SCHOOL OF BIOMEDICAL SCIENCES
VIRTUAL RESEARCH DAY 2021

16 - 17 JUNE

LO KWEE-SEONG
INTEGRATED BIOMEDICAL
SCIENCES BUILDING & ZOOM

cum

NORDIC SYMPOSIUM

CU Medicine HONG KONG
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

40 th Anniversary 四十週年

香港中文大學
The Chinese University of Hong Kong

香港中文大學 生物醫學學院
CUSBS

School of Biomedical Sciences
Virtual Research Day 2021
cum Nordic Symposium

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Professor LUI Wai Yan Vivian
Professor TIAN Xiaoyu

COVER: The three Thematic Research Programs of School of Biomedical Sciences, CUHK
Designed by Ms. SUEN Hoi Ching Ashley, School of Biomedical Sciences, Faculty of Medicine, CUHK

CONTENTS

https://www2.sbs.cuhk.edu.hk/

Welcome Message from the Dean of Faculty of Medicine

I welcome all of you to the School of Biomedical Sciences (SBS) Virtual Research Day 2021 *cum* Nordic Symposium.

Since the establishment of the School, the SBS Research Day has been an annual flagship event, a platform for researchers and collaborators from different disciplines in biomedical sciences to share latest research findings and insights. Amidst COVID-19, this is the second year that the School has to conduct a virtual symposium.

For this joint symposium, we are much honoured to have speakers from members of the Hong Kong-Nordic Research Network, which includes the University of Copenhagen (Denmark), The University of Oslo (Norway), and their close research partners from Mainland China, Sweden and the USA. Furthermore, it is a privilege to also have speakers from Korea and local universities.

These elite speakers facilitating animated discussion of innovations and exchange of new ideas will open doors to more interdisciplinary research and international collaboration in the years to come. The Faculty and clinicians at the Prince of Wales Hospital will continue to support members of the School to pursue excellence in biomedical science research.

I trust that all participants will benefit enormously from the interactions and connections made at this Symposium.

Wishing all of you good health and every success in your future endeavours!

Professor Francis K.L. Chan
Dean, Faculty of Medicine
Choh-Ming Li Professor of Medicine and Therapeutics
The Chinese University of Hong Kong

Welcome Message from the Director of School of Biomedical Sciences

It gives me great pleasure to welcome you to the School of Biomedical Sciences Virtual Research Day 2021 *cum* Nordic Symposium.

Being one of the annual signature events of the School, Research Day continues to be supported by our colleagues, associate members and investigators from local and international tertiary institutions. Due to the COVID-19 pandemic and the social distancing measures, we again decided to organise this event in an online conferencing format so we can stay connected with our collaborators locally and internationally.

This is the twelfth annual Research Day of our School since its founding in 2010. For this year, our School members will present their exciting findings in diverse research topics including cardiovascular disease, neuropsychiatric disorder, stem cell and reproductive biology, obesity and cancer. What makes this year special is the jointly held Nordic Symposium and we are delighted to have distinguished speakers from our strategic collaborative partners from the Hong Kong-Nordic Research Network and Nordic Centre, Fudan University. We are looking forward to hearing their exciting findings in neurodegenerative diseases and anti-aging research. In addition, we are very honoured to have four outstanding keynote speakers joining our Research Day. They are Prof. Jason Kim Seong-Jin from GILO Institute, Prof. Vilhelm Bohr from NIA/UCPH, Prof. Liu Kai from HKUST, and Prof. Megan Ho from BME/CUHK. They will enlighten us with their latest research and would definitely encourage stimulating discussion and cross-pollination of ideas.

I hope all of you will benefit from the diverse scientific sharing and be inspired to extend further collaborations with your colleagues and potential collaborators, which is important to enhance competitiveness in this ever-changing research environment.

Finally, I would like to express my gratitude to members of the Organizing Committee for their arrangement of every detail of the programme with many inspiring topics presented by notable researchers, as well as to the sponsoring companies for their supports in this event.

Andrew M. Chan
Professor and Director
School of Biomedical Sciences
Faculty of Medicine
The Chinese University of Hong Kong

SBS Virtual Research Day 2021 cum Nordic Symposium
16 June 2021 (Wednesday)

14:00-14:15 (HK) 08:00-08:15 (Oslo)	**Opening Ceremony:** Prof. CHAN Ka Leung Francis (Dean of Faculty of Medicine), Prof. CHAN Man Lok Andrew (Director of School of Biomedical Sciences) & Prof. Jon STORM-MATHISEN (Emeritus Professor of Medicine (Anatomy), University of Oslo) Presentation of the prize for SBS Virtual Research Day 2021 *cum* Nordic Symposium Programme Book Cover / Banner Design Competition / Photo Taking

Time	*Title of Presentation*	*Speaker*	*Abstract No.*
Session I *Chairpersons: Prof. CHENG Sze Lok Alfred (SBS) & Prof. SHAM Mai Har (SBS)*			
14:15-15:00 (HK) 08:15-09:00 (Oslo)	Vactosertib, a novel TGF-β type I receptor kinase inhibitor, promotes anti-tumor efficacy in combination with various cancer therapies	Prof. KIM Seong-Jin Jason (GILO)	O1 (Keynote)
15:00-15:25 (HK) 09:00-09:25 (Oslo)	Shear stress and vascular regulation	Prof. HUANG Yu (NVMB)	O2
15:25-15:50 (HK) 09:25-09:50 (Oslo)	β-catenin controls the endodermal commitment of human embryonic stem cells	Prof. FENG Bo (DRB)	O3
15:50-16:00 (HK) **09:50-10:00 (Oslo)**	***10-min Break***		
Nordic Symposium, Session I ***Chairpersons: Prof. Linda BERGERSEN (UiO) & Prof. CHEUNG Chi Kwan Vincent (SBS)***			
16:00-16:30 (HK) 10:00-10:30 (Oslo)	Using machine learning to identify potent mitophagy inducers that ameliorate Alzheimer's disease pathology	Prof. Evandro F. FANG (UiO)	O4
16:30-17:00 (HK) 10:30-11:00 (Oslo)	The role of autophagy in amyloid beta metabolism and neurodegeneration of Alzheimer's disease	Prof. Per NILSSON (KI)	O5
17:00-17:30 (HK) 11:00-11:30 (Oslo)	Olfactory dysfunction and risk of cognitive decline among Community-Dwelling Elderly: the Shanghai Aging Study	Prof. DING Ding (FDU)	O6
17:30-18:00 (HK) 11:30-12:00 (Oslo)	Lactate treatment in Alzheimer's disease	Prof. Linda BERGERSEN (UiO)	O7

End of Day 1

Abbreviations:
ACP = Department of Anatomical and Cellular Pathology, CUHK
BME = Department of Biomedical Engineering, CUHK
CUHK = The Chinese University of Hong Kong, Hong Kong
FDU = Fudan University, China
GILO = GILO Institute, Republic of Korea
HKUST = The Hong Kong University of Science and Technology, Hong Kong
KI = Karolinska Institutet, Sweden
MEDT = Department of Medicine & Therapeutics, CUHK
NIA = National Institute on Ageing, NIH, USA
NTNU = Norwegian University of Science and Technology, Norway
SBS = School of Biomedical Sciences, CUHK
SUR = Department of Surgery, CUHK
UCPH = University of Copenhagen, Denmark
UiO = University of Oslo, Norway

SBS Thematic Research Programs:
CBET = Cancer Biology and Experimental Therapeutics
DRB = Developmental and Regenerative Biology
NVMB = Neural, Vascular, and Metabolic Biology

SBS Virtual Research Day 2021 cum Nordic Symposium
17 June 2021 (Thursday)

Time	*Title of Presentation*	*Speaker*	*Abstract No.*
Session IIA ***Chairpersons: Prof. MOK Chung Tong Vincent (MEDT) & Prof. IP Pak Kan Jacque (SBS)***			
09:00-09:45 (HK) 03:00-03:45 (Oslo) (21:00-21:45, 16 June Baltimore, USA)	DNA damage and mitochondrial dysfunction in neurodegeneration and aging. Intervention with NAD supplementation	Prof. Vilhelm BOHR (NIA & UCPH)	O8 (Keynote)
09:45-10:30 (HK) 03:45-04:30 (Oslo)	Neuronal mechanisms regulating axon regeneration in central nervous system	Prof. LIU Kai (HKUST)	O9 (Keynote)
10:30-10:55 (HK) 04:30-04:55 (Oslo)	A limbic circuit underlying emotional stress-induced repetitive behavior	Prof. YUNG Wing-ho (NVMB)	O10
10:55-11:10 (HK) **04:55-05:10 (Oslo)**	***15-min Break***		
Session IIB ***Chairpersons: Prof. CHIU Wai Yan Philip (SUR) & Prof. LO Kwok Wai (ACP)***			
11:10-11:35 (HK) 05:10-05:35 (Oslo)	Interplay between orphan nuclear receptors and androgen receptor-dependent or -independent growth signalings in prostate cancer	Prof. CHAN Leung Franky (CBET)	O11
11:35-12:00 (HK) 05:35-06:00 (Oslo)	The journey of male gametes – biology of the microenvironment parcels	Prof. FOK Kin Lam Ellis (DRB)	O12
12:00-12:25 (HK) 06:00-06:25 (Oslo)	The role of nucleolar RNA helicase in ribosomal DNA instability	Prof. CHEUNG Hoi Hung Albert (DRB)	O13
12:25-12:50 (HK) 06:25-06:50 (Oslo)	Novel druggable events unfolding in head and neck cancers	Prof. LUI Wai Yan Vivian (CBET)	O14
12:50-14:00 (HK) 06:50-08:00 (Oslo)	***Lunch Break***		
Session III ***Chairpersons: Prof. HUANG Yu (SBS) & Prof. TSANG Chi Man Anna (ACP)***			
14:00-14:45 (HK) 08:00-08:45 (Oslo)	Modulation of membrane deformation by shear through microfluidics for biomedical applications	Prof. HO Yi Ping Megan (BME)	O15 (Keynote)
14:45-15:10 (HK) 08:45-09:10 (Oslo)	Lysosomal cathepsin D in regulation of skeletal growth and homeostasis	Prof. WAN Chao (DRB)	O16
15:10-15:35 (HK) 09:10-09:35 (Oslo)	Adipocyte-derived lactate is a metabolic signal to potentiate obesity-evoked adipose macrophage inflammation	Prof. HUI Xiaoyan Hannah (NVMB)	O17
15:35-16:00 (HK) 09:35-10:00 (Oslo)	***25-min Break***		
Nordic Symposium, Session II ***Chairpersons: Prof. Hilde NILSEN (UiO) & Prof. LEE Tin Lap (SBS)***			
16:00-16:30 (HK) 10:00-10:30 (Oslo)	A germline homozygous mutation in human *Oxidation Resistance 1* gene causes developmental delay, epilepsy and cerebellar atrophy	Prof. Magnar BJØRÅS (NTNU)	O18
16:30-17:00 (HK) 10:30-11:00 (Oslo)	Metabolic control of DNA repair in age-related diseases	Prof. Lene RASMUSSEN (UCPH)	O19
17:00-17:30 (HK) 11:00-11:30 (Oslo)	Base excision repair contributinges to Parkinson's disease pathology	Prof. Hilde NILSEN (UiO)	O20
17:30-17:55 (HK) 11:30-11:55 (Oslo)	Bridging graph embedding and biological networks in the study of gene regulation	Prof. CAO Qin Cara (CBET)	O21
17:55-18:10 (HK) **11:55-12:10 (Oslo)**	Closing Remarks Prof. Stephen K.W. TSUI (SBS) and Prof. Evandro F. FANG (UiO)		

Session I

Speaker Biography

Prof. KIM Seong-Jin Jason, Ph.D.（金聖鎮）is the Director of GILO Institute. He also serves as an Adjunct Professor of the Ireland Cancer Center at Case Western Reserve University, USA, and as a Visiting Professor at Tsukuba University, Japan. Prof. Kim was the Director of Precision Medicine Research Center at the Advanced Institutes of Convergence Technology of Seoul National University and the Director of the CHA Cancer Institute as well as a Distinguished Professor of Medicine at CHA University of Medicine and Sciences in South Korea. He obtained his Ph.D. in applied biochemistry at the University of Tsukuba, Japan, and joined the Chemoprevention Laboratory at the National Cancer Institute (NCI) in Bethesda, Maryland, USA in 1987. At NCI, Prof. Kim served as a tenured senior investigator, working primarily with TGF-β and cancer.

His group was the first to discover that the resistance to TGF-β, a tumor suppressor protein, in most of human cancers can develop through the acquisition of a mutation in a TGF-β receptor gene or loss of TGF-β receptor expression. Prof. Seong-Jin Kim is one of the Personal Genome Pioneers in the world. He became the fifth individual in history, and the first Korean, to have his DNA blueprint decoded. He led the first Korean Genome Sequencing project while he was the Director at the Lee Gil Ya Cancer and Diabetes Institute, South Korea in 2008. Prof. Kim has received many outstanding awards such as HoAm Prize in Medicine in 2002 and International Award from Japanese Cancer Association in 2017, and is regarded one of the most influential researchers in cancer research in Korea.

Five recent representative publications

1. Lee S-J, Park J, et al., **Kim SJ**, Jung HS. “MAST4 knockout shows the regulation of spermatogonial stem cell self-renewal via the FGF2/ERM pathway.” ***Cell Death Differ***, 2020. doi: 10.1038/s41418-020-00670-2.
2. Naka K, Ochiai R, et al., **Kim SJ**. “The lysophospholipase D enzyme Gdpd3 is required to maintain chronic myelogenous leukaemia stem cells.” ***Nature Communications***, 2020; 11(1): 4681.
3. Nakayama M, Hong CP, Oshima H, Sakai E, **Kim SJ**, Oshima M. “Loss of wild-type p53 promotes mutant p53-driven metastasis through acquisition of survival and tumor-initiating properties.” ***Nature Communications***, 2020; 11(1): 2333.
4. Park Y, Pang K, et al., Yang KM, **Kim SJ**. “Destablilization of TRAF6 by DRAK1 suppresses tumor growth and metastasis in cervical cancer cells.” ***Cancer Res***, 2020; 80(12):2537-2549.
5. Pang K, Park J, Ahn SG, et al., Yang KM, **Kim SJ**. “RNF208, an estrogen-inducible E3 ligase, targets soluble Vimentin to suppress metastasis in triple-negative breast cancers.” ***Nature Commun***, 2019; 10(1): 5805.

