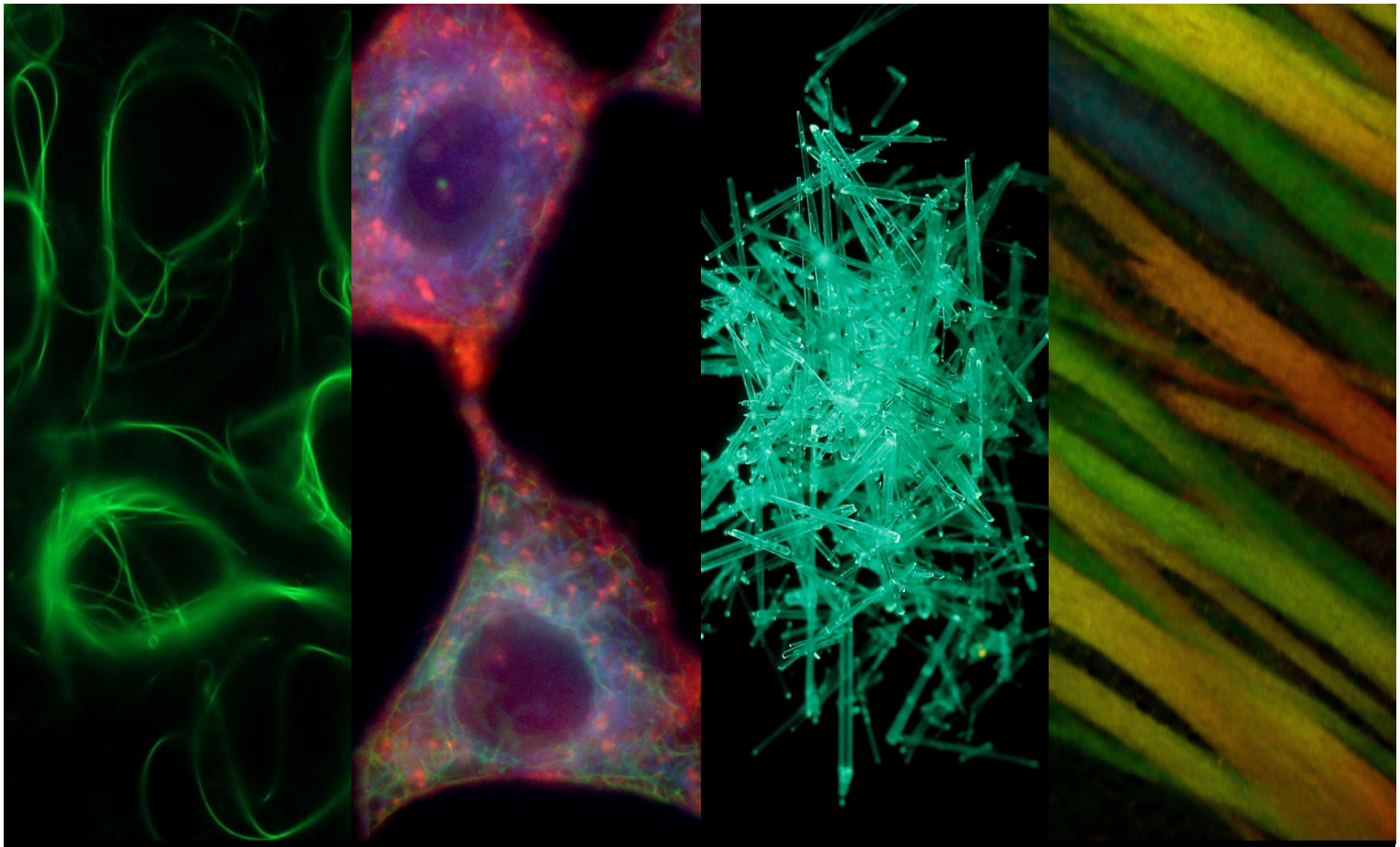

Ming Wai Lau Centre for Reparative Medicine

Karolinska Institutet

COVER PHOTO
Research images of Drs Sijie Chen and Linxian Li's teams.

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A Word from the Director

Karolinska Institutet (KI) has a strong tradition of collaboration and international interactions. KI's research centre in Hong Kong is a continuation of this tradition, representing an inter- and multi-disciplinary approach in biomedical science that brings together scientists with different backgrounds and expertise to solve complex problems in reparative medicine. KI has welcomed the exciting opportunity to create a branch in Hong Kong.

With one node in Hong Kong and one in Stockholm, Karolinska Institutet Ming Wai Lau Centre for Reparative Medicine (MWLC) offers a unique, collaborative environment for research in one of the most rapidly evolving fields with translational implications. A key component of MWLC's research is related to the development of frontline technologies such as imaging and tracing technologies, tissue engineering, next-generation sequencing, single-cell genomics, CRISPR gene editing and mRNA delivery systems to be used in various domains of reparative medicine.

To promote a policy of transparency about research quality assessment, career development and recruitments, we have established an International Scientific Advisory Board (SAB) consisting of highly recognized researchers, and a Local Reference Group (LRG) with prominent representatives of six universities in Hong Kong. Both the SAB and LRG have been instrumental in shaping further the Centre's research profile and in reinforcing local scientific interactions, bringing us even closer to the academic community in Hong Kong.

Working jointly across borders is a central part of cutting-edge research and scientists select partners based on quality rather than geography. By choosing Hong Kong, KI has selected a unique city with commitments to biomedical research, technology, and innovation. The establishment of MWLC meets the needs of scientists by providing a focal point for international collaborations in a challenging research area that requires synergistic cooperation to ensure that all the global considerable investments and efforts will result in great public health achievements.

Sandra Ceccatelli, MD PhD, is a specialist in Child Neuropsychiatry and Professor of Neurotoxicology at the Department of Neuroscience, KI. Her research focuses on the effects of early life adverse events on the developing brain with emphases on long-term neurodevelopmental and emotional-behavioral outcomes. Prof Ceccatelli has served as Chair of Department of Neuroscience and Director of StratNeuro, the Strategic Research Area Neuroscience including KI, Umeå University and the KTH Royal Institute of Technology. In November 2018 she was appointed Director of MWLC.

Prof Sandra Ceccatelli
Director

Vision and Mission

Vision

As part of Karolinska Institutet, the vision of Ming Wai Lau Centre for Reparative Medicine is to significantly contribute to the improvement of human health by conducting cutting-edge research in reparative medicine and related subjects.

Mission

Reparative Medicine is a rapidly expanding area of biomedical research and clinical practice. The realization of reparative medicine requires interdisciplinary expertise and collaborations of institutions and countries.

Ming Wai Lau Centre for Reparative Medicine is established to significantly contribute to the improvement of human health by conducting cutting-edge research in stem cell processing, biomedical engineering, biotechnology, regenerative medicine and precision medicine at Karolinska Institutet (KI), by creating a new platform for synergies between the academia and innovation in Sweden and Hong Kong and fostering future leaders in both the academia and industry.

By building a frontline technology-focused hub in Hong Kong, KI aims to strengthen the interactions with the Hong Kong and Mainland China scientific communities to further contribute to the progress of this research field and its implementation into medical innovation, with emphasis on the following:

1. Creating a technology hub and a KI platform for collaborations with leading local and international institutions, training junior scientists and fostering next-generation science leaders.

2. Capturing the merits of locating on Science Park to create synergies with other Science Park research centres as well as those in local universities.

3. Serving as a "catalyst" for interactions among the academia, biotech industry and the society; facilitating translation of basic research into bedside application and commercialization, as well as inspiring further research in the field.

Achievement Highlights

>$10M*
Research Grants

Grants from Sweden and Hong Kong

Funding support for recruiting local and global research talents

>$2M*
Research Talent Fund

>110
Publications

Publications in international, peer-reviewed journals

Patents pending or granted for translational research and commercialisation

5
Patents

** Amounts shown in Hong Kong dollar.*

Corporate Spin-off

Innorna (HK) Co., Limited

Dr Linxian Li founded Innorna in 2019, a pioneer developer of new therapeutic vaccines in Hong Kong and Mainland China. The company was listed as the 50 most innovative companies, titled "50 Smartest Companies", by MIT Technology Review in 2020. Innorna has raised HK$ 350 Million so far to develop mRNA vaccines and mRNA therapeutics. It is planning to start Phase I clinical trial on mRNA vaccine against Covid-19 Delta plus variant. The current pipeline includes three prophylactic mRNA vaccines, two mRNA drugs for cancer immunotherapy and one mRNA drug for genetic disease.

