

## ***CURRICULUM VITAE of KO Mun-Yee, Josephine, PhD***

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**Position:** Research Assistant Professor  
**Address:** Department of Clinical Oncology, University of Hong Kong (HKU)

### **Education**

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1993-1996 Hong Kong University of Science and Technology (HKUST), Hong Kong  
Bachelor of Science in Biology  
1996-1998 HKUST, Master of Philosophy in Biology  
2000-2005 HKUST, Doctor of Philosophy (part-time) in Biology

### **Work experience**

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1996 - 1998 Teaching Assistant, Department of Biology, HKUST  
2001 - 2005 Technician, Department of Biology, HKUST  
2005 - 2009 Research Associate, Department of Biology, HKUST  
2009 - 2015 Postdoctoral Fellow, Department of Clinical Oncology, HKU  
2015 – Present Research Assistant Professor, Department of Clinical Oncology, HKU

### **Relevant Research Interests:**

My main research interest is elucidation of the underlying mechanisms of molecular genetics and disease pathogenesis of several cancers including colorectal cancer (CRC), esophageal squamous cell carcinoma (ESCC) and nasopharyngeal carcinoma (NPC). My MPhil research focused on CRC molecular genetics. My PhD training aimed to use functional complementation approaches to map tumor suppressor genes (TSGs) in ESCC by microcell-mediated chromosome transfer (MMCT). Tools in molecular biology and various *in vitro* and *in vivo* functional assays are used to characterize candidate TSGs. Currently, I am interested in the elucidation of the genetic susceptibility factors responsible for NPC and ESCC development by the identification of the deleterious germline variants predisposing individuals with higher risk of cancer with the next-generation sequencing (NGS) technologies. Loss-of-function mutations in *BRCA2* involved in DNA double-strand break (DSB) repair and the *TERT* locus at 5p15.33 are hypothesized to play an etiological role in the familial ESCC and NPC development, respectively. I am also interested in translational research utilizing liquid biopsy and NGS analysis as tools for longitudinal monitoring of cancer progression and the molecular mechanism and clonal expansion of tumor evolution leading to disease relapse. Unravelling the genetic loci/pathways involved in these three cancer types will provide insights into novel therapeutics. Understanding the disease pathogenesis and metastasis will finally aid in the early diagnosis and identify potential prognostic biomarkers have implications for disease management and improvement of survival of patients.

## **External funding**

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2013-2015	Genomic studies of ESCC: familial genetic susceptibility and diagnostic biomarkers (Asian Fund for Cancer Research, Co-investigator)	\$1,100,000
2015-2017	The clinical relevance of telomere attrition and NPC genetic susceptibility (Health and Medical Research Fund, Principal investigator)	\$997,845
2017-2019	Optimizing the selection of patients with metastatic colorectal cancer for liver resection - an immunoclinical scoring system incorporating circulating tumor cell enumeration and clinical factors (Health and Medical Research Fund, Co-investigator)	\$946,000
2018-2020	Genomic and functional study of rare deleterious germline mutations in candidate genes associated with familial risk for esophageal carcinoma (Research Grants Council, Principal investigator)	\$971,720
2018-2019	Non-invasive real-time monitoring and next-generation sequencing of circulating tumor cells for improved personalized treatment of metastatic colorectal cancer patients (S.K. Yee Medical Foundation, Co-investigator)	\$926,000
2018-2020	Clinical application of enumeration and genomic characterization for non-invasive detection and real-time monitoring of circulating tumor cells for esophageal carcinoma (Health and Medical Research Fund, Co-investigator)	\$1,200,000

## **HKU internal funding**

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2013	Identifying germline alterations associated with familial esophageal squamous cell carcinoma <b>(Seed Fund for Basic Research, Co-investigator)</b>	\$50,500
2014	Study of alternative splicing of esophageal squamous cell carcinoma through transcriptome analysis in Hong Kong <b>(Small Project Funding, Principal investigator)</b>	\$46,327
2015	Validation and functional characterization of candidate genetic susceptibility loci and the inherited risk for familial esophageal squamous cell carcinoma (ESCC) <b>(Seed Fund for Basic Research, Principal investigator)</b>	\$150,070

2017-2019	Establishing platform technology for use of circulating tumor cells for cancer diagnostics and drug testing (Platform Technology Funding, Co-investigator)	\$1,000,000
2017	Genomic profiling of circulating tumor cells in patients undergoing liver resection for metastatic colorectal cancer <b>(Seed Fund for Basic Research, Co-investigator)</b>	\$77,570
2017	Genomic and functional study of rare deleterious germline mutations in RAD50 associated with familial risk for esophageal carcinoma <b>(Seed Fund for Basic Research, Principal investigator)</b>	\$44,320
2018	Redefining resectability for colorectal liver metastasis: the role of circulating tumor cells and its molecular characteristics <b>(Seed Fund for Basic Research, Co-investigator)</b>	\$55,000

