BIOGRAPHICAL SKETCH

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NAME: Ai Ing, Lim

eRA COMMONS USER NAME (credential, e.g., agency login): AIINGLIM

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Hong Kong Polytechnic University (Hong Kong)	B.Sc. (Hons)	06/2010	Biology
University of Hong Kong (Hong Kong)	M.Phil.	12/2012	Nephrology
Pasteur Institute, Paris-Sorbonne University (Paris, France)	Ph.D.	07/2017	Immunology
National Institutes of Health, National Institute of Allergy and Infectious Disease (Maryland, USA)	Postdoctoral	09/2022	Immunology

A. Personal Statement

I am an incoming Assistant Professor at the Department of Molecular Biology, Princeton University. Our research program aims to establish a mechanistic understanding of maternal-offspring immune crosstalk. First, how does maternal environmental exposure shape the offspring immune system in the long-term. Second, how maternal immunity adapts to physiological changes during pregnancy and lactation.

My works in human and murine immunology have demonstrated that the immune system is highly plastic and can adapt to environmental challenges before birth. Notably, my recent work provided a mechanistic demonstration that discrete signal from mild maternal infection can direct the trajectory of offspring tissue immunity, opening the door to an entirely new line of investigation at the intersection of infectious diseases, immunology, and developmental biology. Using mouse models and multidisciplinary approaches, our future directions are to (**1**) explore the role of maternal pathogens and microbiome on offspring predisposition to immune disorders and cancer; (**2**) dissect the impact of maternal infection on breastmilk composition and breast cancer development; and (**3**) understand the mechanisms of maternal immune adaptation to pregnancy and lactation. Together, our program is highly relevant to human health and this line of research is essential to pave the way to mitigate pregnancy complications, prevent and/or treat immune disorders as well as cancer.

Key research products:

1. **Lim AI**, Chan LY, Lai KN, Tang SC, Chow CW, Lam MF, Leung JC. Distinct role of matrix metalloproteinase-3 in kidney injury molecule-1 shedding by kidney proximal tubular epithelial cells. *Int J Biochem Cell Biol*, 2012 Mar 21; 44:1040. PMID: 22484054
2. **Lim AI**, Menegatti S, Bustamante J, Le Bourhis L, Allez M, Rogge L, Casanova JL, Yssel H, Di Santo JP. IL-12 drives functional plasticity of human group 2 innate lymphoid cells. *J Exp Med*. 2016 Apr 4;213(4):569-83. PMID: 26976630
3. **Lim AI**, Li Y, Lopez-Lastra S, Stadhouders R, Paul F, Casrouge A, Serafini N, Puel A, Bustamante J, Surace L, Masse-Ranson G, David E, Strick-Marchand H, Le Bourhis L, Cocchi R, Topazio D, Graziano

P, Muscarella LA, Rogge L, Norel X, Sallenave JM, Allez M, Graf T, Hendriks RW, Casanova JL, Amit I, Yssel H, Di Santo JP. Systemic human ILC precursors provide a substrate for tissue ILC differentiation. *Cell.* 2017 Mar9;168(6):1086-1100. PMID: 28283063

4. **Lim AI**, McFadden T, Link VM, Han SJ, Karlsson RM, Stacy A, Farley TK, Harrison OJ, Shih HY, Cameron HA, Belkaid Y. Maternal infection promotes offspring tissue-specific immune fitness. bioRxiv. https://doi.org/10.1101/2021.01.13.426542.

B. Positions, Scientific Appointments, and Honors

Positions

Sep 2022	Assistant Professor, Department of Molecular Biology, Princeton University
2017–2022	Postdoctoral fellow, Mentor: Yasmine Belkaid, NIAID, NIH
2013–2017	PhD student, Mentor: James Di Santo, Pasteur Institute and Paris-Sorbonne University
2012–2013	Research Assistant, Mentor: Joseph Leung, The University of Hong Kong
2011–2012	MPhil student, Mentor: Joseph Leung, The University of Hong Kong
2007–2010	Undergraduate researcher, Mentor: Man-Sau Wong, Hong Kong Polytechnic University

Scientific Appointments

2020–Present	Elected member, Immunology Interest Group Steering Committee, NIH
2018–Present	Active reviewer in Frontiers in Immunology Journal
2017–Present	Member, American Society of Immunology
2013–Present	Member, French Society of Immunology
2010–2013	Member, Hong Kong Nephrology Society

