PROSPECTS FOR GENE & EPIGENOME EDITING IN HEPATITIS B DISEASE

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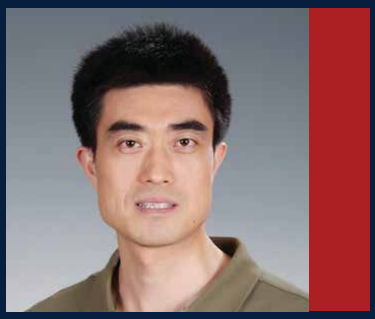
BIOGRAPHY

Prof. Yuen is now the Chair Professor of The University of Hong Kong and Li Shu Fan Medical Foundation Professor in Medicine, and the Chief of the Division of Gastroenterology and Hepatology, Queen Mary Hospital, Hong Kong. He obtained his first bachelor's degree of medicine in 1992. He further pursued his academic excellence through the achievement of obtaining three doctoral degrees including Doctor of Medicine with Sir Patrick Manson Gold Medal in 2001, Doctor of Philosophy in 2005 and Doctor of Science in 2017. Prof. Yuen's research interests include prevention, natural history, serology, virology and treatment of chronic hepatitis B and C, and hepatocellular carcinoma.

He is one of the top internationally renowned researchers in the field of hepatitis B disease. He has now published more than 630 papers in world-renowned medical journals including New England Journal of Medicine, Lancet, Nature Medicine, Lancet Infectious Diseases and Lancet Oncology. He has delivered more than 380 lectures all over the world. Prof. Yuen is now leading most of the international trials examining new drugs including antiviral and immunomodulatory agents for the treatment of chronic hepatitis B. He is also actively performing cutting-edge research on novel markers for hepatitis B infection and occult hepatitis B infection.

ABSTRACT

Chronic hepatitis B infection affects approximately 254 million people in the world. Up to 30% of infected people would develop end-staged liver disease including cirrhosis and liver cancer. Once the disease chronicity is established through transforming the relaxed circular virus DNA into covalently closed circular (ccc) DNA and integration of viral genome to human genome, complete virus elimination becomes practically impossible. These two forms of virus DNAs are residing in the hepatocyte nucleus and are responsible for viral replication and viral antigenemia which is associated with host immune exhaustion. The existing therapy for CHB is only acting against the reverse transcriptional activities of the virus pre-genomic RNA and mRNAs. Gene therapy targeting the cccDNA and integrated hepatitis B virus (HBV) DNA is a potential mean to eradicate the virus, and if not, to profoundly shut down viral activity. At present, there are several upcoming epigenetic modifiers which act by methylating the CpG islands of virus genomes to knock down the HBV translation. In mice models, a single dose of these epigenetic modifiers is associated with a prolonged suppression of cccDNA and integration DNA activities with profound suppression of the levels of HBV DNA and HBV antigen (hepatitis B surface antigen - HBsAg) leading to the status of functional cure. Gene editing using endonucleases to create a double strand breaks of virus DNA leading to cccDNA elimination and integrated DNA inactivation has also been tested. Both approaches are now actively undergoing in human phase 1 clinical trials. The structure/ sequence of the mRNAs and the nucleases are designed to target the conserved HBV sequence. Meticulous experiments to improve the specificity and hence minimize the off-target effects had been performed in different cell line models. These agents need lipid nanoparticles to deliver to the target site i.e. the hepatocytes. The goal of this gene/ epigenome editing is to achieve functional cure of the disease, which is defined as undetectable viral elements namely, HBV DNA and HBsAg in the blood and patients are free of long-term viral suppressive therapy.



FROM GENE EDITING TO NEW FRONTIERS: ADVANCING CELL & GENE THERAPIES

Professor Wensheng Wei, PhD

Professor, School of Life Sciences
Director, Genome Editing Research Center
Peking University

BIOGRAPHY

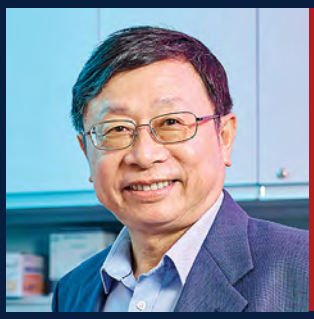
Prof. Wensheng Wei received his bachelor degree in Biochemistry from Peking University, PhD in Genetics from Michigan State University. After postdoctoral training and working as a research associate at Stanford University School of Medicine, Prof. Wei became a principle investigator in the School of Life Sciences at Peking University from 2007. He is currently a professor at the Biomedical Pioneering Innovation Center, Peking-Tsinghua Center for Life Sciences, and the School of Life Sciences at Peking University, Director of the Genome Editing Research Center at Peking University, and Lead Scientist at Changping Laboratory. The Wei group's research primarily focuses on advancing eukaryotic gene editing tools, with particular emphasis on high-throughput functional genomics, gene and cell therapy, and innovative RNA therapeutics utilizing circular RNAs.