Awards and Recognition

- *Dr Linxian Li named to the list of MIT Technology Review Innovators Under 35 China*
- *Prof Gonçalo Castelo-Branco awarded the Anniversary Prize of Swedish Society for Medical Research*
- *Prof Gonçalo Castelo-Branco double rewarded by the Knut and Alice Wallenberg Foundation*
- *Dr Simon Elsässer appointed as one of the 7th generation of Future Research Leaders by Swedish Foundation for Strategic Research*
- *Prof Gonçalo Castelo-Branco awarded the Eric K. Fernström Prize 2020*
- *Dr Simon Elsässer awarded the European Research Council Proof of Concept Grant 2020*
- *Dr Simon Elsässer awarded the 2020 grant from IngaBritt och Arne Lundbergs Forskningsstiftelse*
- *Dr Ning Xu Landén won the LEO Foundation Award in Region EMEA*
- *Dr Simon Elsässer awarded the KI Consolidator grant 2020*
- *Prof Gonçalo Castelo-Branco awarded the Göran Gustafsson Prize 2021 in Medicine*

An International Research Centre Bridging Sweden and Hong Kong

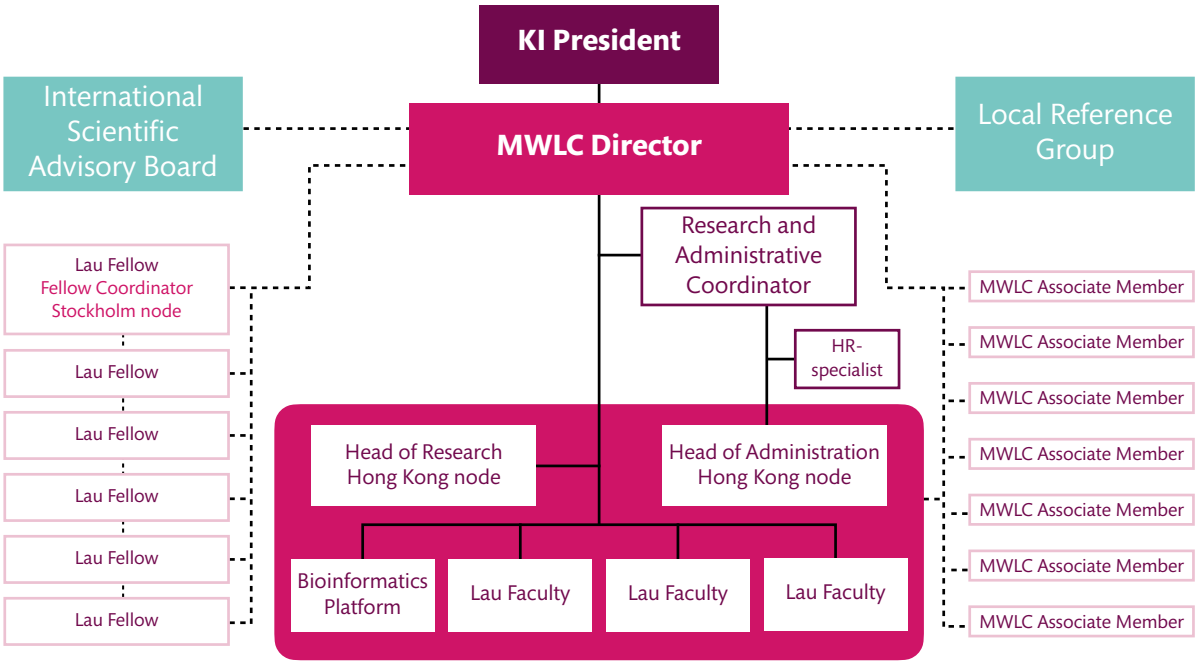
Karolinska Institutet (KI) of Sweden is one of the world's leading medical universities. KI strongly believes that acting on an international arena will contribute to the realization of the shared vision of improving human health. Ming Wai Lau Centre for Reparative Medicine (MWLC), KI's first establishment outside Sweden, and made possible with a generous donation from Mr. Ming Wai Lau, was inaugurated in 2016 and became operational in spring 2017. MWLC has since then played a part in furthering KI's vision by connecting with universities in Hong Kong, Mainland China and beyond.

As part of KI's internationalization strategy, MWLC has strengthened in-depth research collaborations and synergistic partnerships with leading universities in Hong Kong, building on previous and new memoranda of understanding signed between KI and The Chinese University of Hong Kong (CUHK), City University of Hong Kong (CityU), The University of Hong Kong (HKU) and The Hong Kong University of Science and Technology (HKUST). In 2018, MWLC launched the Associate Member Programme to connect outstanding scientists in Hong Kong universities with the Centre's researchers through jointly funded projects. HKU and HKUST granting honorary appointments to our researchers, and MWLC associating collaborators for cross-lab activities are also examples of the Centre's commitment to the Hong Kong scientific community.

MWLC has two nodes, one in Hong Kong based in Hong Kong Science Park and one in Stockholm, currently with four and six research teams, respectively with different expertise in reparative medicine. The Hong Kong node has developed a biotechnology-engineering profile exploring novel technologies, including next-generation sequencing, single-cell genomics, CRISPR gene editing, protein engineering, tissue engineering, 3D bioprinting, 3D tissue imaging technologies, and mRNA delivery systems applicable to reparative medicine. To enforce the technology hub, MWLC appointed Professor Dongan Wang of CityU in 2020 as the Centre's Head of Research.

The research of the Stockholm node aims at establishing leading-edge technologies as well as unravelling the biology behind organ development and damage, with the final objectives of understanding how tissue repair is best done and treatment of human diseases improved.

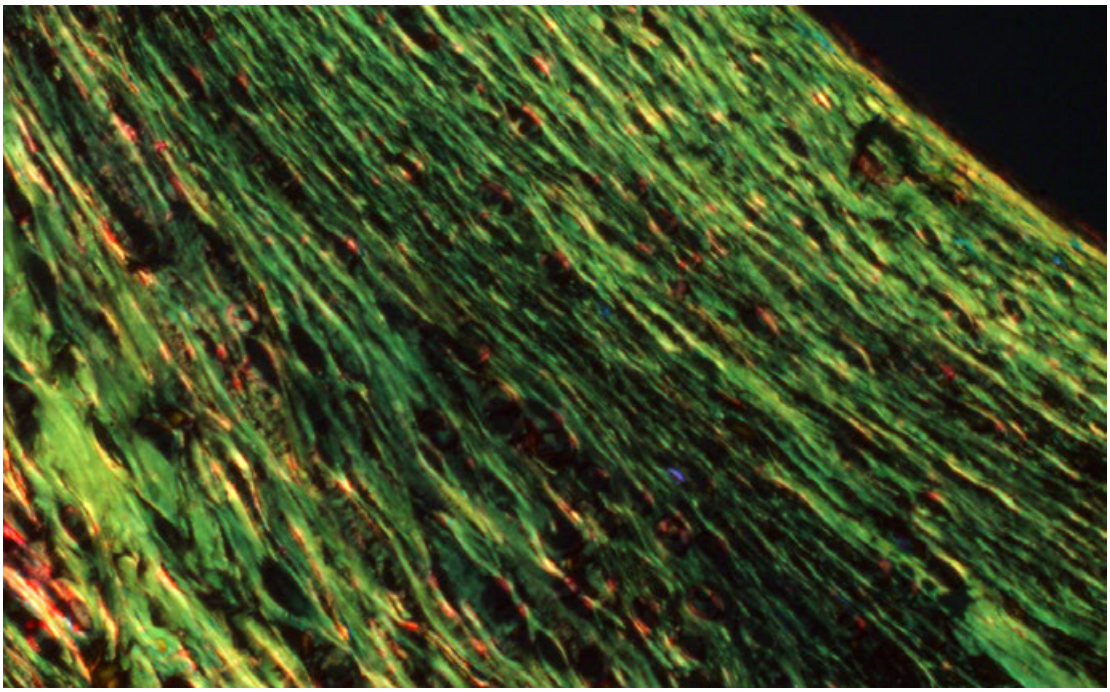
MWLC researchers and collaborators from both nodes are supported by an overarching bioinformatics platform that provides highly specialized bioinformatic analysis with expertise in single-cell genomics, epigenomics and other next generation sequencing-based methodologies.



MWLC Organisation Chart.

MWLC finances scientific meetings, symposia, postgraduate courses organized in both Hong Kong and Stockholm. Details regarding the research groups' focuses and achievements, as well as MWLC's key scientific development and activities are presented in this booklet.

Decellularized Man-made Hyaline Cartilage Graft for Cartilage Tissue Engineering by Prof Dongan Wang



Fluorescent immuno-scanning image of articular cartilage: The superficial layer anatomy revealing high purity and alignment of collagen type 2 (green) and chondrocytes (red) indicating hyaline cartilaginous phenotype. Photo: Dongan Wang.

The key challenge of lower-limb-joint osteochondral regeneration lies in restoration of the avascular articular cartilage. Articular cartilage repair has been a significant challenge due to the limited self-regenerative capability of cartilage tissue. A quality articular cartilage engraftment is validated by the graft's hyaline cartilaginous phenotype and genuine microstructural architecture. Current treatments are frequently reported to result in regeneration of mechanically inferior fibrocartilage. Professor Dongan Wang has developed novel methodology to directly set up a scaffold-free macro-scaled three-dimensional living hyaline cartilage graft (LhCG) with the aid of a biomaterial-based interim scaffolding system. The practical performance of allogeneic decellularized LhCG (dLhCG) is evaluated in the knees of large animal models with full-thickness chondral defects beyond critical sizes for substantial length of duration, from which sound regeneration of articular hyaline cartilage has been achieved, including the recoveries in form and function with correct composition, structure, phenotype and mechanical property. The success in these preclinical trials suggests the readiness of allogeneic dLhCG for clinical trials and applications.

Prof Wang's research focuses on biomaterials, tissue engineering, regenerative medicine and molecular pharmaceutics with specialties of functional biomaterials for tissue engineering and therapeutic cell delivery; nucleic acid delivery for therapeutic engineering; applications of stem cells for translational medicine; and engineered biomimetic tissue platforms for in vitro drug evaluation. Prof Wang has contributed over 150 research/scholarly publications. The journal publications include those published in Nature Materials, Advanced Functional Materials, etc., some of which are editorially quoted by Science, Nature Materials, etc. Prof Wang has been ranked as the Top 2% of the World's Most Highly Cited Scientists by Stanford University according to citations during 1996-2019 in own areas of specialty (Biomedical Engineering). Prof Wang is actively working on higher education in biomaterials, stem cell application, gene therapy and tissue engineering areas. He was awarded with Nanyang Award of Excellence in Teaching (2009) by Nanyang Technological University, Singapore.

