



STEM CELLS AND TISSUE REGENERATION

Stem Cell and Vascular Regeneration



Principal Investigator

Professor Kathy Lui



Team Members

Kevin Yang | Cai Liang | Xisheng Li | Di Liu | Zhangjing Ma | Peng Ye | Kathleen Chan | Zelong Fu | Mary Chau | Vicken Chan | Danny Leung



Research Progress Summary

During the past year, Professor Kathy Lui and her team have been working on the following research projects:



Research on Immune Cell-mediated Cardiovascular Disease and Regeneration

Immune-mediated tissue repair has been an emerging paradigm in the field of Regenerative Medicine (*Eming et al., Science, 2017*). The team has uncovered that both effector and regulatory T-cells are essential in modulating the regeneration of blood vessels and heart muscle. Specifically, they have reported that CD4⁺ conventional T-cells such as Th1 cells inhibit but CD4⁺ Treg promote *de novo* sprouting angiogenesis in type-2 diabetic (T2D) mice (*Leung OM... Lui KO, Cell Reports, 2018*). Besides, CD8⁺ T-cells also regulate vascular regeneration as they observed the plasticity of these cells after blood vessel injury by comparing them in mice with normal and high blood glucose levels (*Liang C... Lui KO, Theranostics, 2020*). CD8⁺ T-cells were in the resting state with an expression of angiogenetic genes possibly facilitating angiogenesis after injury; while the same cells became highly inflammatory

and activated in T2D mice with a direct role in impairing angiogenesis. Therefore, targeting the CD4⁺ and/or CD8⁺ T-cells could rescue vascular regeneration in T2D. In terms of heart muscle regeneration, they have demonstrated that CD4⁺ conventional T-cells such as Th1 and Th17 cells impair heart regeneration (*Li J... Lui KO, Theranostics, 2020*) but CD4⁺ Treg promotes regeneration by potentiating the proliferation of cardiomyocytes in a paracrine manner (*Li J... Lui KO, Theranostics, 2019*). These studies not only help them in understanding the disease pathogenesis but also giving clinically relevant insights into the identification of potential new treatment options for patients with cardiovascular diseases. They have also written two review papers on this topic during the reporting period (*Yang KY... Lui KO, Journal of Leukocyte Biology, 2020*; *Fung THW... Lui KO, Theranostics, 2020*).



Research on the Generation of Human Pluripotent Stem Cell-derived Pancreatic Beta Cells and the Induction of Their Acceptance by a Humanised Immune System

The team has a long-standing interest in stem cell research. This year, they have reported a new differentiation protocol for generating human pancreatic beta-like cells from human embryonic stem cells (hESC-beta cells) and uncovered a cell surface marker for purifying the mature and functional hESC-beta cells using the single-cell RNA-seq technology (*Li X... Lui KO, Stem Cell Reports, 2020*). Besides, they have transplanted these cells in humanised mice and demonstrated that humanised

anti-CD4 and -CD8 monoclonal antibodies are sufficient to induce their acceptance and prevent immune rejection in mice bearing functional human T-cells (*Li J... Lui KO, Biomaterials, 2020*). Taken together, their research gives some new insight into the potential application of these cells for cell therapy, drug screening and disease modelling both *in vitro* and *in vivo*. These new technologies will also help them generate a patient-specific humanised disease model for *in vivo* drug screening.



Research Output and International Recognition

In 2020, there were 6 graduate students (4 PhD and 2 MPhil), 2 research assistants and 1 postdoctoral fellow in the team. One of the PhD students who graduated in 2020 went on to receive postdoctoral training in Mount Sinai Hospital in New York. They have made

significant progress including publications and new research funding. Besides, Prof. Kathy Lui has been invited to join as an Editorial Board Member for several journals including the renowned journal in the field of cardiovascular research - *Circulation Research* (American

Heart Association). Despite the pandemic, she has been invited to give virtual lectures in recognised international conferences, including the 21st International Vascular Biology Meeting organised in Seoul, Korea, in September 2020; the 4th Japanese Circulation Society Council Forum on Basic Cardiovascular Research organised in Nagoya, Japan, in September 2020; the 22nd East Meets West Symposium

on Diabetes and Cardiovascular Risk Factors organised in Hong Kong in October 2020; and the Changan International Cardiovascular Forum organised in Changan, China, in November 2020. Last but not least, she has been elected as the new Chairman of the Hong Kong Society for Immunology in the next term. Overall, the teamwork has attracted some local, regional and international recognition.