Expertise

✧ Transforming growth factor-βs and their receptors in normal physiology and pathology, including especially inflammation, chemoprevention, and carcinogenesis

Vactosertib, a novel TGF-β type I receptor kinase inhibitor, promotes anti-tumor efficacy in combination with various cancer therapies

KIM Seong-Jin

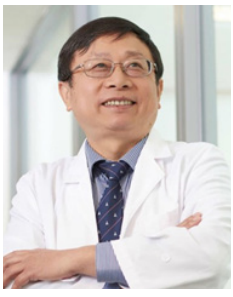
GILO Institute, 92 Myeongdal-ro, Seocho-gu, Seoul 06668, Republic of Korea.

The TGF-β superfamily of ligands plays an active role in many cellular processes. Since the discovery of the prototypic member, TGF-β, almost 20 years ago, there have been tremendous advances in our understanding of the complex biology of this superfamily. Dysregulation of TGF-β pathway contributes to a broad variety of pathologies, including cancer. In epithelial cells, TGF-β functions as a tumor suppressor, where it inhibits proliferation, induces apoptosis, and mediates differentiation. Conversely, in other contexts, TGF-β promotes tumor progression through increasing tumor cell invasion and metastasis. Many studies have identified the overexpression of TGF-β1 in various types of human cancer, which correlates with tumor progression, metastasis, angiogenesis and poor prognostic outcome. Increased production of TGF-β also suppresses immune mechanisms mediating anti-tumor responses. For these reasons, different strategies to block TGF-β pathway in cancer have been developed.

In this talk I will present the rationale for evaluating TGF-β signaling inhibitors as cancer therapeutics, a small-molecule inhibitor that is in development and will dissect how targeting the TGF-β pathway may contribute to fight against cancer.

Session I

Speaker Biography



HUANG Yu（黃聿） received his BSc degree from Fudan University Shanghai Medical College and a PhD degree from University of Cambridge. He is the Professor of Biomedical Sciences and the founding Director of Heart and Vascular Institute, CUHK. He is the elected Fellow of International Society for Heart Research. He was the past President of Asian Society for Vascular Biology and currently the Vice-President for both Chinese Society for Vascular Medicine and Chinese Section of International Society for Heart Research. He is currently the Hong Kong Research Grants Council Senior Research Fellow.

Huang Yu serves as the Grant Review Panel Member for Hong Kong Research Grants Council, Hong Kong Government's Health and Medical Research Fund, Natural Science Foundation of China and The University of Macau Multi-Year Research Grant. He has so far served (past and present) as the editor, guest editor, associate editor and editorial board member for 18 SCI-indexed journals including *British Journal of Pharmacology* (editor) and *Circulation Research* (associate editor). He has co-authored 442 peer-reviewed publications in SCI-indexed journals including *Nature*, *Science*, *Cell Metabolism*, *Circulation Research*, *European Heart Journal*, *PNAS*, *Diabetes*, *Hypertension*, *ATVB*, *Stroke*, *ARS*, *British Journal of Pharmacology*, with 26737 Google scholar citations (*h*-index of 84).

Huang Yu received The Croucher Award - Croucher Senior Research Fellowship in 2014; Higher Education Outstanding Scientific Research Output Award (first-class award, 2019年度高等學校科學研究優秀成果獎-自然科學一等獎; second-class awards, 2017及2012年度高等學校科學研究優秀成果獎-自然科學二等獎, Ministry of Education, China); The State Natural Science Award (second-class award, 2015年度國家自然科學獎二等獎), China; 2020 Wuxi PharmaTech Life Science and Chemistry Award – The Scholar Award (2020年度藥明康德生命化學研究獎學者獎) and several other awards. He was the recipient of The Asian Lecture on Vascular Biology, Shanghai (2018), The Robert F. Furchgott Lecture, Zurich (2013), and The Office of Life Sciences Distinguished Lecture, National University of Singapore, Singapore (2007).

Eleven of his former trainees in CUHK now hold academic position of assistant professorship or above in a number of universities in mainland China, Singapore, Macau and Hong Kong.

Five recent representative publications

1. Qu D, Wang L, Huo M, Song W, Lau CW, Xu J, Xu A, Yao X, Chiu JJ, Tian XY & **Huang Y**. "Focal TLR4 activation mediates disturbed flow-induced endothelial inflammation." ***Cardiovascular Research***, 2020; 116(1):226-236.
2. Song W, Zhang CL, Gou L, He L, Gong YY, Qu D, Zhao L, Jin N, Chan TF, Wang L, Tian XY, Luo JY & **Huang Y**. "Endothelial TFEB (transcription factor EB) restrains IKK (IκB Kinase)-p65 pathway to attenuate vascular inflammation in diabetic db/db mice." ***Arteriosclerosis, Thrombosis and Vascular Biology***, 2019; 39(4):719-730.
3. Zhang H, Liu J, Qu D, Wang L, Wong CM, Lau CW, Huang Y, Wang YF, Huang H, Xia Y, Xiang L, Cai Z, Liu P, Wei Y, Yao X, Ma RCW & **Huang Y**. "Serum exosomes mediate delivery of arginase 1 as a novel mechanism for endothelial dysfunction in diabetes." ***Proceedings of The National Academy of Sciences of The United States of America***, 2018; 115(29):E6927-E6936.
4. Cheang WS, Wong WT, Zhao L, Xu J, Wang L, Lau CW, Chen ZY, Ma RCW, Xu A, Wang N, Tian XY & **Huang Y**. "PPARδ is required for exercise to attenuate endoplasmic reticulum stress and endothelial dysfunction in diabetic mice." ***Diabetes***, 2017; 66(2):519-528.
5. Wang L, Luo JY, Li B, Tian XY, Chen LJ, Huang Y, Liu J, Deng D, Lau CW, Wan S, Ai D, Mak KL, Tong KK, Kwan KM, Wang N, Chiu JJ, Zhu Y & **Huang Y**. "Integrin-YAP/TAZ-JNK cascade mediates atheroprotective effect of unidirectional shear flow." ***Nature***, 2016; 540:579-581. Commented in Nature News and Views, Nature, 540: 531-532.

Expertise

- ✧ Vascular biology
- ✧ Cardio-metabolic disease

Shear stress and vascular regulation

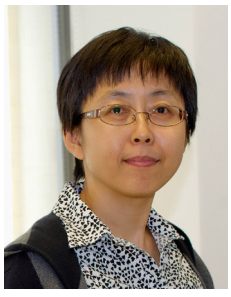
HUANG Yu

School of Biomedical Sciences, Faculty of Medicine; Heart and Vascular Institute, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

The patterns of blood flow and associated hemodynamic shear forces impact on the function of endothelial cells, a monolayer of cells lining the lumen of blood vessels. Laminal flow with high shear stress in relatively straight part of the artery is considered anti-inflammatory and vaso-protective while disturbed flow with low and oscillatory shear stress in vascular bifurcations is believed to be pro-inflammatory and athero-prone. Therefore, flow patterns are one of the most important local regulators in maintaining distinct features of both vascular function and structure through regulating the expression of a spectrum of genes related to vascular health and disease. Deeper understanding of the mechanosensitive signaling transduction in vascular endothelial cells shall help reveal newer molecular targets for possible future therapeutic intervention.

Session I

Speaker Biography



Prof. FENG Bo（馮波） is an Associate Professor in the School Biomedical Sciences (SBS), Faculty of Medicine, The Chinese University of Hong Kong (CUHK). Prof. Feng is an active member in the Developmental and Regenerative Biology program of SBS, and she is also an associate member of the Hong Kong Hub of Paediatric Excellence (HK-HOPE) and the thematic program for Stem Cell and Cell-based Therapies in the Institute for Tissue Engineering and Regenerative Medicine (iTERM). Prof. Feng graduated from Nankai University with B.Sc. (1993) and M.Sc (1996), and received her Ph.D. (2006) from National University of Singapore. She joined Genome Institute of Singapore in 2007 as postdoc and her research on stem cells and reprogramming have been published in *Cell Stem Cell*, *Nature Cell Biology* etc. Prof. Feng joined CUHK to set up her own lab since 2010. Her research has focused on understanding the molecular mechanisms that control the reprogramming, self-renewal, differentiation of stem cells, as well as applying CRISPR-based genome-editing technologies to develop novel cell and gene-based therapy strategies for treating human diseases including cancer.

Five recent representative publications

1. He X, Urip BA, Zhang Z, Ngan CC, **Feng B**. "Evolving AAV-delivered therapeutics towards ultimate cures." ***J Mol Med***, 2021; 99(5):593-617.
2. Wang J*, Zhang C*, **Feng B**. "The rapidly advancing Class 2 CRISPR-Cas technologies: a customizable toolbox for molecular manipulations." ***J Cell Mol Med***, 2020; 24(6):3256-3270.
3. Zhang C*, He X*, Kwok YK, Wang F, Xue J, Zhao H, Suen KW, Wang CC, Ren J, Chen GG, Lai BS, Li J, Xia Y, Chan AM, Chan WY, **Feng B**. "Homology-independent multiallelic disruption via CRISPR/Cas9-based knock-in yields distinct functional outcomes in human cells." ***BMC Biology***, 2018; 16(1):151.
4. He X, Tan C, Wang F, Wang Y, Zhou R, Cui D, You W, Zhao H, Ren J, **Feng B**. "Knock-in of large reporter genes in human cells via CRISPR/Cas9-induced homology-dependent and independent DNA repair." ***Nucleic Acids Res***, 2016; 44(9):e85.
5. Hu J, Lei Y, Wong WK, Liu S, Lee KC, He X, You W, Zhou R, Guo JT, Chen X, Peng X, Sun H, Huang H, Zhao H, **Feng B**. "Direct activation of human and mouse Oct4 genes using engineered TALE and Cas9 transcription factors." ***Nucleic Acids Res***, 2014; 42(7):4375-4390.

Expertise

- ✧ Generation and analysis of ESC/iPSC from mouse and human
- ✧ CRISPR-based genome editing
- ✧ Lentivirus and adeno-associated virus vectors

β-catenin controls the endodermal commitment of human embryonic stem cells

MA Xun, DAI Liujiang, LI Jiangchuan, TAN Chunlai, CHU Ho Ting, WANG Yaofeng, HE Xiangjun, FENG Bo*

School of Biomedical Sciences, Faculty of Medicine; Institute for Tissue Engineering and Regenerative Medicine (iTERM); Hong Kong Hub of Paediatric Excellence (HK-HOPE), The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

WNT/β-catenin signaling pathway is evolutionary conserved and plays an essential role during early embryonic development in the process of forming definitive endoderm (DE), a prevenient lineage that subsequently gives rise to all the endodermal tissue and organs. However, the relevant regulatory mechanism has not been fully understood due to the complex functionality of β-catenin. Embryonic stem cell (ESC) derived from early blastocysts of mouse and human retain the pluripotency property in culture and can undergo *in vitro* DE differentiation in the presence of Activin and Wnt, which much resembles the *in vivo* differentiation process and provides invaluable models to delineate underlying mechanisms. In this study, we used DE differentiation from human ESCs as *in vitro* model and applied CRISPR/Cas9-technology to knock-out β-catenin. The β-catenin null hESCs fail to commit for DE differentiation and can be rescued by full-length β-catenin. By transducing the differently truncated β-catenin variants, each carries distinct deletion(s) or mutations in a functional domain, we observed varied rescue in the subsequent DE induction analysis. Consistently, RNA-seq analysis revealed distinct transcription modules among the β-catenin target genes, indicating that β-catenin control the DE commitment through orchestrating multiple cellular functions during the cell fate transitions.

Session I (Nordic Symposium)

Speaker Biography

Prof. Evandro Fei FANG（方飛） is an Associate Professor of Molecular Gerontology at the University of Oslo and his group is working on the molecular mechanisms of human ageing and age-predisposed neurodegeneration (https://evandrofanglab.com/). More specifically, the Fang laboratory is focusing on the molecular mechanisms of how cells clear their damaged and aged mitochondria, a process termed "mitophagy", as well as the roles of the NAD^+-mitophagy/autophagy axis in healthy ageing and AD inhibition. NAD^+ is a fundamental molecule in life and health and decreases in ageing and AD. He is fascinated with and actively engaged in moving his laboratory findings to translational applications, as involved in 5+ NAD^+-based clinical trials, with the overarching goal to establish novel and safe biological approaches to promote longer and healthier human lives.

He is the founding co-coordinator of the Norwegian Centre on Healthy Ageing network (NO-Age, www.noage100.com), the Norwegian National anti-Alzheimer's disease Network (NO-AD, www.noad100.com), and the Hong Kong-Nordic Research Network.

He has published over 80 papers in international peer-reviewed journals including papers in *Cell*, *Cell Metabolism*, *Nature Reviews MCB*, and *Nature Neuroscience*. He has received several awards, including The Young Scientist Award in the Natural Sciences for 2020 by The Royal Norwegian Society of Sciences and Letters.