Prof Wang is currently a Professor in Department of Biomedical Engineering, City University of Hong Kong (CityU). Before joining CityU, Prof Wang had been appointed, in turn, as Assistant Professor, Associate Professor with tenure, Associate Chair and Program Director of Bioengineering in School of Chemical & Biomedical Engineering, Nanyang Technological University, Singapore. Prof Wang is a Fellow of Royal Society of Chemistry (FRSC, UK). Since August 2020, Prof Wang has been appointed as the Head of Research at Ming Wai Lau Centre for Reparative Medicine, Karolinska Institutet, Hong Kong.

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Seeing is Believing – Fluorescent Probes

by Dr Sijie Chen

Optically cleared mouse brain stained by a fluorescent probe developed in Dr Chen's lab. The probe selectively stains the myelinated structures in the brain tissue. The color represents z-depth. Photo: Alex Wong.

The best way to unveil the mystery of life is to make the biological targets and events visible. Biomolecules and cells are usually too small, and with signals too weak to be observed. Abnormal cellular microenvironments often lead to diseases, but remain invisible until reaching advanced stages when the damages done are already irreversible. Therefore, the development of tools and techniques for visualising various biological targets and for evaluating the intracellular as well as extracellular environments is of great academic and translational significance.

Fluorescence, a dominant methodology used extensively in biology, offers high sensitivity and spatiotemporal resolution to visualise biological events on site and in real time. Fluorescent probes light up the molecules of interest, or show light signal changes (e.g. colour change, intensity change) for tracking biological events. As such, fluorescence-based methodology is widely used in both biological studies and clinical diagnosis, helping scientists and surgeons to track stem cells, image tumours and detect disease-related biomarkers, etc.

Dr Chen's lab is particularly interested in developing novel fluorescence-based tools and techniques for visualising cell structures to understand how these biological fundamental building blocks work and how they intriguingly interact with each other in response to the environments. These tools and techniques are important for regenerative biology and cancer biology, and collectively serve as the basis for developing novel diagnostic methods and therapeutic approaches for various diseases.

Dr Chen has collaborations with Dr Linxian Li and other investigators in Hong Kong, Mainland China, Sweden, and Australia, including Prof Alfonso Ngan (HKU), Prof Ben Zhong Tang (HKUST), Dr Puxiang Lai (PolyU), Dr Weiping Wang (HKU), Dr Xin Zhao (PolyU), Prof Li-li Li (National Center for Nanoscience and Technology, China), Dr Ning Xu Landén (KI), Dr Yuning Hong (La Trobe University) and Prof Treavor Smith (University of Melbourne). These inter-institutional research teams with complementary expertise in chemistry, biology, bioengineering, material science, bioimaging and physics work closely on developing novel imaging and sensing techniques.

Dr Chen received her BSc in Biology from Wuhan University, China in 2009 and PhD in Bioengineering from HKUST in 2013. She worked as a Postdoctoral Fellow in HKUST and then as an Endeavour Fellow in University of Melbourne, Australia and a visiting scientist in Walter and Eliza Hall Institute of Medical Research, Australia. She later joined Prof Ana Teixeira's group as a Postdoctoral Fellow at KI in 2015 before her recruitment to MWLC. Dr Chen has published more than 60 scientific papers, more than 20 of which were published after she joined MWLC and with the Centre's support.

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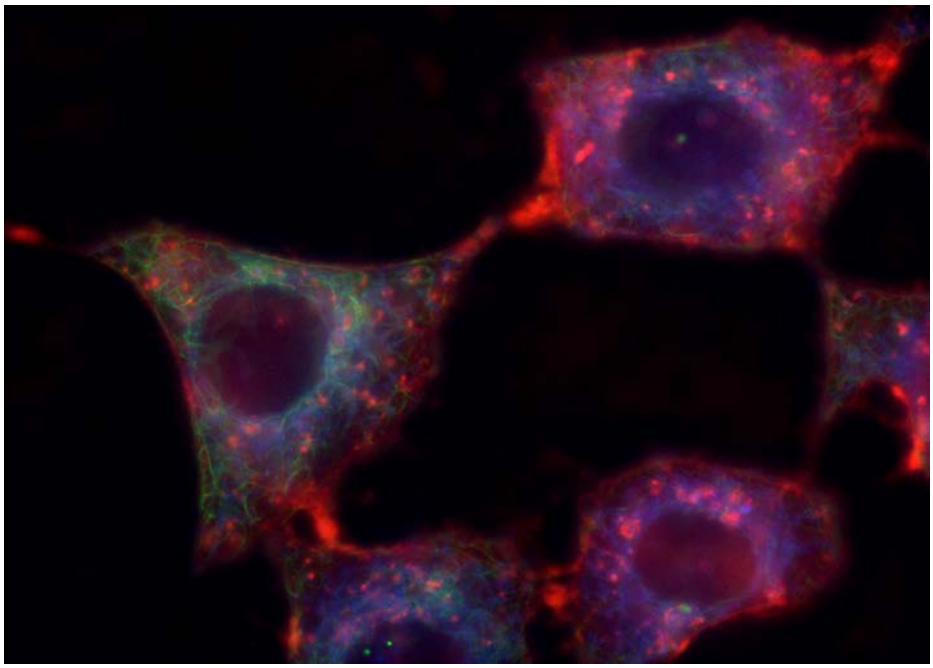
Engineering Advanced Biomaterials
by Dr Linxian Li



Machine learning-assisted cellular substructure staining by a structurally diverse fluorescent dye library. Photo: Yike Yang.

In gene and cell therapy, it is important to engineer the cells by delivering macromolecules, such as RNA, into the proper cells or engineer surfaces by utilising cell-biomaterials interactions to improve their functions. However, the rational design of biomaterials is often laborious and inefficient, since the design criteria are difficult to define. The lack of efficient and accurate tools has limited the development of novel biomaterials for innovative clinical treatment.

Dr Li's lab is dedicated to integrating the combinatorial biomaterials libraries, high-throughput screening and artificial intelligence to break the rate-limiting steps in preclinical research and accelerate the development of biomaterials for clinical therapy. The goal is to develop innovative technology platforms to find the ideal biomaterials for the cell of interest and accelerate the development of novel biomaterials for global healthcare challenges. With a focus on technological advancement, Dr Li and his team are developing new biomaterials for RNA and cell therapeutics.

Dr Li is a biomedical engineer with interdisciplinary expertise in organic chemistry, molecular biology, materials science, and bioengineering. After obtaining his PhD at Heidelberg University, Germany in 2014, he pursued postdoctoral research with Prof Robert Langer at Massachusetts Institute of Technology (MIT), Boston, USA, from 2014-2017. Committed to translating new materials for medical use, Dr Li focuses on developing biomaterials to deliver RNA therapeutics and engineering biomaterials to control cell behaviour. His work has resulted in over 20 publications including papers, patents and patent applications. These patents have been licensed to chemical and biotechnology companies, and several products have been commercialised.

Dr Li is named to the list of MIT Technology Review Innovators Under 35 China in 2017. He is listed as a pioneer for exploring the therapeutic potentials of human messenger RNA (mRNA). These molecules are a new class of drugs that can direct cells in the human body to make proteins to prevent or fight diseases, which can potentially replace the current recombinant proteins and monoclonal antibodies. The major challenge limiting the clinical use of mRNA as therapeutics is the inefficient delivery. The platforms Dr Li developed can rapidly and accurately identify the clinical biomaterials candidate for efficient and safe *in vivo* mRNA delivery, and he has founded Innorna to develop mRNA therapeutics for clinical use.

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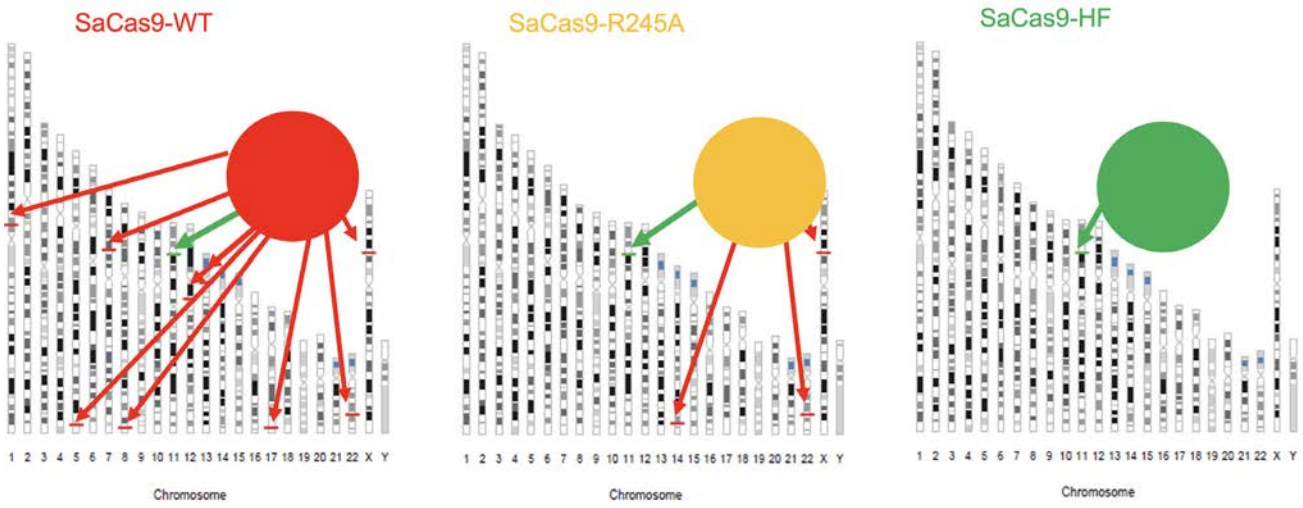
Precise Genome Reparation
by Dr Zongli Zheng



Precise genome targeting. Photo: Zongli Zheng.