Research and Scholarship

Academic Editorship

Member's Name	Details	
	Role	Journal
Kathy Lui	Editorial Board Member (Early Career)	Circulation Research
	Associate Editor	Stem Journal
	Editorial Board Member	Scientific Reports
	Guest Editor	International Journal of Molecular Sciences
Journal of Leukocyte Biology		

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Kathy Lui	Grant Reviewer	Wellcome Trust, U.K.
		Swiss National Science Foundation, Switzerland
	Journal Reviewer	Circulation Research
		Cell Reports
		Theranostics
		Genome Medicine
		Diabetes
		Stem Cells
		Stem Cell Reports
		Development

Reviewer of Journal / Conference

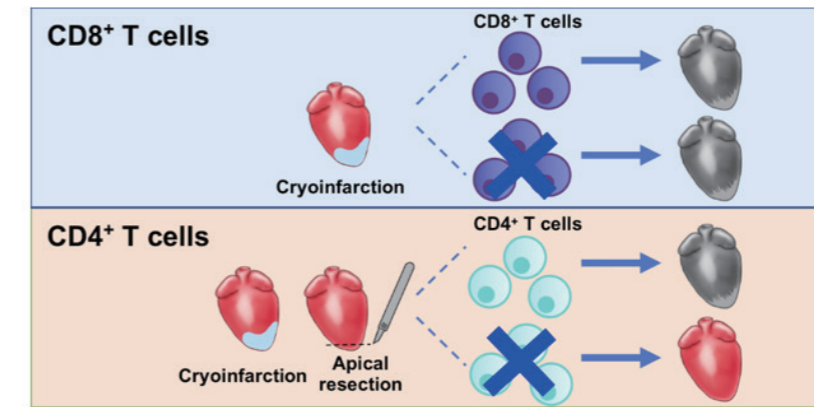
Member's Name	Details	
	Role	Journal / Conference
Kathy Lui	Journal Reviewer	Canadian Journal of Cardiology
		Journal of Cellular and Molecular Medicine
		The Journal of Biological Chemistry
		Science China Life Sciences
	Conference Reviewer	21 st International Vascular Biology Meeting, Seoul, Korea
	Journal Reviewer	Scientific Reports
International Journal of Molecular Science		
Current Genomics		

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Kathy Lui	Modelling Human Congenital Heart Disease in Diabetes Using the ISLI-Cre Lineage-tracing Human Pluripotent Stem Cells	The Chinese University of Hong Kong – Faculty Innovation Award	01/01/2017	31/12/2021	2,500,000
	Unraveling the Impact of Hyperglycemia on Human Second Heart Field Development	The Croucher Foundations – Croucher Innovation Award	01/01/2017	31/12/2021	5,000,000
	Vascular Regeneration	Research Grants Council – Research Matching Grant Scheme 2019	01/11/2019	30/10/2024	500,000
	Paracrine Regulation of Human Pancreatic Beta-like Cell Maturation by RARRES2	CUHK Research Committee – Direct Grant	30/06/2019	29/06/2020	105,000
	Immune Regulation of Tissue Regeneration: From Mechanistic to Potential Clinical Implications	CUHK Research Committee Fund for Research Sustainability of Major Research Grants Council Funding Schemes	01/06/2019	31/05/2021	625,000
	Unraveling the Impact of Hyperglycemia on Human Second Heart Field Development	Research Grants Council – Research Matching Grant Scheme 2020	01/06/2020	31/05/2025	500,000
	Vascular Diseases and Regeneration	National Natural Science Foundation of China – Excellent Young Scientist Fund	01/01/2020	31/12/2022	RMB 1,300,000
	Joint R&D of Magnesium-based Orthopaedic Implants	Research Grants Council – Collaborative Research Fund	01/04/2018	31/03/2021	5,545,807