Five recent representative publications

1. Zhang Y, Zhang Y, Aman Y, Ng CT, Chow WH, Zhang Z, Yue M, Bohm C, Jia Y, Li S, Yuan Q, Griffin J, Chiu K, Wong DSM, Wang B, Jin D, Rogaeva E, Fraser PE, **Fang EF**, George-Hyslop PS, Song YQ*. "Amyloid β toxicity modulates Tau phosphorylation through the Pax6 signalling pathway." ***Brain***, in press.
2. **Fang EF**[#,]*, Hou Y[#], Palikaras K[#], Adriaanse BA, Kerr JS, … Lautrup S, Hasan-Olive M, Caponio D, Dan X, Croteau DL, Akbari M, Greig NH, Fladby T, Nilsen H, Cader MZ, Mattson MP, Tavernarakis N, Bohr VA*. "Mitophagy inhibits Aβ and p-Tau pathologies and cognitive deficits in experimental models of Alzheimer's disease." ***Nature Neuroscience***, 2019; 22(3):401-412.
3. Lautrup S, Sinclair DA, Mattson MP, **Fang EF***. "NAD^+ in brain ageing and neurodegenerative disorders." ***Cell Metabolism***, 2019; 30(4):630-655.
4. **Fang EF**[#], Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, Iser WB, Wollman BN, Morevati M, Li J, Kerr JS, Lu Q, Waltz TB, Tian J, Sinclair DA, Mattson MP, Nilsen H, Bohr VA*. "NAD^+ replenishment improves lifespan and healthspan in Ataxia telangiectasia models via mitophagy and DNA repair." ***Cell Metabolism***, 2016; 24(4):566-581.
5. **Fang EF**[#], Scheibye-Knudsen M[#], Brace L, Kassahun H, Sengupta T, Nilsen H, Mitchell JR, Croteau DL, Bohr VA*. "Defective Mitophagy in XPA via PARP1 hyperactivation and NAD^+/SIRT1 reduction." ***Cell***, 2014; 157(4):882-896.

Using machine learning to identify potent mitophagy inducers that ameliorate Alzheimer's disease pathology

FANG Evandro Fei

Department of Clinical Molecular Biology, University of Oslo and Akershus University Hospital, Norway
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Mitochondrial dysfunction drives energy deprivation, metabolic derailment, and the activation of cell death signalling pathways. It is a common denominator of ageing and age-related neurodegenerative pathologies, such as Alzheimer's disease (AD). Elimination of damaged mitochondria via mitophagy abrogates metabolic dysfunction and neurodegeneration in AD models and subsequently restores cognitive decline. Thus, the identification of potent mitophagy modulators is critical for the development of novel therapeutic intervention strategies. Here, we describe a high-throughput machine-learning approach, which combines a cross-species screening platform, to reveal and characterize novel mitophagy-inducing compounds. By the application of several unsupervised machine learning methods, such as Mol2vec, we identified small molecules from a library of naturally occurring compounds. Experimental validation confirmed that, of these, two potent mitophagy inducers improve memory in Aβ- and Tau-based AD nematode models in a PINK1/Parkin-dependent manner, and in 3xTg AD mice. At the cellular level, induction of mitophagy improves the survival and functionality of glutamatergic and cholinergic neurons in AD models. At the molecular level, upregulation of mitophagy abrogates Aβ pathology by inhibiting Aβ production and promoting microglial phagocytosis of Aβ plaques; mitophagy diminishes Tau pathology through inhibiting multiple p-Tau sites (including p-Tau181 and p-Tau217) and the spreading of pathological Tau. Our findings demonstrate a conserved mechanism of memory loss in both Aβ- and Tau- AD models that is mediated by defective mitophagy, while our highly accurate *in silico* screening platform paves the way for identifying potent mitophagy modulators to promote neuronal health and brain homeostasis during ageing.

Session I (Nordic Symposium)

Speaker Biography

Prof. Per NILSSON is working on finding the molecular underpinnings of Alzheimer's disease. His background is a PhD in molecular biotechnology from Uppsala University, Sweden. He did his postdoc at RIKEN Brain Science Institute, Japan. Since 2016 he is heading a research group at Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Sweden, where he is also vice/acting head of division of neurogeriatrics. Their research is focused on preclinical studies using animal models of Alzheimer's in combination with clinical studies. The research is very much focused on protein homeostasis and the role of autophagy in amyloid β and tau metabolism, the two hallmarks of Alzheimer's disease.

Five recent representative publications

1. Schedin-Weiss S[#], **Nilsson P**[#], Sandebring-Matton A, Axenhus M, Sekiguchi M, Saito T, Winblad B, Saido T, Tjernberg LO. "Proteomics time-course study of App knock-in mice reveals novel presymptomatic $A\beta_{42}$-induced pathways to Alzheimer pathology." ***Journal of Alzheimer's Disease***, 2020; 75(1):321-335.
2. Leal NS, Dentoni G, Schreiner B, Naia L, Piras A, Graff C, Cattaneo A, Meli G, Hamasaki M, **Nilsson P**, Ankarcrona M. "Amyloid beta-peptide increases mitochondria-endoplasmic reticulum contact altering mitochondrial function and autophagosome formation in Alzheimer's disease-related models." ***Cells***, 2020; 9(12):E2552. doi: 10.3390/cells9122552.
3. Loera-Valencia R, Piras A, Ismail MA, Manchanda A, Eyjolfsdottir H, Saido T, Johansson J, Eriksdotter M, Winblad B, **Nilsson P**. "Targeting Alzheimer's disease with gene and cell therapies." ***JIM***, 2018; 284(1):2-36. doi: 10.1111/joim.12759.
4. Saito T, Matsuba Y, Mihira N, Takano J, **Nilsson P**, Itohara S, Iwata N, Saido TC. "Single APP knock-in mouse models of Alzheimer's disease." ***Nat Neurosci***, 2014; 17:661-663.
5. **Nilsson P**, Loganathan K, Sekiguchi M, Matsuba Y, Hui K, Tsubuki S, Tanaka M, Iwata N, Saito T, Saido TC. "Aβ secretion and plaque formation depend on autophagy." ***Cell Reports***, 2013; 5:1-9.

[#] Co-first authors

Expertise

- ✧ Development of Alzheimer mouse models, including models for Aβ, tau and autophagy-deficiency.
- ✧ Animal behaviour focusing on memory and cognition.
- ✧ Preclinical research to find molecular mechanism underlying Alzheimer's with a focus on autophagy by using omics methods including proteomics and single cell RNA sequencing.

The role of autophagy in amyloid beta metabolism and neurodegeneration of Alzheimer's disease

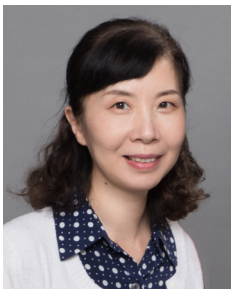
JIANG Richeng[1], TAMBARO Simone[1], SHIMOZAWA Makoto[1], MAYER Johanna[1], SMAILOVICS Una[1], HAYTURAL Hazal[1], GONZALEZ ISLA Arturo[1], TIJMS Betty M[2], MIHAI HARET Robert[1], SHEVENKO Ganna[3], GOBOM Johan[4], ABELEIN Axel[5], SEKIGUCHI Misaki[6], SAITO Takashi[6], SAIDO Takaomi[6], BOGDANOVICS Nenad[1], ZETTERBERG Henrik[4], FRYKMAN Susanne[1], JELIC Vesna[1], WINBLAD Bengt[1], FISAHN Andre[1], BERGQUIST Jonas[3], JELLE VISSER Pieter[1,2] and NILSSON Per[1]

[1] Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Sweden
[2] Alzheimer Center Amsterdam, Department of Neurology, Amsterdam UMC, The Netherlands
[3] Department of Chemistry, Uppsala University, Sweden
[4] Department of Psychiatry and Neurochemistry, Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
[5] Department of Biosciences and Nutrition, Karolinska Institutet, Sweden
[6] RIKEN Center for Brain Science, Japan

Autophagy is impaired in Alzheimer's disease (AD) leading to an increase of autophagosomes in the dystrophic neurites of AD brains. However, it is not known whether this is caused by an induced autophagy or an impaired end stage lysosomal clearance. We found through transcriptome analysis of novel *App* knock-in AD mice, which exhibits robust Aβ pathology, neuroinflammation, synaptic alterations and impaired memory, an early activation of autophagy in the disease progression whereas a downregulation occurs at a later stage of the disease. By analyzing CSF from the mice with label-free mass spectrometry and comparing it to a large cohort of human CSF from different stages of AD, we could link this alteration in autophagy to decorin, an autophagy-activating extracellular matrix protein. To elucidate the role of autophagy in AD including amyloid β (Aβ) metabolism which is one of the drivers for AD, and neurodegeneration, we generated conditional knockout mice of autophagy-related gene 7 (Atg7) in excitatory neurons. Genetic deletion of autophagy induced neurodegeneration through caspase 3 activation. To investigate the effect of a concomitant deletion of autophagy and Aβ pathology, we crossed Atg7 cKO mice with the *App* knock-in AD mice. Interestingly, deletion of autophagy leads to drastically lowered Aβ plaque formation paralleled by an intracellular accumulation of Aβ which induces neurodegeneration. We show this by histological means as well as MRI in living mice. Furthermore, deletion of Atg7 leads to impaired memory and onset of autistic-like behavior which is further worsened in the autophagy deficient *App* knock-in mice. This is due to a decrease in gamma oscillations in the hippocampus. Together, this shows that autophagy plays a key role in Aβ metabolism and that lack of functional autophagy is detrimental to the brain.

Session I (Nordic Symposium)

Speaker Biography



Prof. DING Ding（丁玎） is a professor and neuro-epidemiologist at the Institute of Neurology, Fudan University Huashan Hospital, WHO collaborating centre for research and training in neurosciences, Shanghai, China. Prof. Ding received her medical, public health, and neurology training at the Fudan University. She was the visiting scholar and exchanging scientist at The Chinese University of Hong Kong (2006), the National Institute of Health (USA 2007), and the UCL Institute of Neurology (Queen square, London 2015). She is experienced in epidemiological study of neurological diseases, such as epilepsy, cognitive impairment, cerebrovascular disease, Parkinson's disease, essential trauma, migraine, and autism. She is the principle investigator of the "Shanghai Aging Study (SAS)", a cohort study conducted in China with a study design, operational procedures and diagnostic criteria similar to most cohort studies in western countries. The research cohort was established in 2009 aiming to identify the prevalence of mild cognitive impairment (MCI) and dementia in 4000 older community dwellings in Shanghai. Risk factors of cognitive impairment were also explored and measured at the prospective stage of the SAS. Prof. Ding has over 100 publications including research articles and book chapters. She was awarded the Bruce S. Schoenberg International Award in Neuroepidemiology of American Academy of Neurology in 2006, and the Michael Prize of the International League against Epilepsy in 2013.

Five recent representative publications

1. **Ding D**, Zhou D, Sander JW, Wang W, Li S, Hong Z. “Epilepsy in China: major progress in the last two decades.” ***Lancet Neurology***, 2021; 20(4):316-326.
2. Wang M, **Ding D***, Zhao Q, Wu W, Xiao Z, Liang X, Luo J, Chen J. “Kidney function and dementia risk in community-dwelling older adults: the Shanghai Aging Study.” ***Alzheimers Res Ther***, 2021; 13(1):21.
3. **Ding D**, Xiao Z, Liang X, Wu W, Zhao Q, Cao Y. “Predictive value of odor identification for incident dementia: the Shanghai Aging Study.” ***Frontiers in Aging Neuroscience***, 2020; 12:266. doi: 10.3389/fnagi.2020.00266.
4. **Ding D***, Zhao Q, Wu W, Xiao Z, Liang X, Luo J, Hong Z. “Prevalence and incidence of dementia in an older Chinese population over two decades: the role of education.” ***Alzheimers Dement***, 2020; 16(12):1650-1662.
5. Cui M, Jiang Y, Zhao Q, Zhu Z, Liang X, Zhang X, Wu W, Dong Q, An Y, Tang H, **Ding D***, Chen X*. “Metabolomics and incident dementia in older Chinese adults: The Shanghai Aging Study.” ***Alzheimers Dement***, 2020; 16(5):779-788.

Expertise

- ✧ Experienced in epidemiological study of neurological diseases, such as epilepsy, cognitive impairment, cerebrovascular disease, Parkinson's disease, essential trauma, migraine, and autism.

Olfactory dysfunction and risk of cognitive decline among Community-Dwelling Elderly: the Shanghai Aging Study

Ding DING, Qianhua ZHAO, Xiaoniu LIANG, Wanqing WU, Zhenxu XIAO, Zhen HONG

Institute of Neurology, Huashan Hospital, Fudan University, Shanghai 200040, P.R. China.

Olfactory dysfunction is an important clinical symptom indicating early stage of neurodegenerative diseases. The Shanghai Aging Study provided us a unique opportunity to explore the association between olfactory identification (OI) and cognitive function among community-dwelling elderly in China. OI of each participant was measured by the 12-item identification tests from Sniffin' Sticks Screening test (SSST-12). Dementia and Mild cognitive impairment (MCI) were diagnosed by DSM-IV and Peterson criteria. We used the Cox regression model to explore the association between OI scores and cognitive function, adjusting potential confounders. The mean OI score of participants with MCI was significantly lower than that of those with normal cognition. After adjusted for gender, education, age, lifestyles, medical history, APOE genotype, lower OI score was found to be significantly associated with MCI. Nine hundred and forty-eight participants were successfully followed up for 5 years. After adjusting for baseline MMSE score and confounders, baseline OI was inversely related to the annual rate of change of MMSE score for all participants, especially for non-APOE-ε4 allele carriers. Our study suggests that OI may be an early predictor of incident cognitive decline among older adults.

Session I (Nordic Symposium)

Speaker Biography

Prof. Linda Hildegard BERGERSEN is a professor of physiology at the University of Oslo, Norway and a professor of neurobiology of ageing at the University of Copenhagen, Denmark. She has more than 80 scientific publications and has pioneered the field of 'physical activity and ageing' working on the lactate transport sites and function in brain, leading to the ground-breaking discovering that lactate coordinates effects of physical exercise in the brain through the lactate receptor HCAR1. Since 2004 she has been running her own research laboratory the "Brain and Muscle Energy Group". She has supervised 15 PhD students to their final dissertation. Two of which have made academic positions with lactate research as their main research topic.