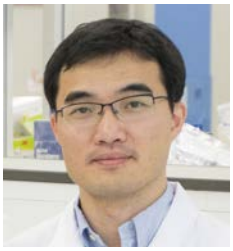
Gene rearrangements can occur in physiological states to create immune diversities in T- and B-cell receptors, as well as in pathological states such as causing cancers. Furthermore, cellular gene rearrangement functions can be exploited for technology tool uses to repair genome following CRISPR-induced DNA double strand breaks.

Adaptive immunity is one of the two main immune defense strategies found in vertebrates. The adaptive immune system is highly adaptable because of somatic hypermutation and V(D) J recombination. This gene rearrangement mechanism allows a small number of genes to generate a vast number of different antigen receptors expressed on lymphocytes. The advances in the next-generation sequencing technology has facilitated high-resolution studies of lymphocyte dynamics along with adaptive immunity. Dr Zheng has developed novel next-generation sequencing technologies and computational algorithms that have been adopted globally for molecular diagnosis of gene rearrangement in cancer patients. Based on single-cell and the powerful gene rearrangement technologies, Dr Zheng's lab is interested in characterizing dynamics of adaptive immunity in aging related disorders. Further, the team is interested in developing new technologies for genomic characterisation and genome-wide functional screening to identify biomarkers and therapeutic targets for aging diseases.

Numerous diseases are rooted in the genetic abnormality at the DNA level. The genetic defects may be inherited from parents or acquired due to environmental stimuli. New technologies like cell manipulation using CRISPR gene editing tools allow one to perform "microsurgery" to repair DNA anywhere in the genome with a great ease, and the modification can be passed down to new cell generations. Hence, this technology holds great promises for the treatments of a variety of diseases. However, the tool is not yet precise enough, limiting its use both in research, where confounded results may arise from off-target edits, and in clinical applications where safety is of paramount importance. Furthermore, in contrast to gene knock-out, gene reparation to restore gene functions following CRISPR editing still suffering for high proportions of undesired editing outcomes. Dr Zheng's lab is interested in developing new technologies for assessing and refining CRISPR gene editing off-target changes in the genome, and to improve desired editing outcome during gene reparation to restore normal gene functions.

Dr Zheng's lab has established collaborations with Drs Mingfang Ji (Zhongshan People's Hospital, China) and Juxiang Chen (Shanghai Changhai Hospital, China), Dr Zhiwei Liu (NIH, USA), Prof Gonçalo Castelo-Branco, Drs Fredrik Lanner, Fang Fang and Weimin Ye from KI, Prof Anderson Shum (HKU), Drs Alan Wong (HKU), Wenjun Xiong (CityU) and Kai Liu (HKUST) from Hong Kong.

Dr Zheng received his PhD degree from KI in 2011 and completed postdoctoral training in Harvard Medical School, Boston, USA. Dr Zheng has developed novel technologies and computational algorithms for molecular diagnostics. The simple and robust diagnostics method named AMP, after initial implementation in top U.S. hospitals (MGH, MSKCC), has been adopted globally in both research and clinical settings, and has helped accelerate recent FDA approvals of new targeted therapies. Dr Zheng has published about 40 original articles that have been cited, in the past 5 years, more than 10,000 times.



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Tackling Multiple Sclerosis One Cell at the Time

by Prof Gonçalo Castelo-Branco

Decoding epigenomic information from individual cells from the mouse brain. Histones are attached to DNA as beads on a string, with different versions decorating the genome as "epigenetic stickers", labelling which genes are turned on or off. The method single-cell CUT&Tag allows to examine tens of thousands of single cells at the same time to determine their histone profiles. Illustration: Amagoia Agirre.

Oligodendrocytes insulate neuronal axons through their myelin containing membranes. Myelin allows the fast and efficient impulse transmission between neurons through saltatory conduction and is important for axonal integrity, thereby being essential for the proper functioning of the central nervous system. Several diseases, such as multiple sclerosis (MS), are characterized by abnormal or defective myelination. Spontaneous remyelination occurs at initial stages of MS, promoted by endogenous oligodendrocyte precursor cells (OPCs). However, this process progressively starts occurring with less efficiency, until it eventually fails.

All cells in a given organism are derived from a single cell (zygote) and thereby share an identical genome. Additional layers of epigenetic information overlaid on the genome achieve the plethora of cellular phenotypes present in development and in the adult body. This epigenetic information is stored at the level of chromatin, the complex where nuclear DNA is packaged together with histones. DNA methylation and post-translational modifications at histones define the epigenetic state of a cell and ultimately cell fate, by controlling key processes, including transcription. Non-coding RNAs have also emerged recently as key regulators of chromatin and cell fate.

The epigenetic and transcriptional states of oligodendrocyte lineage cells define their ability to remain as a precursor cell, differentiate and produce myelin or even de-differentiate into a stem cell state or a glioma initiating cell state. The main focus of Prof Castelo-Branco's research group is to investigate how distinct epigenetic/transcriptional states within the oligodendrocyte lineage are established, by identifying key transcription factors, chromatin modifying complexes and non-coding RNAs that are involved in epigenetic transitions, using technologies such as RNA-Seq (single-cell and bulk), quantitative proteomics and epigenomics, among others. The long term aim of this research group is to design epigenetic based-therapies to induce regeneration (remyelination) in demyelinating diseases, such as MS. Prof Castelo-Branco's lab has performed single-cell transcriptomics and epigenomics identified several cell states within the oligodendrocyte lineage in development and disease (Science 2015, Science 2016, Dev Cell 2018, Nature Medicine 2018, Nature 2019, Nature Communications, 2020, Nature Biotechnology 2021). His lab has generated several web resources from their single-cell omics datasets, compiled in the OligoInternode interface (https://ki.se/en/mbb/oligointernode), where one can enter a gene of interest and investigate its expression pattern in the identified oligodendrocyte lineage populations/states or determine how specific genes of interest are differentially expressed.

Prof Castelo-Branco received his PhD in Medical Biochemistry, KI in 2005. He completed post-doctoral fellowships first at KI and then at University of Cambridge, UK. Prof Castelo-Branco started his research group in 2012 and is a Professor of Glial Cell Biology at the Department of Medical Biochemistry and Biophysics at KI. He has received many prestigious awards and grants, including the European Research Council Consolidator Grant, Swedish Society for Medical Research Jubileum Prize and Knut, Eric K. Fernström prize 2021, Göran Gustafsson Prize in Medicine and Molecular Biology 2021 and Alice Wallenberg Foundation grant for high scientific potential.

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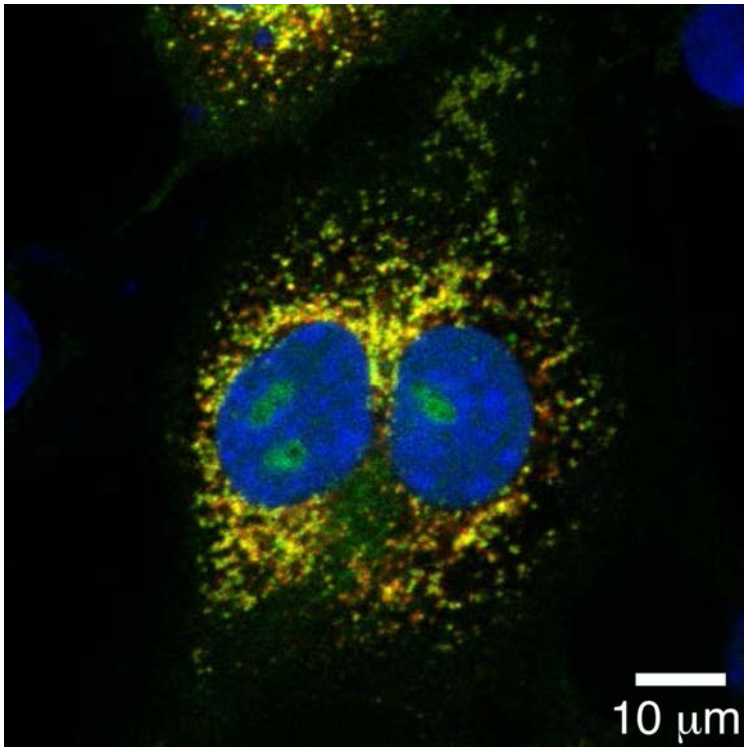
Function of Peptides Encoded by Short Open Reading Frames

by Dr Simon Elsässer



PIGBOS1, a short open reading frame encoded peptide labeled with a synthetic amino acid that allows subsequent attachment of a fluorescent label (green) and HA-tag (red) on mitochondria of live human cells (Lafranchi et. al., 2020, JACS).

Genetic code expansion in mammalian cells: Dr Elsässer and his co-workers are developing technologies for genetic code expansion and noncanonical amino acid mutagenesis in mammalian cells, providing novel ways to probe or control proteins in living cells. At MWLC, his lab is using the technology to understand cell-to-cell communication in living organisms. The technology also provides opportunities for bioengineering and the development of advanced protein-based therapeutics, so-called 'biologicals'.

The small proteome: Dr Elsässer's lab is exploring fundamental biology of small proteins (microproteins) in the human proteome. Being small, fast evolvable, and more versatile in their biochemical and biophysical properties, microprotein may modulate processes that happen in cells, or mediate communication between cells or organs. Yet to date, few microproteins have been studied in detail, as technical limitations of detection and isolation hamper profiling their function at a global scale. The lab is using high-throughput genetic screening to identify functional microproteins encoded in the human genome, focusing on mouse and human development. He leverages his genetic code expansion technology together with imaging and proteomics approaches to elucidate their function.

Quantitative genome biology: Dr Elsässer's lab studies gene regulatory mechanisms that govern pluripotency, lineage commitment and differentiation in early mammalian development using quantitative methods. Combining precise, chemical control of proteins with quantitative proteomic and genomic readouts allows them to dissect dynamic processes involved in DNA metabolism, gene regulation and cellular signaling. Collaborations at MWLC explore epigenetic regulation of early human development (Dr Fredrik Lanner) and single-cell epigenomics (Prof Gonçalo Castelo-Branco).