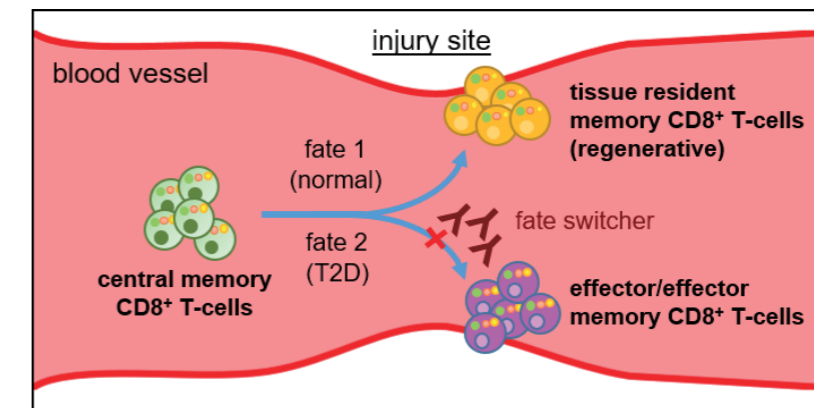
A. Journal Papers

1. Li X, Yang KY, Chan VW, Leung KT, Zhang XB, Wong AS, Chong CCN, Wang CC, Ku M, Lui KO. Single-cell RNA-seq reveals that CD9 is a negative marker of glucose-responsive pancreatic β -like cells derived from human pluripotent stem cells. *Stem Cell Reports*. 2020;15(5):1111-1126. doi:10.1016/j.stemcr.2020.09.009.
2. Yang KY, Ku M, Lui KO. Single-cell transcriptomics uncover distinct innate and adaptive cell subsets during tissue homeostasis and regeneration. *Journal of Leukocyte Biology*. 2020;108(5):1593-1602. doi:10.1002/JLB.6MR0720-131R. [Review]
3. Fung THW, Yang KY, Lui KO. An emerging role of regulatory T-cells in cardiovascular repair and regeneration. *Theranostics*. 2020;10(20):8924-8938. doi:10.7150/thno.47118. [Review]
4. Kirak O, Ke E, Yang KY, Schwarz A, Plate L, Nham A, Abadejos JR, Valencia A, Wiseman RL, Lui KO, Ku M. Premature activation of immune transcription programs in autoimmune-predisposed mouse embryonic stem cells and blastocysts. *International Journal of Molecular Sciences*. 2020;21(16):5743. doi:10.3390/ijms21165743.
5. Li J, Liang C, Yang KY, Huang X, Han MY, Li X, Chan VW, Chan KS, Liu D, Huang ZP, Zhou B, Lui KO. Specific ablation of CD4+ T-cells promotes heart regeneration in juvenile mice. *Theranostics*. 2020;10(18):8018-8035. doi:10.7150/thno.42943.
6. Li Y, Lv Z, Zhang S, Wang Z, He L, Tang M, Pu W, Zhao H, Zhang Z, Shi Q, Cai D, Wu M, Hu G, Lui KO, Feng J, Nieto MA, Zhou B. Genetic fate mapping of transient cell fate reveals N-cadherin activity and function in tumor metastasis. *Developmental Cell*. 2020;54(5):593-607.e5. doi:10.1016/j.devcel.2020.06.021.
7. Tang R, Long T, Lui KO, Chen Y, Huang ZP. A roadmap for fixing the heart: RNA regulatory networks in cardiac disease. *Molecular Therapy - Nucleic Acids*. 2020;20:673-686. doi:10.1016/j.omtn.2020.04.007. [Review]
8. Li J, Li X, Liang C, Ling L, Chen Z, Wong CK, Waldmann H, Lui KO. Coreceptor blockade targeting CD4 and CD8 allows acceptance of allogeneic human pluripotent stem cell grafts in humanized mice. *Biomaterials*. 2020;248:120013. doi:10.1016/j.biomaterials.2020.120013.
9. Liang C, Yang KY, Chan VW, Li X, Fung THW, Wu Y, Tian XY, Huang Y, Qin L, Lau JYW, Lui KO. CD8 + T-cell plasticity regulates vascular regeneration in type-2 diabetes. *Theranostics*. 2020;10(9):4217-4232. doi:10.7150/thno.40663.
10. Han DSC, Ni M, Chan RWY, Chan VWH, Lui KO, Chiu RWK, Lo YMD. The biology of cell-free DNA fragmentation and the roles of DNASE1, DNASE1I3, and DFFB. *The American Journal of Human Genetics*. 2020;106(2):202-214. doi:10.1016/j.ajhg.2020.01.008.
11. Tian X, He L, Liu K, Pu W, Zhao H, Li Y, Liu X, Tang M, Sun R, Fei J, Ji Y, Qiao Z, Lui KO, Zhou B. Generation of a self-cleaved inducible CRE recombinase for efficient temporal genetic manipulation. *The EMBO Journal*. 2020; 39(4):e102675. doi:10.15252/embj.2019102675.
12. He L, Lui KO, Zhou B. The formation of coronary vessels in cardiac development and disease. *Cold Spring Harbor Perspectives in Biology*. 2020;12(5):a037168. doi:10.1101/cshperspect.a037168.