Five recent representative publications

1. Lambertus M, Øverberg LT, Andersson KA, Hjelden MS, Hadzic A, Haugen ØP, Storm-Mathisen J, **Bergersen LH**, Geiseler S, Morland C. "L-lactate induces neurogenesis in the mouse ventricular-subventricular zone via the lactate receptor HCA_1." ***Acta Physiol (Oxf)***, 2021; 231(3):e13587.
2. Cunnane SC, Trushina E, Morland C, Prigione A, Casadesus G, Andrews ZB, Beal MF, **Bergersen LH**, Brinton RD, de la Monte S, Eckert A, Harvey J, Jeggo R, Jhamandas JH, Kann O, la Cour CM, Martin WF, Mithieux G, Moreira PI, Murphy MP, Nave KA, Nuriel T, Oliet SHR, Saudou F, Mattson MP, Swerdlow RH, Millan MJ. "Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing." ***Nat Rev Drug Discov***, 2020; 19(9):609-633.
3. Hasan-Olive MM, Lauritzen KH, Ali M, Rasmussen LJ, Storm-Mathisen J, **Bergersen LH**. "A ketogenic diet improves mitochondrial biogenesis and bioenergetics via the PGC1α-SIRT3-UCP2 axis." ***Neurochem Res***, 2019; 44(1):22-37.
4. Morland C, Andersson KA, Haugen ØP, Hadzic A, Kleppa L, Gille A, Rinholm JE, Palibrk V, Diget EH, Kennedy LH, Stølen T, Hennestad E, Moldestad O, Cai Y, Puchades M, Offermanns S, Vervaeke K, Bjørås M, Wisløff U, Storm-Mathisen J, **Bergersen LH**. "Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1." ***Nat Commun***, 2017; 8:15557.
5. **Bergersen LH**. "Lactate transport and signaling in the brain: potential therapeutic targets and roles in body-brain interaction." ***J Cereb Blood Flow Metab***, 2015;35(2):176-185.

Expertise

✧ Transmission Electron Microscopy- Immunogold method

An increasing number of imaging techniques is in use to study the localization of molecules involved in cell-to-cell signaling. One is the use of immunogold procedure to detect and quantify molecules on electron micrographs. To measure the areas of the subcellular compartments under investigation, the protocol uses an overlay screen with an array of regularly spaced points. Based on this, the densities of the gold-labeled molecules can be calculated. Despite the limited lateral resolution of the immunogold method as used by many investigators (~30 nm), it is possible to measure the content of molecules associated with tiny tissue compartments, e.g., synaptic vesicles and different types of membrane, such as plasma membranes and vesicle membranes. The entire protocol can be completed in ~15 d (for more details see Nature Protocol Bergersen et al., 2008).

Lactate treatment in Alzheimer's disease

Imen BELHAJ[1]*, Ingrid ÅMELLEM[1]*, Hanne WEIDEMANN[1], Jon STORM-MATHISEN[2], Tuula Anneli NYMAN[3] and Linda Hildegard BERGERSEN[1,4]

[1] Brain and Muscle Energy Group, Institute of Oral Biology, University of Oslo, Oslo, Norway.
[2] Institute of Basic Medical Science, SERTA, University of Oslo, Oslo, Norway.
[3] Department of Immunology, Institute of Clinical Medicine, University of Oslo, Oslo University Hospital Rikshospitalet, Oslo, Norway.
[4] Center of Healthy Ageing, Medical Faculty, University of Copenhagen, Copenhagen, Denmark.
* Equal contribution

Alzheimer's disease (AD) as the main form of dementia causes an immense individual and societal burden, increasing with the current increase in lifespan. For AD and other neurodegenerative dementias there is no disease-modifying or other effective medication available. However, many reports have found physical exercise to be beneficial for AD, including a recent population-based prospective cohort (HUNT) study showing that *increase* in cardio-pulmonary fitness over time is associated with strong reductions in risk and mortality of dementia (mostly AD). Our discovery that lactate via HCAR1 brings exercise benefits to the brain implies that this mechanism could supplement physical activity, which will be particularly important in the old or disabled. Whether the HCAR1 mediated body-brain mechanism can help fight AD is therefore an urgent *knowledge need*. Our recent experiments on 5xFAD mice show that lactate injections reduce hallmarks of Alzheimer's disease. The transgenic mice receiving lactate had less accumulations of β-amyloid plaques compared to their control groups. Transgenic mice receiving lactate had less amounts of microglia in their subiculum. Lactate injections also reduced inflammatory responses, resulting in higher expressions of anti-inflammatory cytokine *IL-4* and lower expressions of pro-inflammatory cytokine *IL-1β*.

Session IIA

Speaker Biography

Prof. Vilhelm A. Bohr's early professional training took place at the University of Copenhagen, Denmark, where he earned an M.D. in 1978, and both Ph.D. and D.Sc. degrees in 1987. After training in neurology and infectious diseases at the University Hospital in Copenhagen, he undertook postdoctoral studies in Biochemistry in the laboratory of Dr. Hans Klenow at the University of Copenhagen, where he first became interested in nucleic acid metabolism. He developed this interest further when he held a Visiting Scholar position in the laboratory of Dr. Philip Hanawalt at Stanford University from 1982-1986. In 1986, he obtained a Junior Investigator appointment at the National Cancer Institute (NCI), and advanced to a tenured Senior Investigator appointment in 1988. In 1992, he was appointed Chief of the Laboratory of Molecular Genetics at the National Institute on Aging (NIA). Throughout his career, he has made significant contributions and advanced understanding of DNA repair pathways and mechanisms and the cellular response to oxidative DNA damage and oxidative stress. He has also been especially interested in the repair and function of the mitochondrial genome. Early in his career, he developed a widely-used method for studying DNA repair in the transcribed portion of the genome and found that transcriptionally-active genes are preferentially repaired through a process now known as transcription-coupled nucleotide excision repair (TC-NER). The discovery of TC-NER provided strong evidence of the tight interaction between the cellular machineries for DNA repair and transcription in mammalian cells. In his recent studies, he has made seminal findings about the relationships between DNA damage, DNA repair capacity and aging-associated neurodegeneration, and has proposed important models describing crosstalk between the nuclear and mitochondrial genomes, as well as the importance of energy homeostasis/imbalance and mitochondrial dysfunction in aging-related neurodegenerative disease. Most but not all of the research in his laboratory is funded through the intramural research program at NIA.

Five recent representative publications

1. Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, Iser WB, Wollman BN, Morevati M, Li J, Kerr JS, Lu Q, Waltz TB, Tian J, Sinclair DA, Mattson MP, Nilsen H, **Bohr VA**. "NAD^+ replenishment improves lifespan and healthspan in Ataxia telangiectasia models via mitophagy and DNA repair." ***Cell Metab***, 2016; 24(4):566-581. doi: 10.1016/j.cmet.2016.09.004. PMID: 27732836; PMCID: PMC5777858.
2. Scheibye-Knudsen M, Tseng A, Borch Jensen M, Scheibye-Alsing K, Fang EF, Iyama T, Bharti SK, Marosi K, Froetscher L, Kassahun H, Eckley DM, Maul RW, Bastian P, De S, Ghosh S, Nilsen H, Goldberg IG, Mattson MP, Wilson DM 3rd, Brosh RM Jr, Gorospe M, **Bohr VA**. "Cockayne syndrome group A and B proteins converge on transcription-linked resolution of non-B DNA." P***roc Natl Acad Sci USA***, 2016; 113(44):12502-12507. doi: 10.1073/pnas.1610198113. PMID: 27791127; PMCID: PMC5098674.
3. Lu H, Shamanna RA, de Freitas JK, Okur M, Khadka P, Kulikowicz T, Holland PP, Tian J, Croteau DL, Davis AJ, **Bohr VA**. "Cell cycle-dependent phosphorylation regulates RECQL4 pathway choice and ubiquitination in DNA double-strand break repair." ***Nat Commun***, 2017; 8(1):2039. doi: 10.1038/s41467-017-02146-3. PMID: 29229926; PMCID: PMC5725494.
4. Hou Y, Lautrup S, Cordonnier S, Wang Y, Croteau DL, Zavala E, Zhang Y, Moritoh K, O'Connell JF, Baptiste BA, Stevnsner TV, Mattson MP, **Bohr VA**. "NAD^+ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency." P***roc Natl Acad Sci USA***, 2018; 115(8):E1876-E1885. doi: 10.1073/pnas.1718819115. PMID: 29432159; PMCID: PMC5828618.
5. Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, Lautrup S, Hasan-Olive MM, Caponio D, Dan X, Rocktäschel P, Croteau DL, Akbari M, Greig NH, Fladby T, Nilsen H, Cader MZ, Mattson MP, Tavernarakis N, **Bohr VA**. "Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease." ***Nat Neurosci***, 2019; 22(3):401-412. doi: 10.1038/s41593-018-0332-9. PMID: 30742114; PMCID: PMC6693625.

DNA damage and mitochondrial dysfunction in neurodegeneration and aging. Intervention with NAD supplementation

Vilhelm A. BOHR

Section on DNA repair, National Institute on Aging, NIH, USA

We find that some DNA repair defective diseases with severe neurodegeneration have mitochondrial dysfunction. Our studies involve cell lines, the worm (c.elegans), and mouse models and include the premature aging syndromes Xeroderma pigmentosum group A, Cockaynes syndrome, Ataxia telangiectasia and Werner syndrome. It also includes models of Alzheimers Disease, which I will discuss. We find a pattern of hyperparylation, deficiency in the NAD^+ and Sirtuin signaling and mitochondrial stress, deficient mitophagy. We are pursuing mechanistic studies of this signaling and interventions at different steps to improve mitochondrial health and neurodegeneration. I will discuss intervention studies in these disease models including a new Alzheimer mouse model using NAD supplementation. NAD supplementation stimulates mitochondrial functions including mitophagy and stimulates DNA repair pathways. Based on human postmortem material and IPSC cells we identify mitophagy defects as a prominent feature in Alzheimers disease (AD). Using c.elegans AD models we screened for mitophagy stimulators and identified compounds that subsequentially also show major improvement of AD features in mouse models. We are exploring senescence and cGAS-STING signaling pathways, which will be discussed.

Session IIA

Speaker Biography

Prof. LIU Kai（劉凱）is currently Cheng Associate Professor of Science in Division of Life Science at The Hong Kong University of Science and Technology (HKUST). Prof. Liu received his Bachelor degree from School of Life Sciences at Peking University in 1998, and received his Ph.D. from Rutgers University at New Brunswick in 2006. Then he did his postdoc research at Children's Hospital Boston/Harvard Medical School. In 2011, Prof. Liu joined Division of Life Science at HKUST as Assistant Professor. His research interest focuses on the intrinsic mechanisms regulating axonal regeneration.

Five recent representative publications

1. Yang C*, Wang X*, Wang JY, Wang XJ, Chen W, Lu N, Siniossoglou S, Yao ZP, **Liu K**[#]. "Rewiring neuronal glycerolipid metabolism determines the extent of axon regeneration." ***Neuron***, 2020; 105(2):276-292.
2. Wang H, Wang X, Zhang K, Wang Q, Cao X, Wang Z, Zhang S, Li A[#], **Liu K**[#], Fang Y[#]. "Rapid depletion of ESCRT protein Vps4 underlies injury-induced autophagic impediment and Wallerian degeneration." ***Science Advances***, 2019; 5(2).
3. Li S*, Yang C*, Zhang L, Gao X, Wang X, Liu W, Wang Y, Jiang S, Wong YH, Zhang Y, **Liu K**. "Promoting axon regeneration in the adult CNS by modulation of the melanopsin/GPCR signaling." ***Proc Natl Acad Sci USA***, 2016; 113(7):1937-1942.
4. Du K*, Zheng S*, Zhang Q*, Li S, Gao X, Wang J, Jiang L, **Liu K**. "Pten deletion promotes regrowth of corticospinal tract axons 1 year after spinal cord injury." ***Journal of Neuroscience***, 2015; 35(26): 9754-9763.
5. Li S*, He Q*, Wang H, Tang X, Ho KW, Gao X, Zhang Q, Shen Y, Cheung A, Wong F, Wong YH, Ip NY, Jiang L, Yung WH, **Liu K**. "Injured adult retinal axons with Pten and Socs3 co-deletion reform active synapses with suprachiasmatic neurons." ***Neurobiology of Disease***, 2015;73:366-376.

Expertise

✧ Neural injury, regeneration, and repair

Neuronal mechanisms regulating axon regeneration in central nervous system

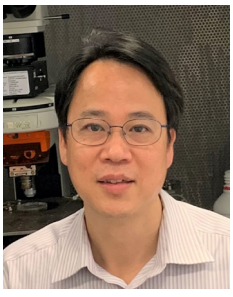
LIU Kai

Division of Life Science, The Hong Kong University of Science and Technology, Hong Kong SAR, P.R. China.

How adult neurons coordinate lipid metabolism to regenerate axons remains elusive. We found that depleting neuronal lipin1, a key enzyme controlling the balanced synthesis of glycerolipids through the glycerol phosphate pathway, enhanced axon regeneration after optic nerve injury. Axotomy elevated lipin1 in retinal ganglion cells, which contributed to regeneration failure in the CNS by favorably producing triglyceride storage lipids rather than phospholipid membrane lipids in neurons. Regrowth induced by lipin1 depletion required triglyceride hydrolysis and phospholipid synthesis. Decreasing triglyceride synthesis by deleting neuronal diglyceride acyltransferases (DGATs) and enhancing PL synthesis through the Kennedy pathway promoted axon regeneration. In addition, peripheral neurons adopted this mechanism for their spontaneous axon regeneration. Our study reveals a critical role of lipin1 and DGATs as intrinsic regulators of glycerolipid metabolism in neurons and indicates that directing neuronal lipid synthesis away from triglyceride synthesis and toward phospholipid synthesis may promote axon regeneration.