Dr Elsässer read Biochemistry at Tübingen University before joining the Graduate Program in Bioscience at Rockefeller University in 2007. He was a Junior Research Fellow at MRC Laboratory of Molecular Biology in Cambridge from 2012 and joined Karolinska Institutet as a SciLifeLab Fellow in 2015.

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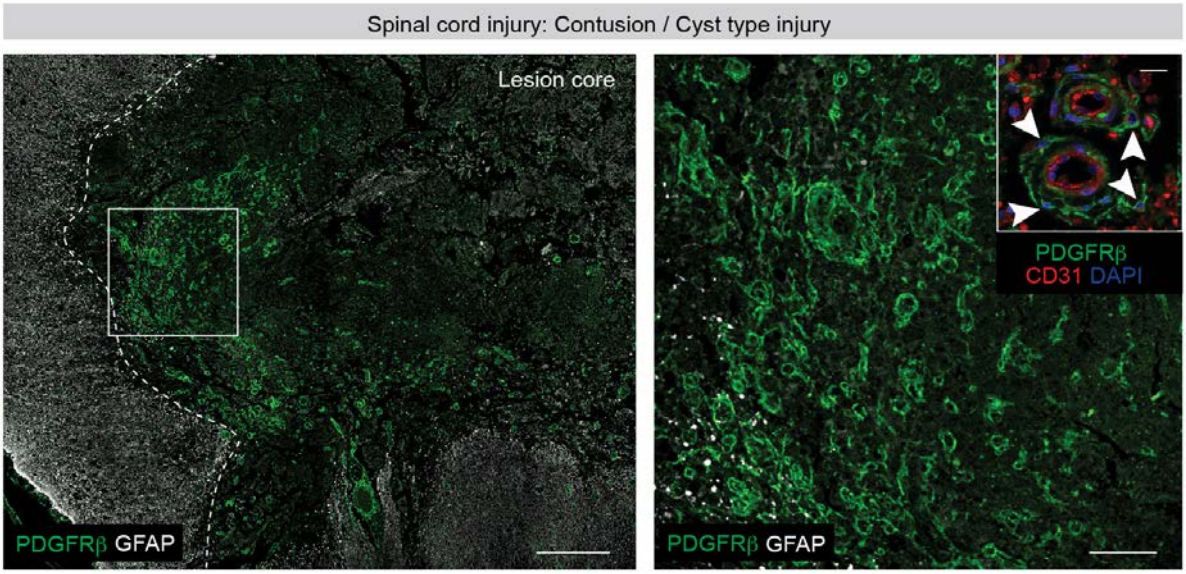
Repair of Central Nervous System Lesions
by Dr Christian Göritz



After an injury, fibrotic scar tissue forms in the human spinal cord (Dias el al., 2021, Nature Comm.).

The healing ability of the central nervous system is very limited and injuries to the brain or spinal cord often result in permanent functional deficits. In many organs, damaged tissue can be repaired by generating new cells of the type that were lost. However, after an injury to the central nervous system, a special type of scar tissue is formed which inhibits this regeneration. Injuries to the brain and spinal cord therefore often lead to permanent loss of functional ability.

It was recognised more than a century ago that nerve fibres of the central nervous system fail to grow through the scar tissue that forms at a lesion. However, this scar tissue is a complex mesh of different cell types and molecules, and it has been unclear exactly how the scar tissue blocks nerve fibre regrowth. The research group of Dr Göritz investigates the origin of scar forming cells, the mechanisms of scar formation and explores possible therapeutic interventions to improve functional recovery.

Dr Göritz and his co-workers identified an important mechanism explaining how scar tissue inhibits nerve fiber regeneration after an injury. They found that a very small population of cells lining blood vessels, which gives rise to a large part of the scar tissue, inhibits nerve fiber growth after a spinal cord injury. When they inhibited scar formation by the blood vessel-associated cells, some nerve fibers could regenerate and reconnect with their targets. This resulted in improved functional recovery after spinal cord injury in mice.

"Our findings give an important explanation as to why functional recovery is so limited following injury to the central nervous system," says Dr Christian Göritz, Associate Professor at the Department of Cell and Molecular Biology and Lau Fellow at MWLC, KI. Recently, Dr Göritz and colleagues compared 10 different central nervous system lesion models in mice and 4 pathologies in humans and showed that fibrotic tissue formation is conserved throughout the central nervous system as well as in mice and humans. In all cases in which fibrotic tissue is formed, a discrete subset of perivascular cells (type A pericytes) is the main source.

Further studies are now needed to explore whether this knowledge can be used to promote recovery following injury to the central nervous system in humans. For this Dr Christian Göritz is establishing close collaborations with Dr Linxian Li (MWLC) and other investigators in Hong Kong, including Dr Kai Liu (HKUST).

Dr Göritz studied Biochemistry in Berlin, Germany. He performed his PhD studies in Strasbourg, France, in a joint Max Planck / CNRS research environment in the field of Neuroscience. For his postdoctoral training, he joined the lab of Prof Jonas Frisén at KI. In 2012 Dr Göritz established his own research group. He is currently an Associate Professor at the Department of Cell and Molecular Biology, KI.

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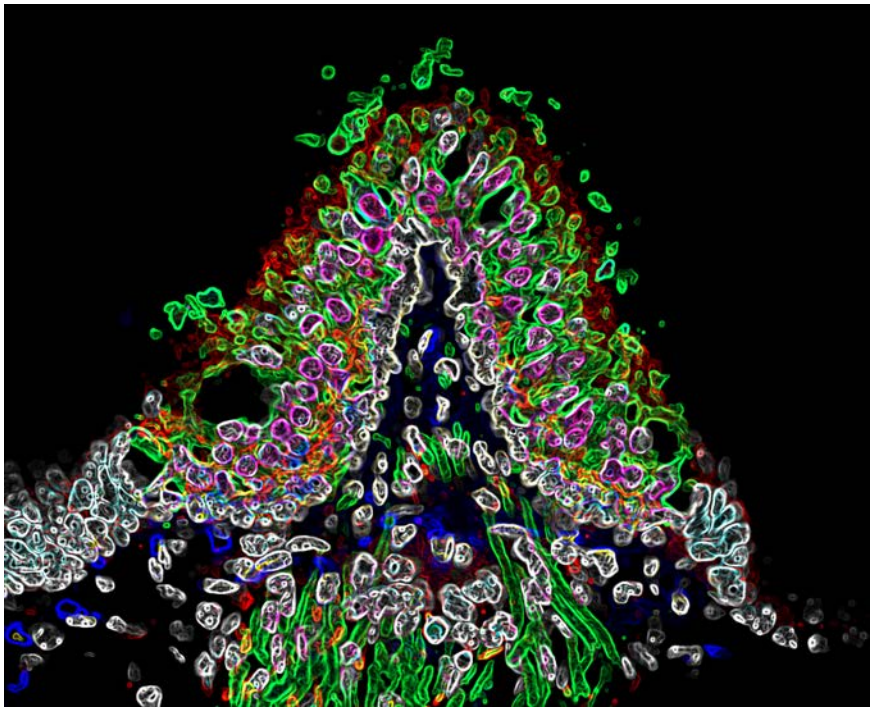
Sensory Systems – Development, Function and Plasticity

by Dr Francois Lallemend



Crista ampullaris of a mouse vestibular system. Photo: Paula Fontanet.

Dr Francois Lallemend and his research group is interested in understanding the molecular principles underlying neuronal diversification and plasticity in the peripheral sensory system.

Sensory systems are necessary in every instant of our life by providing the fundamental link between our physical and biological environments and both our physiology and behavior. Sensory experiences also affect our social cognitive processing and that defects in peripheral sensory processing can be linked to cognitive decline, dementia, anxiety, or social interaction deficits. So, not only our senses are necessary for interacting with our environment, but they also have a great influence on our psychic and the way we interpret the world around us. It is no surprise then to see that most of our central nervous system is devoted to the integration and processing of sensory information.

Work in his lab is focusing on characterizing the development and functional organization of sensory systems, and how particular break down in their individual functional parts can lead to sensory disorders. Dr Lallemend's lab is using a genetic approach to identify the different neuronal elements that transmit sensory information and use advanced technologies to deconstruct the molecular events that participate in their development and in their function in adult. They have also observed that the genetic traits that define the myriad sensory neuron types in the adult can change upon modifications of the neuronal environment, during ageing or following exercise training for instance. Dr Lallemend is therefore very interested in understanding whether such changes in the molecular identity of sensory neurons have a critical role in sensory performance, and whether one can develop new molecular strategies for restoring or improving sensory perception in the clinical setting.

Dr Lallemend received his PhD at the GIGA Neuroscience, in Liege, Belgium in 2005, followed by postdoctoral research at the Department of Medical and Biochemistry and Biophysics, KI from 2006 to 2010 working on neural crest cell lineage. Dr Lallemend established his research group in 2011, and was recruited to the Department of Neuroscience, KI in 2013, where he heads the lab of neuronal specification and connectivity since then. Dr Lallemend is an Associate Professor at the Department of Neuroscience, KI, and a Wallenberg Academy Fellow.

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Decoding the Regulome of Human Skin Wound Healing

by Dr Ning Xu Landén

'Healing blossom'. Color pencil art by Dr Xi Li, the first PhD student from Xu Landén lab, 8th February 2019.

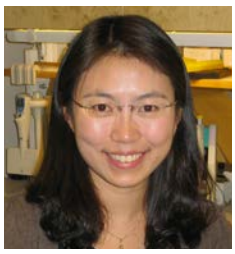
Single-cell RNA sequencing analysis of human skin wounds. Each dot represents one cell, and cell types are indicated with colors. Photo: Ning Xu Landén.

