are hindered by the lack of knowledge about their regulating enzymes (i.e., 'writers' and 'erasers') and functional binding proteins (i.e., 'readers'). To fill this knowledge gap, here I present the development of novel chemical tools and approaches, in combination with the state-of-the-art biochemistry, proteomics and cell biology methods, to comprehensively identify 'writers', 'erasers' and 'readers' of histone PTMs and examine their regulatory mechanisms and cellular functions.

Targeting SaeR of Staphylococcus aureus: an effective non-antibiotic antivirulence approach for the treatment of staphylococcal infections

Richard Y.T. KAO

Staphylococcus aureus, a major human pathogen responsible for various clinical infections, possesses the SaeRS two-component system that regulates multiple virulence factors. While SaeR is crucial for S. aureus infection development, no inhibitors have been reported. In this study, we first employed an in vivo knockdown method to demonstrate the potential of targeting SaeR as an antivirulence strategy. Through high-throughput screening using a GFP-Lux dual reporter system driven by the saeP1 promoter, we identified HR3744 as a promising lead compound. The antivirulence efficacy of HR3744 was evaluated using Western blot, Quantitative Polymerase Chain Reaction, leucotoxicity, and haemolysis tests. In electrophoresis mobility shift assay, HR3744 effectively inhibited the binding of SaeR to DNA probes and WaterLOGSY-NMR test confirmed that HR3744 directly interacted with the DNA-binding domain of SaeR. In silico analysis coupled with mutagenesis studies further supported the specificity of the HR3744 to the target SaeR. A structure-activity relationship study revealed that slight modifications to the molecule abolished its inhibitory effects on SaeR, highlighting the selectivity of HR3744. Interestingly, we discovered that SAV13, an analogue of HR3744, exhibited four times greater potency and demonstrated identical antivirulence properties and target specificity. In mouse infection models, both HR3744 and SAV13 demonstrated in vivo effectiveness. In conclusion, this study identified the first SaeR inhibitor with in vitro and in vivo antivirulence properties, providing evidence for SaeR as a druggable target for the development of antivirulence therapeutics against S. aureus infections.

A peptide inhibitor that rescues nucleotide repeat expansion induced synaptic defects and cell death in C9ALS/FTD

Edwin Chan

Neurodegenerative diseases, including C9ORF72-amyotrophic lateral sclerosis/frontotemporal dementia (C9ALS/FTD), are progressive neurodegenerative disorders caused by repeat expansion in the transcribed regions of disease-associated genes. Synaptic defects and neurite outgrowth abnormalities were observed in C9ALS/FTD-patient neurons. We examined the suppression effects of the repeat RNA binding peptide beta-structured inhibitor for neurodegenerative diseases (BIND) in patient neurons and found that impaired synaptic defects were rescued. Our data provide evidence that the BIND peptide associates with transcribed mutant CAG RNA to inhibit the formation of toxic species.

Rethinking Small-Molecule Drug Discovery–A Medicinal Chemist's Perspective

Billy Wai-Lung Ng

School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

Throughout history, nature has provided the foundation for many medicines. These natural solutions were later refined using rational drug design. Yet, a significant realm of potential treatments remains untapped, largely due to the limited diversity in our drug-screening libraries.

The Ng lab at the Faculty of Medicine, The Chinese University of Hong Kong, focuses on creating novel small molecules to tackle various human diseases. By integrating insights from both modern chemistry and biology, we are developing platforms to design more effective small-molecule therapeutics. A cornerstone of our strategy involves transforming readily available natural products, such as sugars, into intricate drug-screening libraries with rich information content. During this presentation, Prof. Ng will detail the recent endeavors using these versatile libraries for drug discovery, underscoring their potential in treating viral infections, cancers, and neurodegenerative diseases.