## **Publications – Cancer Biology and Immunology**

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### **\*co-first authorship**

1. **\*Ko, J.M.Y.**, Ning, L., Zhao, X.K., Chai, A.W.Y., Lei, L.C., Choi, S.S.A., Tao, L.H., Law, S., Kwong, A., Lee, N.P.Y., Chan, K.T., Lo, A., Song, X., Chen, P.N., Chang, Y.L., Wang, L.D., and Lung, M.L., BRCA2 rare inactivating germline mutations are associated with esophageal squamous cell carcinoma in Chinese. *Int J Cancer*, under revision.
2. Yu, V.Z., **\*Ko, J.M.Y.**, Dai, W., Law, S., and Lung, M.L., Endoplasmic reticulum-localized ECM1b suppresses tumor growth and regulates MYC and MTORC1 through modulating MTORC2 activation in esophageal squamous cell carcinoma. *Cancer Letters*, 2019. Accepted.
3. Leong, M.M.L., Cheung, A.K.L., Dai, W., Tsao, S.W., Tsang, C.M., Dawson, C.W., **Ko, J.M.Y.**, and Lung, M.L., *EBV infection is associated with histone bivalent switch modifications in squamous epithelial cells*. *Proc Natl Acad Sci U S A*, 2019. **116**(28): p. 14144-14153.
4. Lin, W., Yip, Y.L., Jia, L., Deng, W., Zheng, H., Dai, W., **Ko, J.M.Y.**, Lo, K.W., Chung, G.T.Y., Yip, K.Y., Lee, S.D., Kwan, J.S., Zhang, J., Liu, T., Chan, J.Y., Kwong, D.L., Lee, V.H., Nicholls, J.M., Busson, P., Liu, X., Chiang, A.K.S., Hui, K.F., Kwok, H., Cheung, S.T., Cheung, Y.C., Chan, C.K., Li, B., Cheung, A.L., Hau, P.M., Zhou, Y., Tsang, C.M., Middeldorp, J., Chen, H., Lung, M.L., and Tsao, S.W., Establishment and characterization of new tumor xenografts and cancer cell lines from EBV-positive nasopharyngeal carcinoma. *Nat Commun*, 2018. 9(1): p. 4663.