Honors

2022	NIH CIG William E. Paul Award for the Best Paper in Cytokine Research
2021–2026	The Branco Weiss Fellowship Transition Award
2021	Sidney & Joan Pestka Post Graduate Award by Cytokine Society
2021	Best Oral Presentation in NIH Immunology Interest Group Retreat
2021	Keystone Symposia Scholarship: The Microbiome from Mother to Child
2020	ACTERIA Doctoral Thesis Prize for the best European Immunology thesis
2020	Best Oral Presentation in NIH Immunology Interest Group Retreat
2020	NIH Fellows Award for Research Excellence (FARE) Award
2019	Best Oral Presentation in NIH Immunology Interest Group Retreat
2019	NIH Fellows Award for Research Excellence (FARE) Award
2018–2021	Human Frontier Science Program Postdoctoral Fellowship
2018	Awarded Damon Runyon Fellowship (declined due to incompatibility with HFSP)
2018	L'Oréal-UNESCO For Women in Science International Rising Talent Award
2017	L'Oréal-UNESCO For Women in Science National Award in France
2016–2017	Foundation ARC for Cancer Research Fellowship
2016	French Society of Immunology Training Award
2015	Best Oral Presentation at Pasteur Institute Immunology Retreat
2013–2016	European Union Marie Curie Action Fellowship
2012	Basic Science Nephrology Research Grant from Hong Kong Kidney Foundation
2012	Young Investigator Award from International Society of Peritoneal Dialysis
2012	Young Nephrology Investigator Award from Hong Kong Society of Nephrology
2012	Outstanding student award at HKU-Pasteur Institute Cell Biology Course
2012	Best Poster Presentation at Postgraduate Symposium, The University of Hong Kong
2011-2012	The University of Hong Kong Postgraduate Full Scholarship
2007-2010	Hong Kong Polytechnic University International Student Academic Scholarship

C. Contributions to Science

I was the driving force in all three of the contributions described below:

1. Discovered the mechanism of kidney injury molecule-1 shedding

My early research uncovered the mechanistic regulation of kidney injury molecule-1 (KIM-1, an acute kidney injury biomarker) by kidney proximal tubular epithelial cells (PTEC). First, I found that KIM-1 was constitutively released from the apical surface of PTEC and enhanced by two important kidney mediators, human serum albumin (HSA) and TNF-α. This process can be inhibited by broad spectrum inhibitors of matrix metalloproteinases (MMP). Using MMP blockade, I found that MMP-3 contributed to HSA and TNF-α-induced KIM-1 shedding. Using murine renal ischemia and reperfusion models, I uncovered the distinct roles of reactive oxygen species in regulating MMP-3-mediated KIM-1 shedding by PTEC. Further, I discovered that bone morphogenetic protein-7 (BMP-7) can repress the HSA-induced activation on PTEC. These studies provided insight into the KIM-1 shedding that has been observed in kidney injury patients, which advanced the nephrology field by showing that MMP-3 and BMP-7 could be the potential targets for treating acute kidney injury.

1. **Lim AI**, Chan LY, Lai KN, Tang SC, Chow CW, Lam MF, Leung JC. Distinct role of matrix metalloproteinase-3 in kidney injury molecule-1 shedding by kidney proximal tubular epithelial cells. *Int J Biochem Cell Biol*, 2012 Mar 21; 44:1040.
2. **Lim AI**, Tang SC, Lai KN, Leung JC. Kidney injury molecule-1: More than just an injury marker of tubular epithelial cells? *J Cell Physiol*. 2013 May;228(5):917-24.
3. **Lim AI**, Chan LY, Tang SC, Yiu WH, Li R, Lai KN, Leung JC. BMP-7 represses albumin-induced chemokine synthesis in kidney tubular epithelial cells through destabilization of NF-kB-inducing kinase. *Immnol Cell Biol*. 2014 May-Jun; 92(5): 427-35.
4. **Lim AI,** Chan LY, Tang SC, Lai KN, Leung JC. Albumin and glycated albumin activated KIM-1 release in tubular epithelial cells through distinct kinetics and mechanisms. *Inflamm Res*. 2014 Oct;63(10):831-9.