Chronic non-healing wounds are a common and severe medical problem lacking efficient treatments. They are trapped in a constant inflammatory state and fail to progress through the normal stages of wound healing. Although constituting the majority of the transcriptional output of the human genome, the functional importance of non-protein-coding RNA (ncRNAs) has only recently been recognized. Compared to protein-coding genes, ncRNAs' expression and function are more tissue- and cell-type-specific, underscoring their great potential as precise therapeutic and diagnostic entities.

Dr Xu Landén's research aims to understand the role of ncRNAs in the skin immune system in response to injury and identify ncRNAs capable of resolving chronic wound inflammation and reactivating the healing program. For this, her research team is making efforts to (i) establish a gene expression map of human acute, and chronic wounds with single-cell resolution; (ii) identify the biological functions and the underlying molecular mechanisms of wound-related ncRNAs; (iii) develop RNA-based wound treatments. From a new angle, their study will add to our understanding of wound biology and chronic wound pathogenesis, which will open new avenues for disease stratification and highlight novel drug targets for clinical studies.

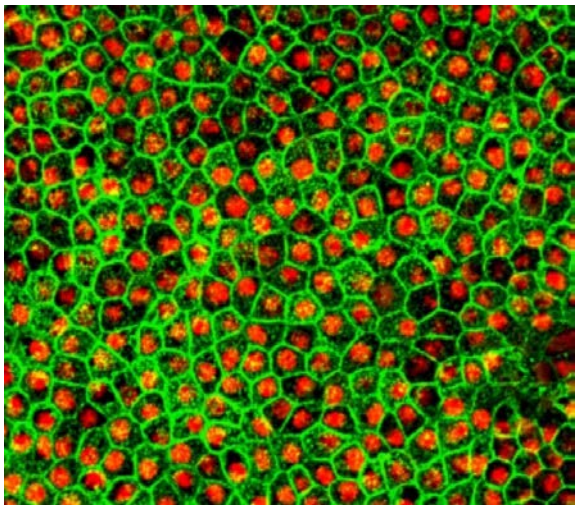
To achieve the goals of this multidisciplinary project, Dr Xu Landén's team collaborates with many investigators with different expertise, including Drs Sijie Chen, Alan Siu-Lun Wong, Virpi Ahola, and Shangli Cheng at MWLC.

Dr Xu Landén received her PhD in Medical Virology from Uppsala University, Sweden, in 2008. She worked from 2009 to 2013 as a Postdoctoral Fellow in Prof Mona Ståhle's group at KI. Dr Xu Landén started her research group in 2014 focusing on skin wound healing and has been an Associate Professor at the Department of Medicine Solna, KI, since 2017. In addition to the MWLC Lau Fellow grant in 2016, she is a Ragnar Söderberg Fellow 2015 and recipient of the LEO Foundation Award 2020 that recognizes young skin researchers with high scientific potential.



For further information, please contact **Dr Ning Xu Landén**, *ning.xu@ki.se*

Uncovering the Secrets of Early Human Embryo Development and Treating Blindness Using Embryonic Stem Cells by Dr Fredrik Lanner



Retinal pigment epithelial (RPE) cells manufactured for treatment of macular degeneration. In green is antibody staining for CD140b, a novel cell surface marker for RPE cells identified by the Lanner lab. Photo: Fredrik Lanner.

Embryonic stem cells, which are isolated from the human blastocyst, can be propagated indefinitely and directed to mature into virtually any cell type of the adult human, offering great potential for reparative medicine to replace lost or damaged tissues. However, we have a very superficial knowledge of how these early immature cells are established and controlled in the embryo. Better understanding of these cells will not only improve our possibilities in efficiently and safely mature them to clinically cell types but could also offer increase understanding of the causes of infertility.

The Lanner laboratory has mapped the first week of human development using single-cell mRNA sequencing and uncovered new insights into how the first cell types are established and when the equivalent of embryonic stem cells emerge (Petropoulos et al Cell 2016). They have further established novel markers of these immature pluripotent stem cells, which can be used to classify the stem cells into different developmental stages (Collier et al., Cell Stem Cell 2017). Through the use on primate embryo culture the lab has mapped post-implantation development up to gastrulation and identifies a role for ISL1 in the amnion, required for proper mesoderm induction (Yang et al Nature Communication 2021). The lab is currently investing much attention to synthetic stem cell based embryology and validation of embryo models (Posfai et al Nature Cell Biology 2021, Posfai et al Stem Cell Reports 2021, Zhao et al bioRxiv 2021). Together with Dr Simon Elsässer lab they have recently found that Polycomb repressive complex 2 shields human naïve stem cells from extraembryonic differentiation (Kumar et al bioRxiv 2021).

In order to use embryonic stem cells in reparative medicine the cells must be established under Good Manufacturing Practice (GMP). For this purpose the lab has derived a new line (KARO1) within the GMP manufacturing facility at Karolinska University Hospital. Another hurdle that needs to be addressed is the immunological barrier when transplanting allogeneic cells. For that reason the laboratory has explored the use of genome editing to evade the immune system by eliminating HLA presentation (Petrus-Reurer et. al., Stem Cell Reports 2020).

Finally, building on their established xeno-free and defined protocol to generate stem cell derived retinal cells (Plaza-Reyes et al 2016 Stem Cell Reports) they have identified cell surface markers for retinal pigmented epithelial cells and established a streamlined protocol for RPE differentiation (Petrus-Reurer et. al., Stem Cell Transl Med. 2020, Plaza Reyes et. al., Nature Communication 2020). They are now producing their clinical cell batch to initiate First Human Dose trial in 2022 in close collaboration with St. Erik Eye Hospital and Novo Nordisk to test our stem cell-based treatment strategy of age-related macular degeneration.

Dr Fredrik Lanner undertook his PhD studies at the Karolinska Institutet with focus on generating vascular cells from embryonic stem cells. He then joined Janet Rossants team at The Hospital for Sick Children in Toronto to study early mammalian biology where he identified the fundamental role of FGF signaling during the formation of pluripotent cells in the mouse blastocyst and embryonic stem cells. Returning to Karolinska Institutet in 2012 he initiated his own lab with focus towards human embryo development and stem cell based reparative therapies.

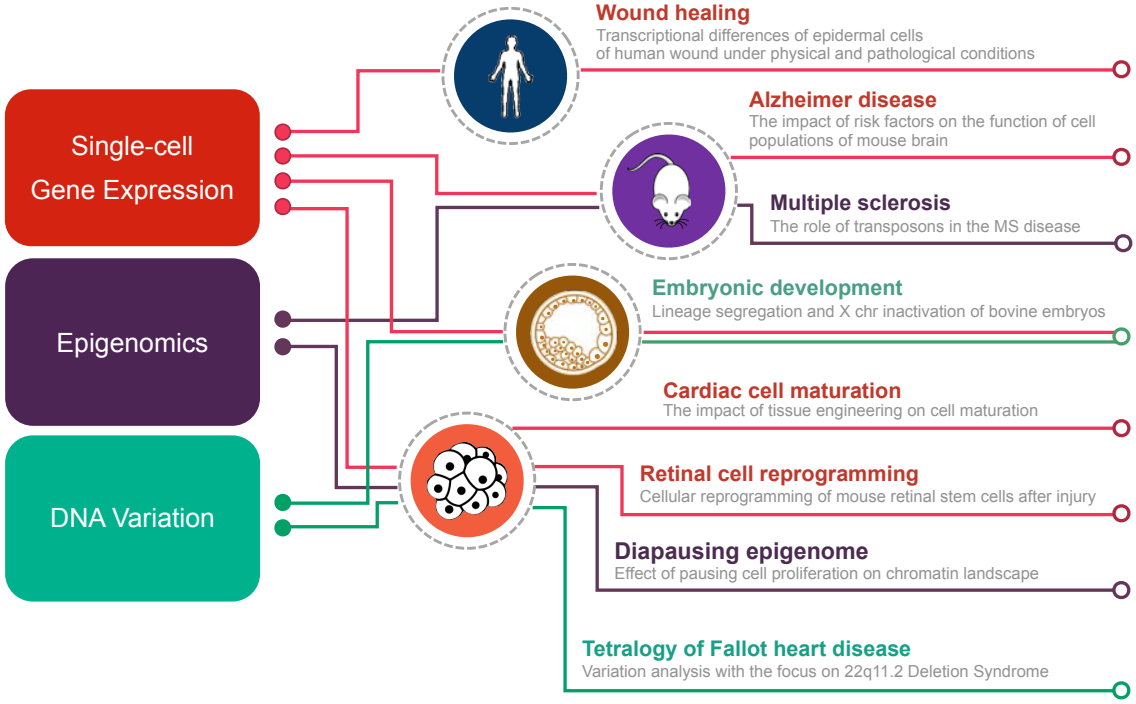
For further information, please contact
Dr Fredrik Lanner, *fredrik.lanner@ki.se*

Bioinformatics Platform

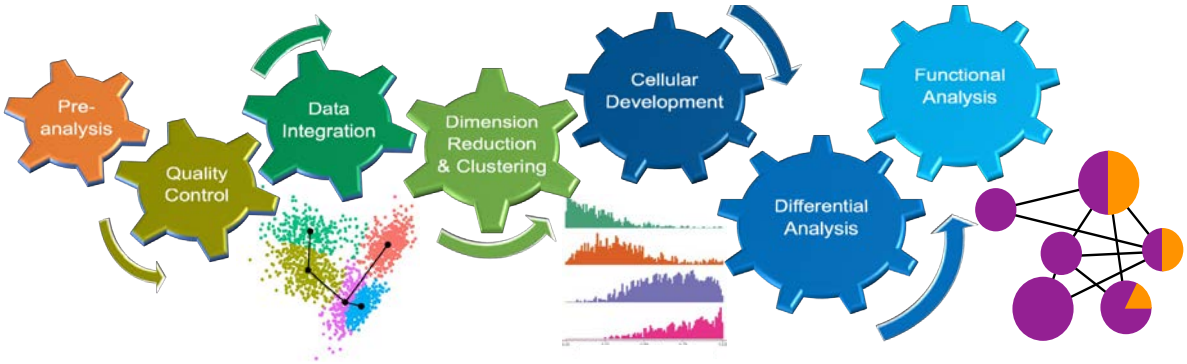
The Bioinformatics Platform, coordinated by Dr Virpi Ahola, offers expertise and networking possibilities to MWLC researchers and Associate Members, thus linking the Hong Kong and Stockholm nodes as well as the local universities. Scientists of the Platform provide computational support in the research areas of transcriptomics, genomics/epigenomics and systems biology. Research collaboration includes design of experiments, data management, modelling and visualisation of the research data as well as scientific writing. Support is also given in the form of consulting researchers in various bioinformatics-related questions. To promote knowledge exchange, the Platform organises seminars on bioinformatics methods and their applications in the biomedical and biotechnological fields.