Session IIA

Speaker Biography



Prof. YUNG Wing Ho（容永豪）graduated from The Chinese University of Hong Kong (CUHK) in biology and biochemistry with first class honors. He was a recipient of the Commonwealth Scholarship and the Croucher Foundation Fellowship that supported his DPhil study and post-doctoral training in the University of Oxford, under the supervision of Prof. Julian Jack, FRS. He is currently a Professor in the School of Biomedical Sciences. He received the Master Teacher of the Year award, Faculty of Medicine in 2007 and the Research Excellence Award, CUHK in 2013. He has broad research interests in understanding the functions and mechanisms of the nervous system in health and in disease, emphasizing the underlying neural circuits and the roles of neuroplasticity. This is achieved by employing a multitude of cutting-edge neuroscience and computational techniques.

Five recent representative publications

1. Li C, Yang X, Ke Y, **Yung WH**. "Fully affine invariant methods for cross-session registration of calcium imaging data." ***eNeuro***, 2020; 7(4):ENEURO.0054-20.2020.
2. Mu MD, Geng HY, Rong KL, Peng RC, Wang ST, Geng LT, Qian ZM, **Yung WH**, Ke Y. "A limbic circuitry involved in emotional stress-induced grooming." ***Nature Communications***, 2020; 11(1):2261.
3. Li C, Chan DCW, Yang X, Ke Y, **Yung WH**. "Prediction of forelimb reach results from motor cortex activities based on calcium imaging and deep learning." ***Frontiers in Cellular Neurosciences***, 2019; 13:88.
4. Cui Q, Li Q, Geng H, Chen L, Ip NY, Ke Y, **Yung WH**. "Dopamine receptors mediate strategy abandoning via modulation of a specific prelimbic cortex-nucleus accumbens pathway in mice." ***Proc Natl Acad Sci USA***, 2018; 115(21):E4890-E4899.
5. Li Q, Ko H, Qian ZM, Yan LYC, Chan DCW, Arbuthnott G, Ke Y, **Yung WH**. "Refinement of learned skilled movement representation in motor cortex deep output layer." ***Nature Communications***, 2017; 8:15834.

Expertise

- ✧ Electrophysiology
- ✧ Brain imaging
- ✧ Animal behaviour

A limbic circuit underlying emotional stress-induced repetitive behavior

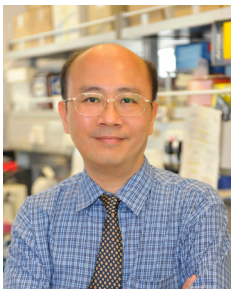
MU Mingdao, GENG Hongyan, RONG Kanglin, KE Ya, YUNG Wing-Ho

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Prolonged exposure to negative stressors could be harmful if a subject cannot respond appropriately. Strategies evolved to respond to stress, including repetitive displacement behaviours, are important in maintaining behavioural homoeostasis. In rodents, self-grooming is a frequently observed repetitive behaviour believed to contribute to post-stress de-arousal with adaptive value. Here we identified a rat limbic di-synaptic circuit that regulates stress induced self-grooming with positive affective valence. This circuit links hippocampal ventral subiculum to ventral lateral septum and then lateral hypothalamus tuberal nucleus. Optogenetic activation of this circuit triggers delayed but robust excessive grooming with patterns closely resembling those evoked by emotional stress. Consistently, inhibition of this circuit significantly suppresses grooming triggered by emotional stress. Our results uncover a previously unknown limbic circuitry involved in regulating stress-induced self-grooming and pinpoint a critical role of ventral lateral septum in this ethologically important behaviour.

Session IIB

Speaker Biography



Prof. Franky L. CHAN（陳良）is currently a Professor at the School of Biomedical Sciences, The Chinese University of Hong Kong (CUHK). He received his PhD from the University of Hong Kong in 1989 and did postdoctoral research at the McGill University in Montreal of Canada (1989-1992). He then joined the Department of Anatomy, CUHK, as the Lecturer in 1992 and then became the Professor in the same Department in 2008. He has been studying the prostate gland and prostate cancer for almost 30 years and published more than 130 original research papers in major ISI-indexed journals, including *Theranostics*, *Oncogene*, *Cancer Research*, *Journal of Pathology*, *PNAS*, *Journal of Clinical Endocrinology* and *Metabolism*, and *Endocrinology*. His research primarily focuses on hormonal carcinogenesis of prostate gland. His current studies in prostate cancer focus on: (1) functional roles of orphan nuclear receptors and their interplay with AR-dependent and –independent pathways in prostate cancer, (2) molecular pathways involved in castration-resistant prostate cancer and neuroendocrine prostate cancer, (3) growth regulation of prostate cancer stem cells, (4) epithelial-mesenchymal-transition and metastasis in prostate cancer and (5) immunotherapy of prostate cancer.

Five recent representative publications

1. Zhou J, Wang Y, Wu D, Wang S, Chen Z, Xiang S and **Chan FL**. "Orphan nuclear receptors as regulators of intratumoral androgen biosynthesis in castration-resistant prostate cancer." ***Oncogene***, 2021; 40(15):2625-2634.
2. Xu Z, Ma T, Zhou J, Gao W, Li Y, Yu S, Wang Y and **Chan FL**. "Nuclear receptor ERRα contributes to castration-resistant growth of prostate cancer via its regulation of intratumoral androgen biosynthesis." ***Theranostics***, 2020; 10(9): 4201-4216.
3. Wang Z, Li Y, Wu D, Yu S, Wang Y and **Chan FL**. "Nuclear receptor HNF4α performs a tumor suppressor function in prostate cancer via its induction of p21-driven cellular senescence." ***Oncogene***, 2020; 39(7):1572-1589.
4. Xiao L, Wang Y, Xu K, Hu H, Xu Z, Wu D, Wang Z, You W, Ng CF, Yu S and **Chan FL**. "Nuclear receptor LRH-1 functions to promote castration-resistant growth of prostate cancer via its promotion of intratumoral androgen biosynthesis." ***Cancer Research***, 2018; 78(9):2205-2218.
5. Xu Z, Wang Y, Xiao ZG, Zou C, Zhang X, Wang Z, Wu D, Yu S and **Chan FL**. "Nuclear receptor ERRα and transcription factor ERG form a reciprocal loop in the regulation of *TMPRSS2:ERG* fusion gene in prostate cancer." ***Oncogene***, 2018; 37(48): 6259-6274.

Interplay between orphan nuclear receptors and androgen receptor-dependent or -independent growth signalings in prostate cancer

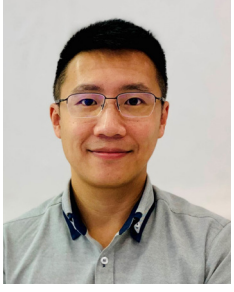
WANG Yuliang, GAO Weijie, LI Youjia, CHOW Sin Ting, XIE Wenjuan, ZHANG Xingxing, ZHOU Jianfu and CHAN Leung Franky

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

It is well-established that both the initial and advanced growth of prostate cancer depends critically on androgens and thus on the activated androgen receptor (AR) -mediated signaling pathway. The unique hormone-dependent feature of prostate cancer forms the biological basis of hormone or androgen-deprivation therapy (ADT) that aims to suppress the AR signaling by androgen depletion or AR antagonists. ADT still remains the mainstay treatment option for locally advanced or metastatic prostate cancer. However, most patients upon ADT will inevitably develop therapy-resistance and progress to relapse in the form of castration-resistant disease (castration-resistant prostate cancer or CRPC) or even a more aggressive androgen-independent subtype (therapy-related neuroendocrine prostate cancer or NEPC). Recent advances show that besides AR, some ligand-independent members of nuclear receptor superfamily-designated as orphan nuclear receptors (ONRs), as their endogenous physiological ligands are either absent or not yet identified to date, also play significant roles in the growth regulation of prostate cancer via multiple AR-dependent or -independent (AR-bypass) pathways or mechanisms. In this review, we summarize the recent progress in the newly elucidated roles of ONRs in prostate cancer, with a focus on their interplay in the AR-dependent pathways (intratumoral androgen biosynthesis and suppression of AR signaling) and AR-independent pathways or cellular processes (hypoxia, oncogene- or tumor suppressor-induced senescence, apoptosis and regulation of prostate cancer stem cells). These ONRs with their newly characterized roles not only can serve as novel biomarkers but also as potential therapeutic targets for management of advanced prostate cancer.

Session IIB

Speaker Biography



Prof. FOK Kin Lam Ellis（霍建霖）obtained his Ph.D. in physiology from the School of Biomedical Sciences (SBS), The Chinese University of Hong Kong in 2009. He continued his research after graduation and then moved to the Department of Medicine, McGill University in Canada as Postdoc Fellow in 2012. He joined SBS as a Research Assistant Professor in 2015, and he became an Assistant Professor in 2017.

Prof. Fok's research mainly focuses on male reproduction and the reproductive tract microenvironment. His previous researches have studied the sperm maturation process in detail and uncovered the dual role of a small peptide human β-defensin 1 in regulating the motility and bactericidal activity of sperm. Recently, his lab has used multi-omics approaches to characterize the microenvironment of the male reproductive tract. Over the years, Prof. Fok has published over 40 peer-review articles in decent journals including *Science Translational Medicine*, *Cell Research* and *PNAS*. Prof. Fok has served as an invited reviewer for international journals and a grant reviewer for overseas funding bodies. He is also an associated editor for *Frontiers in Reproductive Health*.

Five recent representative publications

1. Shi J[#], **Fok KL**[#], Dai P[#], Qiao F, Zhang M, Liu H, Sang M, Ye M, Liu Y, Zhou Y, Wang C, Sun F*, Xie G*, Chen H*. "Spatial-temporal landscape of mouse epididymal cells and specific mitochondria-rich segment defined by large-scale single-cell RNAseq." ***Cell Discovery***, 2021.
2. Chen Z, Li X, Jin J, Zhou W, Chen J, **Fok KL**. "Connective tissue growth factor mediates spermatogonial migration associated with differentiation." ***Biochimica et Biophysica Acta (Molecular Cell Research)***, 2020; 1867(7):118708. PMID: 32240712.
3. Li F, Han J, Cao T, Lam W, Fan B, Tang W, Chen S, **Fok KL***, Li L*. "Design of self-assembly dipeptide hydrogels and machine learning via their chemical features." ***Proceedings of the National Academy of Sciences***, 2019; 116(23):11259-11264. PMID: 31110004.
4. **Fok KL**[#], Bose R[#], Sheng K, Chang CW, Katz-Egorov M, Culty M, Su S, Yang M, Ruan YC, Chan HC, Iavarone A, Lasorella A, Cencic R, Pelletier J, Nagano M, Xu W, Wing SS. "Huwe1 regulates the establishment and maintenance of spermatogonia by suppressing DNA damage response." ***Endocrinology***, 2017; 158(11):4000-4016. PMID: 28938460.
5. Diao R[#], **Fok KL**[#], Chen H[#], Yu MK, Duan Y, Chung CM, Li Z, Wu H, Li Z, Zhang H, Ji Z, Zhen W, Ng CF, Gui Y, Cai Z, Chan HC. "Deficient human β-defensin 1 underlies male infertility associated with poor sperm motility and genital tract infection." ***Science Translational Medicine***, 2014; 6(249):249ra108. PMID: 25122636.

* Co-correspondence

[#] Equal contributions

Expertise

- ✧ Genetic engineering: CRISPR/Cas9, gene delivery
- ✧ Cell biology: germline stem cells, extracellular vesicles in reproductive tracts
- ✧ Animal models & clinical samples: germ cell transplantation, transgenic mice, seminal microbiome

The journey of male gametes – biology of the microenvironment parcels

Ellis FOK[1], Kathleen CHOY[1], CHAN Sze Yan[1], Jing JIN[1], David CHAN[2], Howard YIM[3]

[1] School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] Department of Obstetrics and Gynecology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[3] Microbiome Research Centre, St George and Sutherland Clinical School, The University of New South Wales, Sydney, Australia

Infertility affects 15% of couples worldwide. However, the etiology of infertility remains largely unknown. The microenvironments of the male and female reproductive tracts are essential for the production of gametes, sperm functions required for fertilization, implantation and embryo development. To date, a plethora of hormones, cytokines and growth factors are known to contribute to the microenvironment. Recently, emerging evidence revealed the involvement of new players such as extracellular vesicles and microbiota in modulating the biology of the gametes along the reproductive tracts and thus the fertility. In today's seminar, we will first reveal the involvement of extracellular vesicles in spermatogenesis in the testis. We will then look at the roles of a small antimicrobial peptide in sperm chemotaxis in the female reproductive tracts and in formulating the seminal microbiome of the male tract. Finally, we will discuss the potential applications of our findings on reproductive technologies.

Session IIB

Speaker Biography

Prof. CHEUNG Hoi Hung Albert（張凱鴻）was graduated from The Chinese University of Hong Kong (CUHK), where he received his M.Phil. and Ph.D. degrees. His early predoctoral and postdoctoral trainings were done at the U.S. National Institute of Health (NIH). He joined the School of Biomedical Sciences, CUHK as a Research Assistant Professor in 2014 and subsequently became an Assistant Professor in 2019. His primary research interest is studying stem cell aging. In particular, he studies the role of DNA and RNA helicases in the maintenance of genome stability in stem cells, and the molecular mechanism leading to aging and aging-related diseases when the function of the helicases is lost.