2. Cytokine control of human innate lymphocyte cells

During my doctoral training with Prof. James Di Santo at Pasteur Institute, we focused on the roles of cytokines on human innate lymphoid cell (ILC) development and function. First, I found that IL-12 drives ILC2 plasticity, which contrasts with the idea that ILC2 cells represent a stable sub-lineage. This ILC2 plasticity also occurs in the inflamed gut of Crohn's disease patients. As ILC2 are systemically distributed, their ability to produce type 1 cytokines could provide a rapid source of these important cytokines in diverse disease contexts; for example, during various inflammation and infectious diseases. Second, I identified human ILC precursors from peripheral blood and tissues of healthy individuals. This work redefined $CD117^{+}$ ILC in circulation, which were previously considered to be ILC3 based on surface phenotypes similarities, as ILC precursors. In addition, this data challenged the dogma about where ILC differentiation originated, in which fetal liver and adult bone marrow had been considered the "factories" for ILC generation. We proposed a new model of "ILC-poiesis", in which circulating ILC precursors migrate into tissues and differentiate into mature ILC subsets, depending on micro-environmental signals. We further developed a strategy to isolate human ILC precursors from the peripheral blood of healthy individuals, which allowed us to easily obtain human ILC precursors by syringe rather than surgery to obtain bone marrow samples. Moreover, we were able to generate large quantities of specific ILC subsets in the laboratory, which enabled us to perform cellular therapy by transferring tailor-made ILC to patients. These offer the potential to serve as novel therapeutic interventions to fight against cancer, infection, or metabolic diseases in the future. Furthermore, the *in vitro* and *in vivo* models established in my doctoral studies provided new tools for the scientific community to use in exploring human ILC biology. These lines of investigation opened a new field to study human ILC and have enormous potential to develop ILC for cellular therapy in the future.

1. **Lim AI**, Menegatti S, Bustamante J, Le Bourhis L, Allez M, Rogge L, Casanova JL, Yssel H, Di Santo JP. IL-12 drives functional plasticity of human group 2 innate lymphoid cells. *J Exp Med*. 2016 Apr 4;213(4):569-83.
2. **Lim AI**, Verrier T, Vosshenrich C, Di Santo JP. Developmental options and functional plasticity of innate lymphoid cells*. Curr Opin Immunol*. 2017 Mar 27;44:61-68.
3. **Lim AI**, Li Y, Lopez-Lastra S, Stadhouders R, Paul F, Casrouge A, Serafini N, Puel A, Bustamante J, Surace L, Masse-Ranson G, David E, Strick-Marchand H, Le Bourhis L, Cocchi R, Topazio D, Graziano P, Muscarella LA, Rogge L, Norel X, Sallenave JM, Allez M, Graf T, Hendriks RW, Casanova JL, Amit I,

Yssel H, Di Santo JP. Systemic human ILC precursors provide a substrate for tissue ILC differentiation. *Cell.* 2017 Mar9;168(6):1086-1100.
4. Di Santo, **Lim AI**, Yssel H. 'ILC-poiesis': generating tissue ILCs from naive precursors. *Oncotarget*. 2017 Sep 19;8(47):81729-81730.
5. **Lim AI**, Di Santo JP. ILC-poiesis: Ensuring tissue ILC differentiation at the right place and time. *Eur J Immunol.* 2019 Jan;49(1):11-18.

3. Maternal restricted infection promotes offspring tissue-specific immune fitness

The concept that beyond adaptive immunity, innate cells and tissues can develop long-term altered states, has gained considerable traction over the past few years. To what extent immune imprinting occurs preferentially at specific developmental window remains largely unclear. My work demonstrated that discrete signals imposed by maternally restricted infection can have a profound impact on the offspring, in a way that enhances protective immunity for the long term. Mechanistically, I showed that this “tissue memory” in the offspring is mediated by a specific interaction between infection-induced maternally derived cytokine, interleukin-6, and fetal epithelial stem cells. We proposed a model of “pre-birth immune education”, in which maternal microbial exposure can be coopted by the developing fetus to develop optimal immune fitness. My findings have broad implications for our understanding of how infection-induced defined signals direct the tissue-specific immune trajectories in the offspring. Further, we demonstrated that *in utero* encountered signals can refine microbial-epithelial-immune crosstalk for the long term. Thus, this work brings forward a new, mechanistically grounded concept that will open the door to numerous lines of investigation of profound evolutionary and clinical relevance in maternal-offspring crosstalk.

1. **Lim AI**, Harrison OJ, Belkaid Y. Pre-birth memory. Nat Immunol. 2019 Mar; 20(3):254-256.
2. **Lim AI,** McFadden T, Link VM, Han SJ, Karlsson RM, Stacy A, Farley TK, Lima-Junior D, Harrison OJ, Desai JV, Lionakis MS, Shih HY, Cameron HA, Belkaid Y. Prenatal maternal infection promotes tissue-specific immunity and inflammation in offspring. *Science*. 373. eabf3002 (2021).

Complete list of publications: https://www.ncbi.nlm.nih.gov/myncbi/ai%20ing.lim.2/bibliography/public/