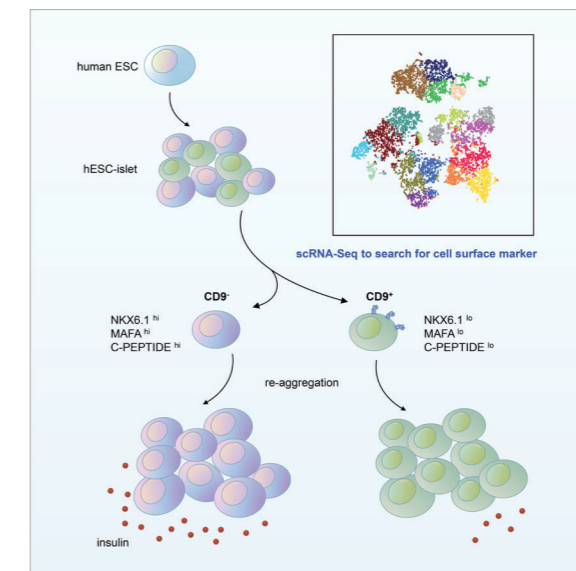
CD4 but not CD8 T-cells regulate postnatal heart regeneration

Source: Li J, Liang C, Yang KY, Huang X, Han MY, Li X, Chan VW, Chan KS, Liu D, Huang Z-P, Zhou B, Lui KO. Specific ablation of CD4+ T-cells promotes heart regeneration in juvenile mice. *Theranostics*. 2020;10(18):8018-8035. doi:10.7150/thno.42943.



CD8 T-cell plasticity regulates of vascular function in diabetes

Source: Liang C, Yang KY, Chan VW, Li X, Fung THW, Wu Y, Tian XY, Huang Y, Qin L, Lau JYW, Lui KO. CD8 + T-cell plasticity regulates vascular regeneration in type-2 diabetes. *Theranostics*. 2020;10(9):4217-4232. doi:10.7150/thno.40663.



Single cell transcriptomics identifies that CD9 is a cell specific marker for the purification of human stem cell derived pancreatic beta cells

Source: Li X, Yang KY, Chan VW, Leung KT, Zhang XB, Wong AS, Chong CCN, Wang CC, Ku M, Lui KO. Single-cell RNA-seq reveals that CD9 is a negative marker of glucose-responsive pancreatic β -like cells derived from human pluripotent stem cells. *Stem Cell Reports*. 2020;15(5):1111-1126. doi:10.1016/j.stemcr.2020.09.009.