Selected recent 3 publications:

- Wu Z, Shi J, Lamao Q, ..., Yuan P, Han W, **Wei W.** Glycan shielding enables TCR-sufficient allogeneic CAR-T therapy. **Cell** (2025)
- Zhang X, Zhang X, Ren J, Li J, Wei X, Yu Y, Yi Z, **Wei W.** Precise modelling of mitochondrial diseases using optimized mitoBEs. **Nature** (2025)
- Qu L, Yi Z, Shen Y, Lin L, ..., Wang J, Xie XS, **Wei W.** Circular RNA vaccines against SARS-CoV-2 and emerging variants. **Cell** (2022)

ABSTRACT

This presentation explores advancements in cellular and RNA-based therapies, with a focus on allogeneic CAR-T therapy, γδ T cell function enhancement, and RNA-based treatments. Achieving allogeneic CAR-T therapy has been difficult due to immuno-rejection and lack of persistence. Our research using genome-wide CRISPR screens identified specific genetic modifications in allogeneic T cells that reduce immune clearance by multiple effectors. The first-in-human anti-CD19 allogeneic CAR-T therapy in a clinical trial has shown a 100% response rate and effective tumor control. Additionally, we found that certain genetic alterations in human Vγ9Vδ2 T cells enhance cytotoxicity and persistence, driving their transition towards an NK cell-like phenotype, enabling effective leukemia cell killing. In RNA-based therapies, the LEAPER 2.0 system for efficient RNA editing has been validated in a non-human primate model, showing significant improvements in motor abilities with lasting effects on Duchenne muscular dystrophy. In mitochondrial gene editing, we introduce mitochondrial DNA base editors (mitoBEs), which combine transcription activator-like effector (TALE)-fused nickase and a deaminase for precise base editing in mitochondrial DNA. Engineered mitoBEs optimized to reduce off-target effects were used to develop mouse models of mitochondrial diseases, displaying phenotypes corresponding to human conditions like Leigh disease and LHON. The edited mitochondrial DNA persisted across tissues and was maternally inherited, highlighting the potential for lasting therapeutic impact. These innovations collectively hold substantial promise for precision medicine, therapeutic RNA editing, and organelle gene editing.



TARGETING THE ENDOTHELIUM IN CARDIO-METABOLIC DISEASES

Professor Yu Huang, PhD

Chair Professor of
Biomedical Sciences and Vascular Biology
Jeanie Hu Professorship in
Biomedical Sciences
Head, Department of Biomedical Sciences
City University of Hong Kong

BIOGRAPHY

Prof. Yu Huang received a PhD from University of Cambridge. He was Chair Professor in CUHK until October 2021. He is Jeanie Hu Professor of Biomedical Sciences and Head of Department at CityUHK. He is Vice President of Chinese Section of International Society for Heart Research (ISHR), foreign member of the Academy of Europe, Fellow of ISHR, International Union for Physiological Sciences, and British Pharmacological Society. He received Inaugural RGC – Senior Research Fellow Award, ISHR Peter Harris Distinguished Scientist Award. He is Associate Editor of Circulation Research. He co-authors 526 SCI-indexed publications with over 37,700 Google scholar citations and h-index of 101.

ABSTRACT

Healthy vascular endothelium is the critical player in maintaining vascular homeostasis through releasing several vaso-protective substances called endothelium-derived relaxing factors (EDRFs) such as nitric oxide. By contrast, loss of EDRFs in diseased endothelial cells unmasks the vaso-harmful impact of endothelium-derived contracting factors such as vaso-constrictive prostaglandins. This disrupted balance in endothelium is called endothelial dysfunction, an important initial event that triggers the pathogenesis of vascular diseases in hypertension, diabetes, and atherosclerosis. Any drug intervention that target endothelial dysfunction proves to be effective in inhibiting vascular inflammation and disturbed blood flow-associated development of atherosclerosis (supported by RGC-TRS and SRFS).

PRECISE GENE THERAPY FOR GENETIC DEAFNESS

Professor Guisheng Zhong, PhD

Associate Professor, School of Life Science and Technology, and iHuman Institute
ShanghaiTech University

BIOGRAPHY

Prof. Guisheng Zhong received his bachelor's degree from Anhui University, his master's degree from the University of Science and Technology of China, and his PhD from Cornell University. After completing postdoctoral training at Cornell University and Harvard University, Dr. Zhong became an Assistant Professor at the School of Life Science and Technology (SLST) and iHuman institute, ShanghaiTech University in 2015. He was promoted to Tenured Associate Professor at ShanghaiTech University in 2020. Prof. Zhong's research is centered on elucidating the biological mechanisms of hearing and developing innovative therapies for hereditary deafness. His lab employs a multifaceted strategy that combines the development of novel gene delivery tools with new molecular strategies to achieve precise control of gene expression within the cochlea. The ultimate goal of this work is to express functional deafness genes in a near-natural manner to restore natural hearing function.

ABSTRACT

Hereditary hearing loss affects millions worldwide, with gene therapy emerging as a promising treatment. This seminar explores advances in precise gene delivery and expression control, focusing on AAV-based strategies. We highlight the development of the ARBITER workflow to engineer cochlear cells specific cis-regulatory elements, successfully restoring hearing in Slc26a5 mutant mice. Additionally, I discuss recent preclinical/ clinical results in OTOF gene therapies and describe the challenge to treat GJB2 deafness patients, offering insights into overcoming challenges in treating genetic deafness.