Five recent representative publications

1. Liu Z & **Cheung HH**. "Stem cell-based therapies for Parkinson disease." ***Int J Mol Sci***, 2020; 21(21):8060. https://doi.org/10.3390/ijms21218060
2. Wang Z, Miu KK, Zhang X, Wan TY, Lu G, **Cheung HH**, Lee HM, Kong PS, Chan JCN & Chan WY. "Hepatic miR-192-3p re-activation alleviates steatosis by targeting glucocorticoid receptor." ***JHEP Reports***, 2020; 2(6):100179. https://doi.org/10.1016/j.jhepr.2020.100179
3. Tu J, Wan C, Zhang F, Tian Y, Cao L, Law PWN, Y Tian, Lu G, Rennert OM, Chan WY & **Cheung HH**. "Genetic correction of Werner syndrome gene reveals impaired pro-angiogenic function and HGF insufficiency in mesenchymal stem cells." ***Aging Cell***, 2020; 19(5):e13116. https://doi.org/10.1111/acel.13116
4. Wang W, Lu G, Su X, Tang C, Li H, Xiong Z, Leung CK, Wong MS, Liu H, Ma JL, **Cheung HH**, Kung HF, Chen ZJ, Chan WY. "Pten-mediated Gsk3β modulates the naïve pluripotency maintenance in embryonic stem cells." ***Cell Death Dis***, 2020; 11(2):107. https://doi.org/10.1038/s41419-020-2271-0
5. Tu J, **Cheung HH**, Lu G, Chan CL, Chen ZJ, Chan WY. "microRNA-126 is a tumor suppressor of granulosa cell tumor mediated by its host gene EGFL7." ***Front. Oncol***, 2019; 9:486. doi:10.3389/fonc.2019.00486. https://doi.org/10.3389/fonc.2019.00486

Expertise

- ✧ Pluripotent stem cell
- ✧ Organoid
- ✧ Aging

The role of nucleolar RNA helicase in ribosomal DNA instability

LI Chang, LIU Zhaohui, ZHANG Fujia, LEUNG On Wah, CHEUNG Hoi Hung

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

In yeast, chromatin instability of ribosomal DNA (rDNA) is a driver of aging. The mechanism of rDNA instability in higher eukaryotes as well as their role in aging are not clearly defined. A human diploid genome contains approximately 300–400 copies of rDNA repeats sequestered as clusters in five acrocentric chromosomes. rDNA is organized in the nucleolus, a membraneless subnuclear organelle where rDNA transcription, rRNA processing, and ribosome biogenesis occur. The nucleolus does not simply serve as a factory for ribosome assembly. Similar to centromeres and telomeres, rDNA is highly repetitive and enriched with heterochromatin, which contains repressive epigenetic marks (e.g., H3K9me3). Loss of constitutive heterochromatin is a cause of genomic instability, leading to growth arrest, cellular senescence, and aging. In the nucleolus, perinucleolar heterochromatin plays a role in rDNA silencing, and dysregulation of this process leads to nucleolar disorganization and rDNA instability, which may be attributed to increased nucleolar stress. In this talk, I will discuss the mechanisms leading rDNA instability, which is regulated by nucleolar helicases. Downregulation of such helicases could lead to loss of heterochromatin and rDNA instability, and the implication in aging.

Session IIB

Speaker Biography

Prof. LUI Wai Yan Vivian（呂偉欣）is an Associate Professor, and the Deputy Chief for Cancer Biology and Experimental Therapeutics of Biomedical Sciences at The Chinese University of Hong Kong. She obtained her Ph.D. (Hons) training in Molecular Pharmacology at the University of Pittsburgh, School of Medicine, USA, followed by post-doctoral trainings at Duke University and University of Pittsburgh, USA. Her research focuses on precision medicine development, and immunogenomics for head and neck cancers using integrative omics and clinical outcome big data. She was the first to discover the clinical druggability of PI3K and MAPK1 mutations in head and neck cancer.

Prof. Lui is the Program leader of a pan-cancer precision medicine Research Impact Fund, Co-PI of 2 active multi-institutional precision medicine program grants, and PI of 6 additional gene-drug sensitivity grants (all active, totaling USD 10.3 millions) from Hong Kong and the US. Prof. Lui has received 18 awards and fellowships, including the United College Early Career Research Excellence Award (CUHK), and the SH Ho Visiting Professorship for Stanford, USA (Stanford-CUHK exchange). She has published 102 research articles (H-Index of 40) in renowned scientific Journals including *Cancer Discovery*, *JAMA Oncology*, *Nature Communications*, *PNAS*, *Journal of National Cancer Institute, Journal of Clinical Investigation*, *Clinical Cancer Research*, *Oncogene*, *Communications Biology*, etc. She serves in the Pharmacogenomics Working Group, National Society of Genetic Counselors, USA to promote Pharmacogenomic Education for treatment and public awareness internationally.

Five recent representative publications

1. Bruce J*, To KF*, **Lui VWY***, Chung GTY*, Chan YY, Tsang CM, Yip KY, Ma BBY, Woo JKS, Hui EP, Mak MKF, Lee SD, Chow C, Velapasamy S, Or YYY, El Ghamrasni S, Wu M, Kwan JSH, Liu Y, Chan JYK, van Hasselt A, Young LS, Dawson CW, Paterson IC, Yap LF, Tsao SW, Liu FF, Chan ATC, Pugh TJ*, Lo KW*. "Whole-genome profiling of nasopharyngeal carcinoma reveals convergence of host genomic alterations and EBV latency on inflammatory NF-kB activation and immune escape." (Accepted, ***Nat Communications***, 2021)
2. Johnson D, Burtness B, Leeman C, **Lui VWY**, Bauman J, Grandis JR. "Head and neck squamous cell carcinoma." ***Nature Review Disease Primers*** (Invitation from Editor), 2020. https://doi.org/10.1038/s41572-020-00224-3
3. Ngan HL, Poon PHY, Su YX, Chan JYK, Lo KW, Yeung CK, Liu Y, Wong E, Li H, Lau CW, Piao W, **Lui VWY**. "Erlotinib sensitivity of MAPK1p.D321N mutation in head and neck squamous cell carcinoma." ***NPJ Genom Med***, 2020; 5(1):17. PubMed PMID: 32351709.
4. Van Allen EM#, **Lui VWY**#, Egloff AM, Goetz EM, Li H, Johnson JT, Duvvuri U, Bauman JE, Stransky N, Zeng Y, Gilbert BR, Pendleton KP, Wang L, Chiosea S, Sougnez C, Wagle N, Zhang F, Du Y, Close D, Johnston PA, McKenna A, Carter SL, Golub TR, Getz G, Mills GB, Garraway LA, Grandis JR. "Genomic correlate of exceptional erlotinib response in head and neck squamous cell carcinoma." ***JAMA Oncol***, 2015; 1(2):238-244. PubMed PMID: 26181029.
5. **Lui VWY**, Hedberg ML, Li H, Vangara BS, Pendleton K, Zeng Y, Lu Y, Zhang Q, Du Y, Gilbert BR, Freilino M, Sauerwein S, Peyser ND, Xiao D, Diergaarde B, Wang L, Chiosea S, Seethala R, Johnson JT, Kim S, Duvvuri U, Ferris RL, Romkes M, Nukui T, Ng PKS, Garraway LA, Hammerman PS, Mills GB, Grandis JR. "Frequent mutation of the PI3K pathway in head and neck cancer defines predictive biomarkers." ***Cancer Discov***, 2013; 3(7):761-769. PubMed PMID: 23619167.

* Equal contributions

\# Co-first authorships

Expertise

- ✧ Integrated Cancer Genomic-Proteomic bioinformatics for therapeutics and translational research.
- ✧ Functional genomics and platform development for druggable mutations and driver mutations in human oncogenesis.
- ✧ Molecular mechanisms of mutation-based drug sensitivity for targeted therapies.
- ✧ Mechanisms of viral-mediated oncogenesis in aerodigestive tract cancers and Nasopharyngeal cancer.
- ✧ Precision Medicine development, and Patient-oriented pharmacogenomics.

Novel druggable events unfolding in head and neck cancers

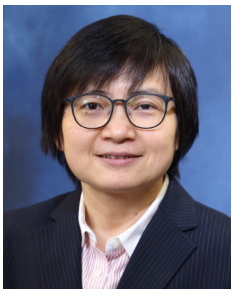
LUI Wai Yan Vivian

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Global head and neck cancer incidences are rapidly rising, approaching ~0.85 millions per year. Effective therapies are still lacking. Using patient-derived cultures with genomic characterization, patient-derived xenografts, exceptional responder gene-drug sensitivity profiles, and bioinformatics, we have recently identified multiple novel druggable nodes for precision medicine development for this aggressive cancer. We have also developed a novel integrative transcriptomics-metastasis methodology, which uncovers multiple new targets for anti-metastatic therapy development for head and neck cancer.

Session III

Speaker Biography



Prof. HO Yi-Ping Megan（何亦平）is currently an Assistant Professor in the Department of Biomedical Engineering at The Chinese University of Hong Kong. She received her B.S. and M.S. in Power Mechanical Engineering from National Tsing-Hua University, Taiwan. She received her Ph.D. in Mechanical Engineering from the Johns Hopkins University in USA. After her postdoctoral training with Duke University in USA, she received the Young Elite Researcher Award from the Danish Research Council for Independent Research and started her independent career in the Interdisciplinary Nanoscience Centre and the Department of Molecular Biology and Genetics at Aarhus University in Denmark. She is a co-founder of two start-up companies situated in Demark, Zymonostics and vPCiR, focusing on enzyme-based diagnostics. She has published 59 peer-reviewed journal articles, 6 book chapters, 74 conference papers and holds 2 granted patents. The results that she presented have been recognized internationally by the American Society of Gene Therapy and Controlled Release Society. Her research team is focused on developing nanosensors and microfluidics as diagnostic tools to expand the capacity of disease detection and treatment evaluation.

Five recent representative publications

1. Qu F, Zhao S, Cheng G, Rahman MH, Xiao Q, Chan RWY, **Ho YP***. "Double emulsion-pretreated microwell culture for in vitro production of multicellular spheroids and in situ analysis." ***Microsystems & Nanoengineering***, 2021 (Accepted).
2. Wei Y[#], Cheng G[#], Ho HP, **Ho YP***, Yong KT*. "Thermodynamic perspectives on liquid-liquid droplet reactors for biochemical applications." ***Chemical Society Reviews***, 2020; 49(18): 6555-6567. ([#]Equal Contribution).
3. Rahman MH, Xiao Q, Zhao S, Qu F, Chang C, Wei AC, **Ho YP***. "Demarcating the membrane damage for the extraction of functional mitochondria." ***Microsystems & Nanoengineering***, 2018; 4(1): 39.
4. Jepsen ML, Harmsen C, Godbole AA, Nagaraja V, Knudsen BR, **Ho YP***. "Specific detection of the cleavage activity of mycobacterial enzymes using a quantum dots based DNA nanosensor." ***Nanoscale***, 2016; 8(1): 358-364.
5. Chiu YL, Chan HF, Phua KKL, Zhang Y, Juul S, Knudsen BR, Leong KW*, **Ho YP***. "Synthesis of fluorosurfactants for emulsion-based biological applications." ***ACS Nano***, 2014; 8(4):3913-3920.

* Corresponding author

[#] Equal first authors

Expertise

- ✧ DNA nanosensors
- ✧ Diseases diagnostics via enzymatic activities
- ✧ Microfabrication
- ✧ Microfluidics

Modulation of membrane deformation by shear through microfluidics for biomedical applications

HO Yi-Ping Megan

[1] Department of Biomedical Engineering, Faculty of Engineering, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] Centre for Novel Biomaterials, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[3] Hong Kong Branch of CAS Center for Excellence in Animal Evolution and Genetics, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[4] The Ministry of Education Key Laboratory of Regeneration Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.

Existing development of microfluidics has shown great success in biomedical applications. This talk will highlight our recent initiatives on exploiting microfluidics for the manipulation and analysis of individual cells and subcellular organelles. In particular, we have explored the possibility of modulating hydrodynamic shear stress at microscale to selectively disrupt cellular membrane while maintaining the mitochondrial membrane intact. This microscaled cell shredder is able to preserve the morphological integrity of extracted mitochondria, particularly at low cell concentrations. We have also investigated a microfluidics-based method to encapsulate protein payloads into red blood cells (RBCs) by controlling membrane deformation either transiently or extendedly in a microfluidic channel. Mouse RBCs loaded by the proposed microfluidics method exhibit higher enzymatic activity and membrane integrity compared to the counterparts loaded by osmotic entrapment. These efforts are expected to find clinical applications in diagnostics, prognostics and treatment evaluation, as well as to expand our fundamental understanding towards disease development.

Session III

Speaker Biography

Prof. WAN Chao（萬超） is an Associate Professor in School of Biomedical Sciences (SBS), Faculty of Medicine, The Chinese University of Hong Kong (CUHK). He serves as Deputy Managing Director of SBS Core Laboratories, and Co-Director of MOE Key Laboratory for Regenerative Medicine (CUHK-Jinan University). Prof. Wan obtained his Ph.D. in Shanghai Jiaotong University School of Medicine in 2002, then worked as a resident Orthopaedic Surgeon in Longhua Hospital, Shanghai University of Traditional Chinese Medicine. Since 2003, he pursued postdoctoral training in School of Medicine, The Queen's University of Belfast, UK, and School of Medicine, University of Alabama at Birmingham (UAB), USA until 2007. He was then appointed as an Instructor in Department of Pathology, UAB, and an Instructor in Department of Orthopaedic Surgery, Johns Hopkins University. Prof. Wan joined CUHK as an Assistant Professor in 2009. His research interests include the molecular and cellular mechanisms of the oxygen sensing and growth factor pathways in skeletal development, degeneration and regeneration, and discovery of novel therapies for bone and cartilage tissue repair or regeneration. His research work has been published in international journals including *Proc Natl Acad Sci USA*, *J Clin Invest*, *Nat Med*, *Cell*, *Bone Res*, and *Biomaterials*. Prof. Wan serves as a member of education committee of International Chinese Musculoskeletal Research Society, editorial board of *J Orthop Translat*, and editorial review board of *J Orthop Res*, and a reviewer of more than 20 international journals. His research work was supported by Hong Kong Research Grants Council, Health and Medical Research Fund, National Natural Science Foundation of China, Ministry of Science and Technology, and Shenzhen Science, Technology and Innovation Commission.