5. Ng, H.Y., Li, J., Tao, L., Lam, A.K., Chan, K.W., **Ko, J.M.Y.**, Yu, V.Z., Wong, M., Li, B., and Lung, M.L., Chemotherapeutic Treatments Increase PD-L1 Expression in Esophageal Squamous Cell Carcinoma through EGFR/ERK Activation. *Transl Oncol*, 2018. 11(6): p. 1323-1333.
6. **Ko, J.M.Y.**, Tsang, K.H., Dai, W., Choi, S.S.A., Leong, M.M., Ngan, R.K., Kwong, D.L., Cheng, A., Lee, A.W., Ng, W.T., Tung, S., Lee, V.H., Lam, K.O., Chan, C.K., and Lung, M.L., Leukocyte telomere length associates with nasopharyngeal carcinoma risk and survival in Hong Kong Chinese. *Int J Cancer*, 2018. 143(9): p. 2289-2298.
7. Chai, A.W.Y., Cheung, A.K.L., Dai, W., **Ko, J.M.Y.**, Lee, N.P.Y., Chan, K.T., Law, S.Y., and Lung, M.L., Elevated levels of serum nidogen-2 in esophageal squamous cell carcinoma. *Cancer Biomark*, 2018. 21(3): p. 583-590.
8. Wong, V.C., \***Ko, J.M.Y.**, Lam, C.T., and Lung, M.L., Succinct workflows for circulating tumor cells after enrichment: From systematic counting to mutational profiling. *PLoS One*, 2017. 12(5): p. e0177276.
9. Dai, W., **Ko, J.M.Y.**, Choi, S.S.A., Yu, Z., Ning, L., Zheng, H., Gopalan, V., Chan, K.T., Lee, N.P., Chan, K.W., Law, S.Y., Lam, A.K., and Lung, M.L., Whole-exome sequencing reveals critical genes underlying metastasis in oesophageal squamous cell carcinoma. *J Pathol*, 2017. 242(4): p. 500-510.
10. Zheng, H., Dai, W., Cheung, A.K., **Ko, J.M.Y.**, Kan, R., Wong, B.W., Leong, M.M., Deng, M., Kwok, T.C., Chan, J.Y., Kwong, D.L., Lee, A.W., Ng, W.T., Ngan, R.K., Yau, C.C., Tung, S., Lee, V.H., Lam, K.O., Kwan, C.K., Li, W.S., Yau, S., Chan, K.W., and Lung, M.L., Whole-exome sequencing identifies multiple loss-of-function mutations of NF-kappaB pathway regulators in nasopharyngeal carcinoma. *Proc Natl Acad Sci U S A*, 2016. 113(40): p. 11283-11288.
11. Ng, H.Y., **Ko, J.M.Y.**, Yu, V.Z., Ip, J.C., Dai, W., Cal, S., and Lung, M.L., DESC1, a novel tumor suppressor, sensitizes cells to apoptosis by downregulating the EGFR/AKT pathway in esophageal squamous cell carcinoma. *Int J Cancer*, 2016. 138(12): p. 2940-51.
12. Dai, W., Zheng, H., Cheung, A.K., Tang, C.S., **Ko, J.M.Y.**, Wong, B.W., Leong, M.M., Sham, P.C., Cheung, F., Kwong, D.L., Ngan, R.K., Ng, W.T., Yau, C.C., Pan, J., Peng, X., Tung, S., Zhang, Z., Ji, M., Chiang, A.K., Lee, A.W., Lee, V.H., Lam, K.O., Au, K.H., Cheng, H.C., Yiu, H.H., and Lung, M.L., Whole-exome sequencing identifies MST1R as a genetic susceptibility gene in nasopharyngeal carcinoma. *Proc Natl Acad Sci U S A*, 2016. 113(12): p. 3317-22.
13. Chai, A.W., Cheung, A.K., Dai, W., **Ko, J.M.Y.**, Ip, J.C., Chan, K.W., Kwong, D.L., Ng, W.T., Lee, A.W., Ngan, R.K., Yau, C.C., Tung, S.Y., Lee, V.H., Lam, A.K., Pillai, S., Law, S., and Lung, M.L., Metastasis-suppressing NID2, an epigenetically-silenced gene, in the pathogenesis of nasopharyngeal carcinoma and esophageal squamous cell carcinoma. *Oncotarget*, 2016. 7(48): p. 78859-78871.
14. Yu, V.Z., Wong, V.C., Dai, W., **Ko, J.M.Y.**, Lam, A.K., Chan, K.W., Samant, R.S., Lung, H.L., Shuen, W.H., Law, S., Chan, Y.P., Lee, N.P., Tong, D.K., Law, T.T., Lee, V.H., and Lung, M.L., Nuclear Localization of DNAJB6 Is Associated With Survival of Patients With Esophageal Cancer and Reduces AKT Signaling and Proliferation of Cancer Cells. *Gastroenterology*, 2015. 149(7): p. 1825-1836 e5.