The current projects of the Platform focus on the emerging topics in the areas of neuroscience, dermatology and stem cell-based research on heart diseases, and investigate fundamental questions of cell and molecular biology. For example, a deeper understanding of diseases is gained by comparing gene function between infected and control individuals using big data sets obtained from stem cell lines or tissues from mouse or human. Other applications focus on the discovery and analysis of DNA variants and epigenetic modifications. Such high-throughput data is typically generated using the most recent next-generation sequencing technology.

Currently the Platform is specialised in the analysis of single-cell level gene expression data, and integration of such data from different applications and data sources. For the analysis and visualisation of data, the Platform has developed computational pipelines and interactive applications. Diversity of methods applied at the Platform varies from machine learning to other state-of-the-art data science methods.

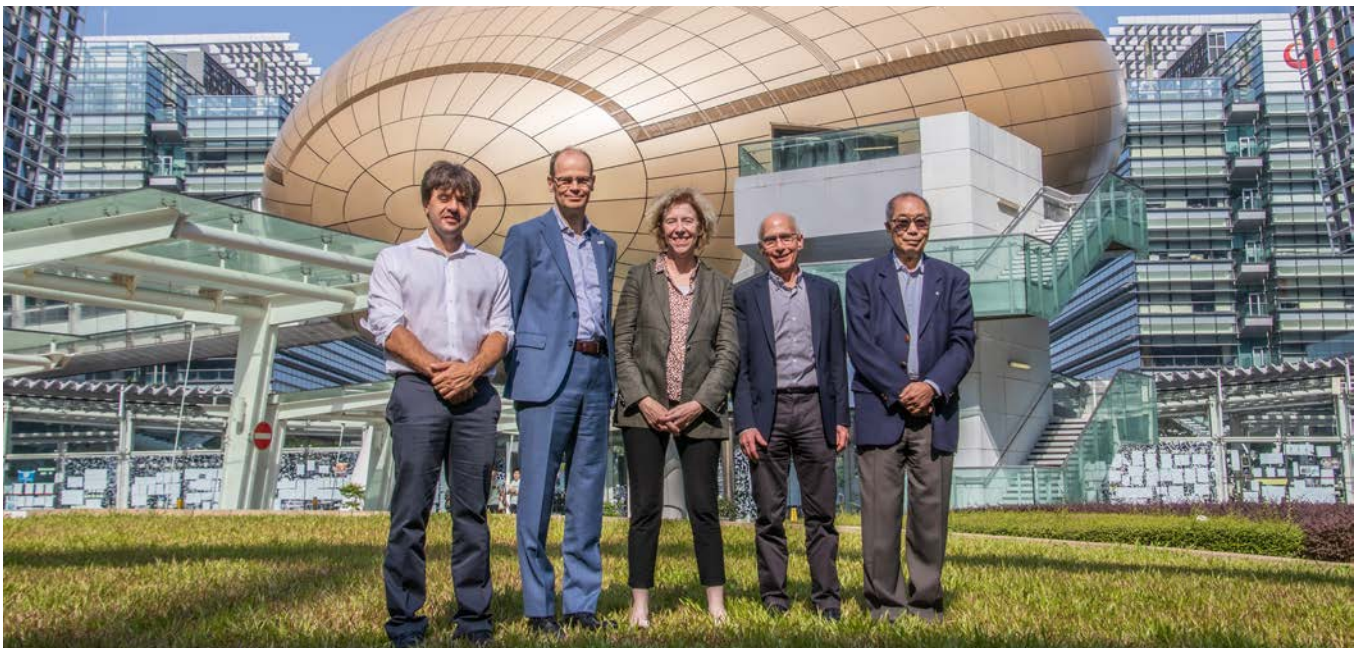


Overview of current projects of the Bioinformatics Platform.



In-house pipeline for single-cell gene expression data.

International Scientific Advisory Board



The International Scientific Advisory Board (SAB) was established in 2018 and comprised five highly qualified and internationally renowned scientists with expertise in areas relevant for MWLC's research. SAB provides expert, non-binding advice for MWLC to make strategic decisions in accomplishing its mission.

In 2019, SAB conducted a major review of MWLC's research and activities. Principal investigators were interviewed and reports presented to the Centre management. The overall recommendation was for MWLC to expand and align its research profile by putting more emphasis on bioengineering and biotechnology.

Membership of SAB is as follows:

Photo: Linda Tammisto
University of Helsinki

Prof Eero Castrén (Chair)
Academy Professor, Neuroscience Center
University of Helsinki

Photo: Stanford University

Prof Karl Deisseroth
DH Chen Professor of Bioengineering and of Psychiatry and of Behavioral Sciences, Department of Bioengineering
Stanford University

Investigator
Howard Hughes Medical Institute

Photo: Photography Department
University Health Network

Prof Tak Wah Mak
Professor, Departments of Medical Biophysics and Immunology
University of Toronto

Senior Scientist
Princess Margaret Cancer Centre

Photo: Kris Snibbe
Harvard University

Prof Lee Rubin
Professor, Stem Cell and Regenerative Biology
Executive Committee Member and Program Leader, Harvard Stem Cell Institute
Harvard University

Prof Fiona M Watt
Director, Centre for Stem Cells & Regenerative Medicine
King's College London

Executive Chair
Medical Research Council

Local Reference Group

The Local Reference Group (LRG) consisting of six prominent leaders and academics from universities in Hong Kong was established in 2018. Its function is to provide expert, non-binding advice to help MWLC strategize its development with a focus on leveraging support from the academic community in Hong Kong and Mainland China.

Membership of LRG is as follows:

Prof Wai Yee Chan
Pro-Vice-Chancellor / Vice-President
Li Ka Shing Professor of Biomedical Sciences
The Chinese University of Hong Kong

Prof Roland Chin
Professor Emeritus, Department of Computer Science
President Emeritus
Hong Kong Baptist University

Prof Nancy Ip
Vice-President for Research and Development
The Morningside Professor of Life Science
Chair Professor, Division of Life Science
Director of the State Key Laboratory of Molecular Neuroscience
The Hong Kong University of Science and Technology

Prof Paul Tam
Clinical Professor
Li Shu-Pui Professor in Surgery
Chair Professor, Division of Paediatric Surgery
Director of Dr Li Dak-Sum Research Centre
The University of Hong Kong

Prof Wing-Tak Wong
Deputy President and Provost
Chair Professor of Chemical Technology
The Hong Kong Polytechnic University

Prof Yuan-Ting Zhang
Chair Professor of Biomedical Engineering
City University of Hong Kong

MWLC Associate Member Programme

MWLC launched the Associate Member Programme in 2018 with an objective of fostering collaboration with universities in Hong Kong. Applications were open to faculty members across the life science campuses in Hong Kong. After an extremely competitive selection process, eight outstanding scientists from four universities were appointed as MWLC Associate Members in autumn 2019. Members were provided funding support to conduct collaborative projects with MWLC researchers, and / or develop novel research platforms or technologies that promote research in MWLC focus areas.

The outcome of the projects was evaluated in 2021 and membership was renewed for seven Associate Members to continue their collaboration with a refined scope based on the findings from their first year's work. Their projects are listed below:

Prof Yiu-Fai Cheung
Clinical Professor
Bryan Lin Professor in Paediatric Cardiology
Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine
The University of Hong Kong

Collaborative Project with Dr Fredrik Lanner
Single-cell mapping of developmental trajectories underlying the congenital heart disease of tetralogy of Fallot in a human induced pluripotent stem cell model - a focus on 22q11.2 Deletion Syndrome

Dr Danny Leung
Assistant Professor
Division of Life Science
Director, Center for Epigenomics Research
Associate Director, HKUST-BGI Joint Research Center
The Hong Kong University of Science and Technology

Collaborative Project with Dr Zongli Zheng
Epigenetic dysregulation of human endogenous retroviruses in multiple sclerosis

Prof Kai Liu
Associate Professor
Cheng Associate Professor of Science
Division of Life Science
Associate Director, HKUST-Nan Fung Life Sciences Joint Laboratory
The Hong Kong University of Science and Technology

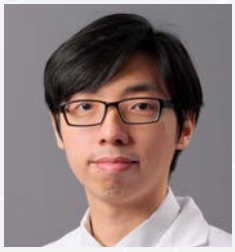
Collaborative Project with Drs Sijie Chen, Linxian Li and Zongli Zheng
Development of novel strategies for neural repair by targeting both intrinsic and extrinsic barriers of axon regeneration