Five recent representative publications

1. **Wan C***, Zhang F, Yao H, Li H, Tuan RS*. "Histone modifications and chondrocyte fate: regulation and therapeutic implications." ***Front Cell Dev Biol***, 2021; 9:626708.
2. Yang Z, Kou S, Wei X, Zhang F, Li F, Wang X, Lin Y, **Wan C***, Zhang W*, Sun F*. "Genetically programming stress-relaxation behavior in entirely protein-based molecular networks." ***ACS Macro Lett***, 2018; 7:1468-1474.
3. Wang J*, Zhang F, Tsang WP, **Wan C***, Wu C. "Fabrication of injectable high strength hydrogel based on 4-arm star PEG for cartilage tissue engineering." ***Biomaterials***, 2017; 120:11-21.
4. Tsang WP, Zhang F, He Q, Cai W, Huang J, Chan WY, Shen Z, **Wan C***. "Icaritin enhances mESC self-renewal through upregulating core pluripotency transcription factors mediated by ERα." ***Sci Rep***, 2017; 7:40894.
5. Wang PZ, Zhang F, He Q, Wang J, Shiu HT, Shu Y, Tsang WP, Liang S, Zhao K, **Wan C***. "Flavonoid compound Icariin activates hypoxia inducible factor-1α in chondrocytes and promotes articular cartilage repair." ***PLoS One***, 2016; 11(2):e0148372.

* Corresponding author

Expertise

- ✧ Skeletal disease animal models
- ✧ Bone and cartilage tissue engineering
- ✧ 3D bioprinting
- ✧ Osteoblast, chondrocyte, and osteoclast differentiation

Lysosomal cathepsin D in regulation of skeletal growth and homeostasis

ZHANG Fengjie[1,2], TSANG Wing Pui[1,2], HE Qiling[3], ZHAO Yichen[1,2], ZHANG Jianhua[4], SAFTIG Paul[5], WAN Chao[1,2]

[1] Key Laboratory for Regenerative Medicine, Ministry of Education, School of Biomedical Sciences, Faculty of Engineering, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] Key Laboratory for Regenerative Medicine, Ministry of Education (Shenzhen Base), School of Biomedical Sciences Core Laboratory, Shenzhen Research Institute, The Chinese University of Hong Kong, Shenzhen 518057, P.R. China.
[3] Department of Microbiology, The University of Alabama at Birmingham, AL 35294, USA.
[4] Department of Pathology, The University of Alabama at Birmingham, AL 35294, USA.
[5] Institute of Biochemistry, Christian-Albrechts-University Kiel, Kiel, Germany.

Deficiency or mutation of genes encoding lysosomal enzymes or transport proteins causes a group of inherited metabolic disorders - lysosomal storage disorders (LSDs). Skeletal pathologies are frequently observed in LSDs, yet the relevance of specific lysosomal enzymes in the regulation of bone turnover remains largely unknown. Cathepsin D (CtsD), the principal lysosomal aspartate protease and a main endopeptidase, functions in the normal activity of autophagosome and lysosome. It is indicated that CtsD exists and is altered during skeletal development or injury. However, the molecular and cellular mechanisms of CtsD mediated autophagosome or lysosome function in the skeletal growth and homeostasis remain unclear. In this study, we showed that global knockout of CtsD in mice significantly decreased length of long bones with impaired growth plate development. This phenotype was accompanied by decreased size of chondrocytes and accumulation of proteoglycan in the extracellular matrix. Mice lacking CtsD had dramatically decreased bone mass compared with their control littermates as indicated by decreased bone volume, bone volume/total volume, trabecular number, trabecular thickness and increased trabecular separation in the microCT analysis. Histomorphometry analysis revealed that the phenotype was characterized by decreased osteoblast numbers, osteoblast surface/bone surface and mineral apposition rate, increased osteoclast numbers, osteoclast surface/bone surface and erosion surface/bone surface. At molecular level, siRNA mediated knockdown of CtsD in MC3T3E1 cells attenuated osteoblast differentiation and downregulated LC3BII expression, which was accompanied by decreased levels of P62 and PI3K-Akt-mTOR signals. Intriguingly, knockdown of CtsD in RAW264.7 cells increased osteoclast differentiation with decreased LC3BII expression but elevated P62 and PI3K-Akt-mTOR signals. This was accompanied by alterations in the formation of autophagosome and differential gene profiles associated with the autophagy pathway during differentiation of osteoblasts and osteoclasts, respectively. These results suggest that CtsD mediated autophagy pathway plays important roles in regulation of bone mass and homeostasis through distinct mode of actions in osteoblasts and osteoclasts. Fine tuning of CtsD activity may serve as a potential therapeutic target for the maintenance of bone mass.

Session III

Speaker Biography

Prof. HUI Xiaoyan Hannah（惠曉艷）obtained her B.Sc. (First Class Honours) in Biotechnology from Shanghai Jiao Tong University and completed her Ph.D. study in Shanghai Institute of Biological Sciences, Chinese Academy of Sciences (SIBS, CAS). She then pursued her postdoctoral training at Department of Medicine, The University of Hong Kong and was later took up her post as Research Assistant Professor at the same department. In 2021, she joined the School of Biomedical Sciences, The Chinese University of Hong Kong as Assistant Professor.

The research interest of Prof. Hui lies solely on adipose tissue - a highly plastic organ in our body. Her lab is using genetically engineered mouse models, primary cells/tissues and human iPS-derived adipocytes as model systems. By adopting state-of-the-art, multidisciplinary approaches, the goal of her laboratory is to understand the molecular basis of adipose tissue remodelling and its physiological relevance in obesity and cardio-metabolic diseases. Ultimately she seeks to develop biomedicine that can "re-educate" the adipose tissue.

Prof. Hui is the principal investigator of research grants including General Research fund (GRF), Health and Medical Research Fund (HMRF) and NSFC (Young Excellent Scientist). Her research work has been published in top-ranked journals including *Cell Metab*, *J Clin Invest*. She also receives awards such as National Science and Technology Progress Award (2020).

Five recent representative publications

1. Pan Y, **Hui X**, Hoo RLC, Ye D, Chan CYC, Feng T, Wang Y, Lam KSL & Xu A. "Adipocyte-secreted exosomal microRNA-34a inhibits M2 macrophage polarization to promote obesity-induced adipose inflammation." ***J Clin Invest.***, 2019; 29(2):834-849.
2. Zhao S, Chu Y, Zhang Y, Zhou Y, Jiang Z, Wang Z, Mao L, Li K, Sun W, Li P, Jia S, Wang C, Xu A, Loomes K, Tang S, Wu D, **Hui X*** & Nie T. "Linifanib exerts dual anti-obesity effect by regulating adipocyte browning and formation." ***Life Sci.***, 2019; 222: 117-124.
3. **Hui X***, Zhang M, Gu P, Li K, Gao Y, Wu D, Wang Y & Xu A. "Adipocyte SIRT1 controls systemic insulin sensitivity by modulating macrophages in adipose tissue." ***EMBO Rep.***, 2017; 18(4):645-657.
4. Nie B, Nie T, **Hui X***, Gu P, Mao L, Li K, et al., Xu A, Wu D & Ding S. "Brown adipogenic reprogramming induced by a small molecule." ***Cell Rep.***, 2017; 18(3):624-635.
5. **Hui X***, Gu P, Zhang J, Nie T, Pan Y, Wu D, Feng T, Zhong C, Wang Y, Lam KS & Xu A. "Adiponectin enhances cold-induced browning of subcutaneous adipose tissue via promoting M2 macrophage proliferation." ***Cell Metab.***, 2015; 22(2):279-290.

Expertise

- ✧ Chronic inflammation in obesity and metabolic diseases
- ✧ Adipose tissue thermogenesis

Adipocyte-derived lactate is a metabolic signal to potentiate obesity-evoked adipose macrophage inflammation

FENG Tianshi[1], YANG Wah[2], XU Yong[3], XU Aimin[1], HUI Xiaoyan Hannah[1,4]

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[2] The First Affiliated Hospital of Jinan University, Guangzhou, P.R. China.
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Adipose tissue macrophage (ATM) polarization to M1-like phenotype is a key culprit in adipose inflammation and pathology of metabolic complications. But the metabolic cues that drive ATM polarization is not fully characterized. Our study demonstrates that in adipocytes, elevated lactate production, previously regarded as the by-product of anaerobic or aerobic glycolysis, serves as a metabolic signal to drive ATM polarization to the M1 status in the context of obesity. Adipocyte-selective deletion of lactate dehydrogenase A (*Ldha*), the enzyme converting pyruvate to lactate, protects mice from obesity-associated glucose intolerance and insulin resistance, accompanied by a lower percentage of M1-like ATM and reduced production of proinflammatory cytokines. Adipocyte-derived lactate fosters the activation of M1 macrophages by directly binding to the catalytic domain of prolyl hydroxylase domain-containing2 (PHD2) in a competitive manner with α-ketoglutarate and preventing hypoxia inducible factor (HIF-1α) degradation. Lactate-induced IL-1β was abolished in PHD2-deficient macrophages. Human adipose lactate level is positively linked with local inflammatory features and systemic insulin resistance index independent of the body mass index (BMI). Our study establishes a critical role of adipocyte-derived lactate in shaping the pro-inflammatory microenvironment in adipose and identifies PHD2 as a direct sensor of lactate, which functions to connect energy metabolism and chronic inflammation.

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Nordic Symposium (Session II)

Speaker Biography

Prof. Magnar BJØRÅS is a Principle Investigator of the research group of Cellular responses to DNA damage at Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU), Trondheim and at Clinic of Laboratory Medicine, Oslo University Hospital/ University of Oslo. Bjørås is an expert on genome dynamics with particular emphasis on oxidative stress, DNA base lesion repair and maintenance of epigenetic DNA methylation (epigenome stability).

Cellular genomes are continuously challenged by physical, chemical and biological agents that introduce changes of the chemical structure of the DNA. Intracellular reactive metabolites such as reactive oxygen species and alkylating compounds are important inducers of such changes. Nevertheless, mutation frequencies are low because of very efficient pathways for DNA repair and DNA recombination, which remove DNA damage and conserve at least one functional copy of the genome.

The main focus of the Bjørås group has been on mechanism of repair of endogenous DNA base lesion and genome stability. He has made major contributions to characterization of many new DNA repair enzymes from bacteria, yeast and mammalian. His research group has solved the atomic structure (3D) of many DNA-protein complexes revealing several new mechanisms of DNA base damage recognition and catalysis. His group has several studies on the role of oxidative DNA base lesion repair in cardiovascular disease, neurodegeneration, cognition and behavior, suggesting novel functions of DNA glycosylases beyond canonical DNA repair. Recently his group has established research activity on lysosomal storage disorders in rare neurodegenerative disease.

Five recent representative publications

1. Yang M, Lin X, Segers F, …Aukrust P, **Bjørås M**. "OXR1A, a coactivator of PRMT5 regulating histone arginine methylation." ***Cell Reports***, 2020; 30(12):4165-4178.
2. Li M, Zhao X, Wang W, Shi H, Pan Q, Lu Z, Perez SP, Suganthan R, He C, **Bjørås M***, Klungland A*. "Ythdf2-mediated m6A mRNA clearance modulates neural development in mice." ***Genome Biology***, 2018; 19(1):69.
3. Bjørge MD, Hildrestrand GA, Scheffler K, Suganthan R, Rolseth V, …… Klungland A and **Bjørås M**. "Synergistic actions of Mutyh and Ogg1 DNA glycosylases modulate anxiety-like behaviour." ***Cell Reports***, 2016; 13(12):2671-8.
4. Weel-Sneve R, Kristiansen KI, Odsbu I, Dalhus B, Booth J, Rognes T, Skarstad K and **Bjørås M**. "Single transmembrane peptide DinQ modulates nucleoid compaction and recombination." ***PLoS Genetics***, 2013, 9(2):e1003260.
5. Sejersted Y, Hildrestrand GA, Kunke D, Rolseth V, Krokeide SZ, Neurauter CG, Suganthan R, Atneosen-Åsegg M, Fleming AM, Saugstad OD, Burrows CJ, Luna L, **Bjørås M**. "Endonuclease VIII-like 3 (Neil3) DNA glycosylase promotes neurogenesis induced by hypoxia-ischemia." ***Proc Natl Acad Sci USA***, 2011; 108(46):18802-7.

Expertise

- ✧ DNA repair assays, protein crystallography, stem cell technology, neuronal differentiation protocols in monolayer and 3D (organoids)

A germline homozygous mutation in human *Oxidation Resistance 1* gene causes developmental delay, epilepsy and cerebellar atrophy

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We report three patients with a novel homozygous mutation in the TLDC domain of the OXR1 protein, resulting in developmental delay, epilepsy, and cerebellar atrophy in early childhood. Patient derived lymphoblasts show impaired cell proliferation, increased apoptosis, and abnormally high sensitivity to oxidative stress with elevated DNA damage. These processes are rescued by TLDc domain replacement. Furthermore, we established neuronal 2D and 3D models using patient derived induced pluripotent stem cells. Monolayer neuronal models displayed growth and differentiation defects, suggesting that OXR1 modulates physiological levels of ROS, promotes neurogenesis and neuronal development. Organoids revealed impaired early development of several brain regions with detailed cyto-architecture information. Moreover, we identified altered spatial-temporal histone modification landscapes mediated by PRMTs and show that the PRTM5/MEP50 target H4R3me2s is regulated by the TLDc domain. These findings reveal essential roles for OXR1 in neuronal protection, brain development and pathology.

Nordic Symposium (Session II)

Speaker Biography

Prof. Lene Juel RASMUSSEN is a Professor of Molecular Aging at Center for Healthy Aging and Department of Cellular and Molecular Medicine, University of Copenhagen. She is the Executive Director at Center for Healthy Aging.

Center for Healthy Aging is a research center that studies how more people can have a healthy life and healthy aging. The approach to research is interdisciplinary and the center studies aging and aging processes from cell to society.