Prof Ben Zhong Tang
Adjunct Professor of Chemistry
The Hong Kong University of Science and Technology

Collaborative Project with Dr Sijie Chen
Aggregation-induced emission (AIE) dots: inspiring future healthcare

Dr Weiping Wang
Assistant Professor
Dr Li Dak-Sum Research Centre and Department of Pharmacology and Pharmacy
Principal Investigator, The State Key Laboratory of Pharmaceutical Biotechnology
The University of Hong Kong

Collaborative Project with Drs Sijie Chen and Linxian Li
Development of near-infrared light-triggered drug delivery system



Dr Alan Wong
Assistant Professor
School of Biomedical Sciences and Department of Electrical and Electronic Engineering
The University of Hong Kong

Collaborative Project with Dr Zongli Zheng
Technologies for genetics and genomics research

Dr Wenjun Xiong
Associate Professor
Department of Biomedical Sciences
City University of Hong Kong

Collaborative Project with Dr Zongli Zheng
A CRISPR screen for diverse codes of cellular reprogramming in mouse retinas

MWLC Members

Management

Sandra Ceccatelli
Director

Agneta Wallin Levinovitz
Research and Administrative Coordinator

Anna Däckfors
HR-specialist

Dongan Wang
Head of Research,
Hong Kong node

Emily Ip
Head of Administration,
Hong Kong node

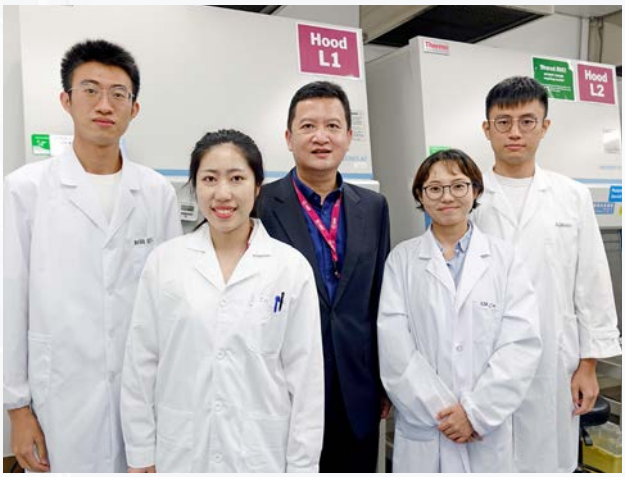
Bioinformatics Platform

Virpi Ahola
Computational Biologist
Coordinator, Bioinformatics Platform

Shangli Cheng
Postdoctoral Researcher in Bioinformatics

Jilin Zhang
Bioinformatician

Dongan Wang Lab

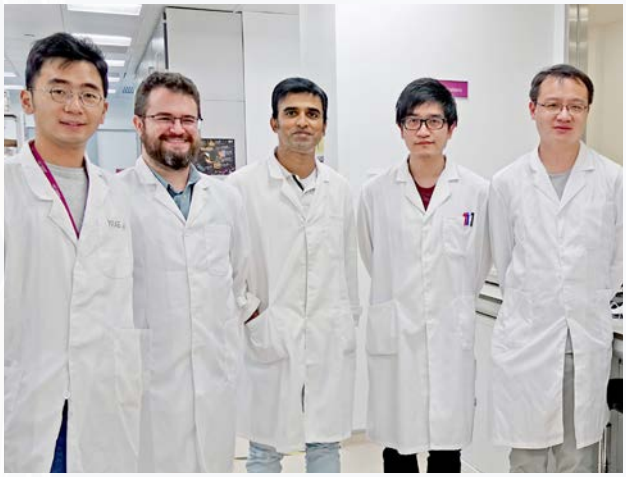


From left to right: Bangheng Liu, Chao Tao, Dongan Wang, Chloe Jin, Adrian Ma

Sijie Chen Lab

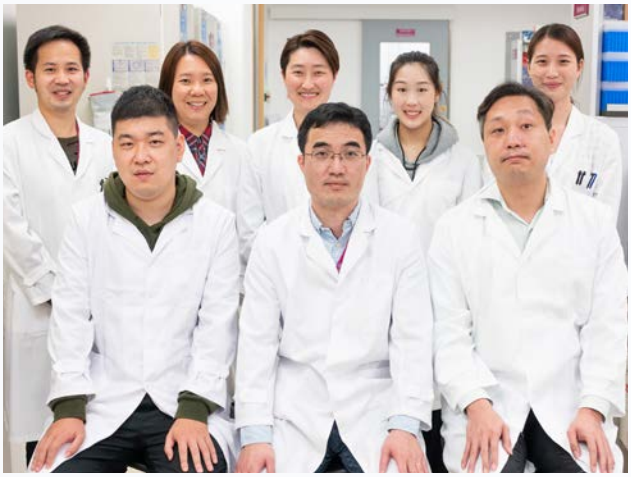
Back, from left to right: Fei Wang, Kam Chuen, Blake Ho, Steven Zhao; Front, from left to right: Quanzhi Yang, Sijie Chen, Alex Wong

Linxian Li Lab



From left to right: Yike Yang, Callum Stewart, Balakrishna Moku, Kyler Chow, Linxian Li

Zongli Zheng Lab

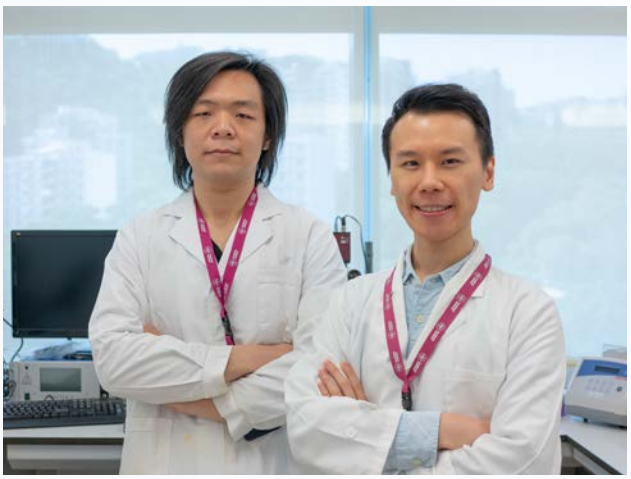


Back, from left to right: Bang Wang, Maggie Chow, Jan Keung, Silvia Mak, Limei Ai; Front, from left to right: Miao Yu, Zongli Zheng, Yee Man Chan

Administrative Team

From left to right: Heather Chan, Molly Yang

Technical Team



From left to right: Charlie Yap, Patrick Chan

Selected Publications 2020-2021

2020

Bonetti, A., Agostini, F., Suzuki, A. M., Hashimoto, K., Pascarella, G., Gimenez, J., Roos, L., Nash, A. J., Ghilotti, M., Cameron, C. J. F., Valentine, M., Medvedeva, Y. A., Noguchi, S., Agirre, E., Kashi, K., Samudyata, Luginbühl, J., Cazzoli, R., Agrawal, S., Luscombe, N. M., Blanchette, M., Kasukawa, T., Hoon, M., Arner, E., Lenhard, B., Plessy, C., Castelo-Branco, G., Orlando, V., & Carninci, P. (2020). **RADICL-seq identifies general and cell type–specific principles of genome-wide RNA-chromatin interactions**. *Nature Communications*, *11*(1), 1018.

Faure, L., Wang, Y., Kastriti, M. E., Fontanet, P., Cheung, K. K. Y., Petitpré, C., Wu, H., Sun, L. L., Runge, K., Croci, L., Landy, M. A., Lai, H. C., Consalez, G. G., de Chevigny, A., Lallemend, F., Adameyko, I., & Hadjab, S. (2020). **Single cell RNA sequencing identifies early diversity of sensory neurons forming via bi-potential intermediates**. *Nature Communications*, *11*(1), 4175.

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Gao, H., Kam, C., Chou, T. Y., Wu, M.-Y., Zhao, X., & Chen, S. (2020). **A simple yet effective AIE-based fluorescent nano-thermometer for temperature mapping in living cells using fluorescence lifetime imaging microscopy**. *Nanoscale Horizons*, *5*(3), 488–494.

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Lv, W., Long, K., Yang, Y., Chen, S., Zhan, C., & Wang, W. (2020). **A Red Light-Triggered Drug Release System Based on One-Photon Upconversion-Like Photolysis**. *Advanced Healthcare Materials*, *9*(21), 2001118.

Marisca, R., Hoche, T., Agirre, E., Hoodless, L. J., Barkey, W., Auer, F., Castelo-Branco, G., & Czopka, T. (2020). **Functionally distinct subgroups of oligodendrocyte precursor cells integrate neural activity and execute myelin formation**. *Nature Neuroscience*, *23*(3), 363–374.

Meineke, B., Heimgärtner, J., Eirich, J., Landreh, M., & Elsässer, S. J. (2020). **Site-Specific Incorporation of Two ncAAs for Two-Color Bioorthogonal Labeling and Crosslinking of Proteins on Live Mammalian Cells**. *Cell Reports*, *31*(12), 107811.

Miao, L., Lin, J., Huang, Y., Li, L., Delcassian, D., Ge, Y., Shi, Y., & Anderson, D. G. (2020). **Synergistic lipid compositions for albumin receptor mediated delivery of mRNA to the liver**. *Nature Communications*, *11*(1), 2424.

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Wagner, M., Yoshihara, M., Douagi, I., Damdimopoulos, A., Panula, S., Petropoulos, S., Lu, H., Pettersson, K., Palm, K., Katayama, S., Hovatta, O., Kere, J., Lanner, F., & Damdimopoulou, P. (2020). **Single-cell analysis of human ovarian cortex identifies distinct cell populations but no oogonial stem cells**. *Nature Communications*, *11*(1), 1147.

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