Prof. Rasmussen's own research focus at understanding the processes of cellular aging, the genetic origins of complex diseases, as well as the impact of environmental factors, which is the central challenge of modern biomedicine. Basic research into cells and genes is important for understanding how we decline throughout life and become more liable to disease. Having the knowledge means we might be able to postpone the point in life at which illnesses associated with old age typically occur, and thus give many people more years of high quality life.

Her research group identifies molecular targets for the treatment of age-related diseases and investigates the powerhouses of the cells – the mitochondria. Research in mitochondria touches several disease-related fields at the clinical level, because mitochondrial dysfunction or mutations contribute to the ontogeny of cancer, diabetes, blindness, deafness, migraine, and diseases of the heart, kidney, liver, and muscles. Furthermore, mitochondrial dysfunction is involved in aging and neurodegenerative disorders such as Parkinson and Alzheimer's dementia.

Prof. Rasmussen received The Olav Thon Research Grant Award in 2016, became elected member of The Norwegian Academy of Science and Letters in 2019, and has been Chair of the Steering Committee for International Alliance of Research Universities from 2014-2016.

Five recent representative publications

1. Aman Y, Frank J, Lautrup SH, Matysek A, Niu Z, Yang G, Shi L, Bergersen LH, Storm-Mathisen J, **Rasmussen LJ**, Bohr VA, Nilsen H, Fang EF. "The NAD^+-mitophagy axis in healthy longevity and in artificial intelligence-based clinical applications." ***Mech Aging Dev***, 2020; 185:111194. doi: 10.1016/j.mad.2019.111194.
2. Lauridsen PE, **Rasmussen LJ***, Desler C. "Mitochondrial oxidative phosphorylation capacity of cryopreserved cells." ***Mitochondrion***, 2019; 47:47-53. doi: 10.1016/j.mito.2019.04.011.
3. Hasan-Olive MM, Lauritzen KH, Ali M, **Rasmussen LJ**, Storm-Mathisen J, Bergersen LH. "A ketogenic diet improves mitochondrial biogenesis and bioenergetics via the PGC1α-SIRT3-UCP2 axis." ***Neurochem Res***, 2019; 44(1):22-37. doi: 10.1007/s11064-018-2588-6.
4. Fakouri NB, Durhuus JA, Regnell CE, Angleys M, Desler C, Hasan- Olive MDM, Martín-Pardillos A, Tsaalbi-Shtylik A, Thomsen K, Lauritzen M, Bohr VA, de Wind N, Bergersen LH, **Rasmussen LJ**. "Rev1 contributes to proper mitochondrial function via the PARP-NAD^+-SIRT1-PGC1α axis." ***Sci Rep***, 2017; 7(1):12480. doi: 10.1038/s41598-017-12662-3.
5. Martín-Pardillos A, Tsaalbi-Shtylik A, Chen S, Lazare S, van Os RP, Dethmers-Ausema A, Fakouri NB, Bosshard M, Aprigliano R, van Loon B, Salvatori DCF, Hashimoto K, Dingemanse-van der Spek C, Moriya M, **Rasmussen LJ**, de Haan G, Raaijmakers MHG, de Wind N. "Genomic and functional integrity of the hematopoietic system requires tolerance of oxidative DNA lesions." ***Blood***, 2017; 130(13):1523-1534. doi: 10.1182/blood-2017-01-764274.

* Co-corresponding author

Expertise

✧ Cellular and molecular biology

Metabolic control of DNA repair in age-related diseases

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Aging is defined as the gradual decline of cellular, tissue and organismal homeostasis resulting in cellular senescence, organismal dysfunction and, ultimately, death. Mitochondrial function plays an important role in aging as well as onset of multiple human age-related diseases such as cognitive decline, neurological abnormalities, and cancer. Using various model systems, we have shown that mitochondrial dysfunction results in complex genomic instability, which involves nucleotide metabolism as well as multiple major DNA repair and DNA lesion synthesis/bypass pathways. DNA lesions that escape repair will arrest the replication fork, which can lead to replication stress, DNA breaks, and genome instability. To ensure the continuation of replication at damaged DNA templates, translesion synthesis (TLS) polymerases can transiently displace the replicative polymerases and replicate across the lesion. Since TLS polymerases frequently introduce the incorrect nucleotide opposite the lesion, TLS is a mutagenic process. Rev1 is a TLS polymerase that coordinate the recruitment of other TLS polymerases at the damage site and regulate the TLS. Rev1-deficient mice display mild progeroid symptoms suggesting a role for TLS in preventing premature aging. We investigated the molecular mechanisms underlying progeria in these mice and found that the absence of a functional Rev1 protein causes multifactorial mitochondrial dysfunction including abnormal mitochondrial morphology. This phenotype is particularly evident during cellular stress. The mitochondrial abnormalities appear to be caused by NAD^+ depletion triggered by activation of the DNA damage sensor PARP-1.

Nordic Symposium (Session II)

Speaker Biography

Prof. Hilde L. NILSEN is currently a Professor at Institute of Clinical Medicine, University of Oslo, Norway and the Unit Head for Precision Medicine, Akershus University Hospital, Norway. She obtained her Ph.D. degree from the Faculty of Chemistry and Chemical technology at Norwegian University of Science and Technology, Norway. She then served as a Postdoctoral Research Fellow with Dr. Tomas Lindahl at Cancer Research UK, Clare Hall Laboratories, UK.

Professor Nilsen's group is interested in the quality control mechanisms that maintain function of DNA and RNA throughout the lifetime of cells and organisms.

DNA repair enzymes remove damaged or inappropriate bases from DNA. Historically, studies of DNA repair has been motivated by the need for these mechanisms in order to prevent mutations - changes in the genetic code. Studies of DNA repair is therefore important in order to understand how cancer develops and how cancer can be treated. In recent years it has become clear that DNA repair enzymes have many important functions in cells other than to prevent mutations, most importantly in neurobiology to prevent neurodegenerative diseases. Her group has also recently demonstrated that some DNA repair proteins also contribute to RNA quality control. More details about Prof. Nilsen can be viewed at https://www.med.uio.no/klinmed/english/people/aca/hildni/.

Five recent representative publications

1. Kroustallaki P, Lirussi L, Carracedo S, You P, Esbensen QY, Götz A, Jobert L, Alsøe L, Sætrom P, Gagos S, **Nilsen H**. "SMUG1 promotes telomere maintenance through telomerase RNA end processing." ***Cell Reports***, 2019; 28, 1690-1702.
2. Kassahun H, Sengupta T, Schiavi A, Maglioni S, Skjeldam HK, Arczewska KC, Brockway NL, Estes S, Eide L, Ventura N, **Nilsen H**. "Constitutive MAP-kinase activation suppresses germline apoptosis in NTH-1 DNA glycosylase deficient *C. elegans*." ***DNA repair***, 2018; 61, 46-55.
3. Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, Iser WB, Wollman BN, Morevati M, Li J, Kerr JS, Lu Q, Waltz TB, Jane TJ, Sinclair DA, Mattson MP, **Nilsen H**, Bohr VA. "NAD^+ replenishment improves lifespan and healthspan in Ataxia telangiectasia models via mitophagy and DNA repair." ***Cell Metabolism***, 2016; 24, 566-581.
4. Arczewska KD, Tomazella GG, Lindvall JM, Kassahun H, Maglioni S, Torgovnick A, Henriksson J, Matilainen O, Marquis BJ, Nelson BC, Jaruga P, Babaie E, Holmberg C, Burglin TR, Ventura N, Thiede B, **Nilsen H**. "Active transcriptomic and proteomic reprogramming in the *C. elegans* nucleotide excision repair mutant *xpa-1*." ***Nucleic Acids Research***, 2013; 41(10), 5368-81.
5. Jobert L, Skjeldam HK, Dalhus B, Galashevskaya A, Vaagbø CB, Bjørås M, **Nilsen H**. "The human base excision repair enzyme directly interacts with DKC1 and contributes to RNA quality control." ***Mol Cell***, 2013; 49(2), 339-45.

Expertise

- ✧ DNA base excision repair in genome maintenance and RNA quality control
- ✧ Animal models DNA repair disorders (*C. elegans*, mice)
- ✧ The contribution of DNA damage and repair in ageing and age-related disorders

Base excision repair contributinges to Parkinson's disease pathology

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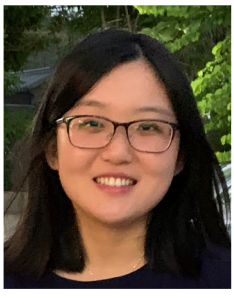
Ageing, genomic stress and mitochondrial dysfunction are risk factors for age-related neurodegenerative pathologies, such as Parkinson's disease (PD). Although a growing body of evidence associates genomic instability with ageing and mitochondrial dysfunction, the mechanisms underlying this association are poorly understood.

DNA base excision repair (BER) is the prominent pathway for repair of oxidative damage to DNA bases. Given the prominent role of oxidative stress in the etiology of PD and the importance of BER in neurons, we hypothesized that BER may serve as a major source of genomic stress in neurons. Comprehensive understanding of the role of BER in neurodegeneration in mammals has been elusive, in part because mammalian cells express as many as 11 distinct DNA glycosylases with overlapping substrate specificities. The *Caenorhabditis elegans* genome possesses a simpler DNA glycosylase repertoire, encoding only two DNA glycosylases. The nematode enables *a priory* targeted genetic studies in BER initiation as redundancy is lower than in mammals. Therefore, *C. elegans* serves as an ideal model organism to systematically investigate whether incomplete or inefficient BER drives neuronal loss. Here, new data implicating BER as a driver of PD pathology in *C. elegans* will be presented.

Nordic Symposium (Session II)

Speaker Biography



Prof. CAO Qin Cara（曹沁）completed her Ph.D. in Computer Science and Engineering (CSE) from The Chinese University of Hong Kong (CUHK). She then continued her postdoctoral research at School of Biomedical Sciences and CSE in CUHK for three years and became a Research Assistant Professor. Her research areas are Bioinformatics and Computational Biology. Prof. Cao has received awards including Young Scholars Thesis Award from CUHK, Young Scientist Award 2nd Runner-up from Hong Kong Institution of Science and Top-10 paper in 2016-17 at RECOMB/ISCB Regulatory Systems Genomics. She has published papers in international journals including *Nature Genetics*, *Nature Machine Intelligence*, *Nature Communications*, *Cell Reports*, *Briefings in Bioinformatics* and *BMC Genomics*.

Five recent representative publications

1. **Cao Q**[#], Zhang Z[#], Fu AX, Wu Q, Lee TL, Lo E, Cheng ASL, Cheng C, Leung D, & Yip KY. "A unified framework for integrative study of heterogeneous gene regulatory mechanisms." ***Nature Machine Intelligence***, 2020; 2(8):447-456.
2. Ho EYK[#], **Cao Q**[#], Gu M, Chan RWL, Wu Q, Gerstein M, & Yip KY. "Shaping the nebulous enhancer in the era of high-throughput assays and genome editing." ***Briefings in Bioinformatics***, 2020; 21(3):836-850.
3. Jiang Q[#], Ang JYJ[#], Lee AY, **Cao Q**, Li KY, Yip KY & Leung DCY. "G9a plays distinct roles in maintaining DNA methylation, retrotransposon silencing, and chromatin looping." ***Cell Reports***, 2020; 33(4), 108315.
4. Zhang J[#], Lee D[#], Dhiman V[#], Jiang P[#], Xu J[#], McGillivray P[#], Yang H[#], Liu J, Meyerson W, Clarke D, Gu M, Li S, Lou S, Xu J, Lochovsky L, Ung M, Ma L, Yu S, **Cao Q**, Harmanci A, Yan KK, Sethi A, Gürsoy G, Schoenberg MR, Rozowsky J, Warrell J, Emani P, Yang YT, Galeev T, Kong X, Liu S, Li X, Krishnan J, Feng Y, Rivera-Mulia JC, Adrian J, Broach JR, Bolt M, Moran J, Fitzgerald D, Dileep V, Liu T, Mei S, Sasaki T, Trevilla-Garcia C, Wang S, Wang Y, Zang C, Wang D, Klein RJ, Snyder M, Gilbert DM, Yip K, Cheng C, Yue F*, Liu XS*, White KP* & Gerstein M*. "An integrative ENCODE resource for cancer genomics." ***Nature Communications***, 2020; 11(1):1-11
5. **Cao Q**, Anyansi C, Hu X, Xu L, Xiong L, Tang W, Mok MTS, Cheng C, Fan X, Gerstein M, Cheng ASL & Yip KY. "Reconstruction of enhancer-target networks in 935 samples of human primary cells, tissues and cell lines." ***Nature Genetics***, 2017; 49(10):1428-1436.

Expertise

- ✧ Reconstruction of gene regulatory networks by machine learning models
- ✧ Analysis of multi-omics data and 3D genome structures
- ✧ Development of bioinformatics algorithms, pipelines and tools

Bridging graph embedding and biological networks in the study of gene regulation

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Graph embedding methods have been applied widely in modeling complex networks in recent years. Given a network and an induced similarity function between its nodes, the goal is to find a low dimensional representation of the network nodes so that the given similarity is preserved as much as possible. The successful applications in social networks, recommendation systems and knowledge graphs have inspired researchers to begin to apply the techniques in biological networks. Previous studies attempting to model the quantitative relationships between gene expression levels and regulatory mechanisms have considered only one or a few mechanisms at a time, which cannot provide a full picture of the complex interactions among different mechanisms. In this talk, I will introduce our recently published work on a flexible graph embedding framework that can integrate very different types of data for studying their joint effects on gene expression. We demonstrate the use of our framework in integrating several diverse types of data that are related to gene expression in different ways, including DNA contacts in three-dimensional genome architecture, protein-protein interactions, genomic neighborhoods and broad chromatin accessibility domains. The modeling results reveal that these several types of data are able to model gene expression fairly well individually, but even better when integrated. I will also introduce the extension of our model in two ongoing projects related.

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