15. Lung, H.L., Man, O.Y., Yeung, M.C., **Ko, J.M.Y.**, Cheung, A.K., Law, E.W., Yu, Z., Shuen, W.H., Tung, E., Chan, S.H., Bangarusamy, D.K., Cheng, Y., Yang, X., Kan, R., Phoon, Y., Chan, K.C., Chua, D., Kwong, D.L., Lee, A.W., Ji, M.F., and Lung, M.L., SAA1 polymorphisms are associated with variation in antiangiogenic and tumor-suppressive activities in nasopharyngeal carcinoma. *Oncogene*, 2015. 34(7): p. 878-89.
16. Ip, J.C., **Ko, J.M.Y.**, Yu, V.Z., Chan, K.W., Lam, A.K., Law, S., Tong, D.K., and Lung, M.L., A versatile orthotopic nude mouse model for study of esophageal squamous cell carcinoma. *Biomed Res Int*, 2015. 2015: p. 910715.
17. Dai, W., Cheung, A.K., **Ko, J.M.Y.**, Cheng, Y., Zheng, H., Ngan, R.K., Ng, W.T., Lee, A.W., Yau, C.C., Lee, V.H., and Lung, M.L., Comparative methylome analysis in solid tumors reveals aberrant methylation at chromosome 6p in nasopharyngeal carcinoma. *Cancer Med*, 2015. 4(7): p. 1079-90.
18. Cheung, A.K., Ip, J.C., Chu, A.C., Cheng, Y., Leong, M.M., **Ko, J.M.Y.**, Shuen, W.H., Lung, H.L., and Lung, M.L., PTPRG suppresses tumor growth and invasion via inhibition of Akt signaling in nasopharyngeal carcinoma. *Oncotarget*, 2015. 6(15): p. 13434-47.
19. Cheng, Y., Ho, R.L., Chan, K.C., Kan, R., Tung, E., Lung, H.L., Yau, W.L., Cheung, A.K., **Ko, J.M.Y.**, Zhang, Z.F., Luo, D.Z., Feng, Z.B., Chen, S., Guan, X.Y., Kwong, D., Stanbridge, E.J., and Lung, M.L., Anti-angiogenic pathway associations of the 3p21.3 mapped BLU gene in nasopharyngeal carcinoma. *Oncogene*, 2015. 34(32): p. 4219-28.
20. **Ko, J.M.Y.**, Dai, W., Wun Wong, E.H., Kwong, D., Tong Ng, W., Lee, A., Kai Cheong Ngan, R., Chung Yau, C., Tung, S., and Li Lung, M., Multigene pathway-based analyses identify nasopharyngeal carcinoma risk associations for cumulative adverse effects of TERT-CLPTM1L and DNA double-strand breaks repair. *Int J Cancer*, 2014. 135(7): p. 1634-45.
21. Lung, M.L., Cheung, A.K., **Ko, J.M.Y.**, Lung, H.L., Cheng, Y., and Dai, W., The interplay of host genetic factors and Epstein-Barr virus in the development of nasopharyngeal carcinoma. *Chin J Cancer*, 2014. 33(11): p. 556-68.
22. **\*Ko, J.M.Y.**, Zhang, P., Law, S., Fan, Y., Song, Y.Q., Zhao, X.K., Wong, E.H., Tang, S., Song, X., Lung, M.L., and Wang, L.D., Identity-by-descent approaches identify regions of importance for genetic susceptibility to hereditary esophageal squamous cell carcinoma. *Oncol Rep*, 2014. 32(2): p. 860-70.
23. Cheng, Y., Cheung, A.K., **Ko, J.M.Y.**, Phoon, Y.P., Chiu, P.M., Lo, P.H., Waterman, M.L., and Lung, M.L., Physiological beta-catenin signaling controls self-renewal networks and generation of stem-like cells from nasopharyngeal carcinoma. *BMC Cell Biol*, 2013. 14(1): p. 44.
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25. Lo, P.H., **Ko, J.M.Y.**, Yu, Z.Y., Law, S., Wang, L.D., Li, J.L., Srivastava, G., Tsao, S.W., Stanbridge, E.J., and Lung, M.L., The LIM domain protein, CRIP2, promotes apoptosis in esophageal squamous cell carcinoma. *Cancer Lett*, 2012. 316(1): p. 39-45.

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27. Wong, V.C., **Ko, J.M.Y.**, Qi, R.Z., Li, P.J., Wang, L.D., Li, J.L., Chan, Y.P., Chan, K.W., Stanbridge, E.J., and Lung, M.L., Abrogated expression of DEC1 during oesophageal squamous cell carcinoma progression is age- and family history-related and significantly associated with lymph node metastasis. *Br J Cancer*, 2011. 104(5): p. 841-9.
28. Lung, H.L., Cheung, A.K., **Ko, J.M.Y.**, Cheng, Y., Stanbridge, E.J., and Lung, M.L., Deciphering the molecular genetic basis of NPC through functional approaches. *Semin Cancer Biol*, 2011.
29. Cheung, A.K., **Ko, J.M.Y.**, Lung, H.L., Chan, K.W., Stanbridge, E.J., Zabarovsky, E., Tokino, T., Kashima, L., Suzuki, T., Kwong, D.L., Chua, D., Tsao, S.W., and Lung, M.L., Cysteine-rich intestinal protein 2 (CRIP2) acts as a repressor of NF-kappaB-mediated proangiogenic cytokine transcription to suppress tumorigenesis and angiogenesis. *Proc Natl Acad Sci U S A*, 2011. 108(20): p. 8390-5.
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31. Lo, P.H., Lung, H.L., Cheung, A.K., Apte, S.S., Chan, K.W., Kwong, F.M., **Ko, J.M.Y.**, Cheng, Y., Law, S., Srivastava, G., Zabarovsky, E.R., Tsao, S.W., Tang, J.C., Stanbridge, E.J., and Lung, M.L., Extracellular protease ADAMTS9 suppresses esophageal and nasopharyngeal carcinoma tumor formation by inhibiting angiogenesis. *Cancer Res*, 2010. 70(13): p. 5567-76.
32. Chan, K.C., **Ko, J.M.Y.**, Lung, H.L., Sedlacek, R., Zhang, Z.F., Luo, D.Z., Feng, Z.B., Chen, S., Chen, H., Chan, K.W., Tsao, S.W., Chua, D.T., Zabarovsky, E.R., Stanbridge, E.J., and Lung, M.L., Catalytic activity of matrix metalloproteinase-19 is essential for tumor suppressor and anti-angiogenic activities in nasopharyngeal carcinoma. *Int J Cancer*, 2010.
33. Cheung, A.K., Lung, H.L., **Ko, J.M.Y.**, Cheng, Y., Stanbridge, E.J., Zabarovsky, E.R., Nicholls, J.M., Chua, D., Tsao, S.W., Guan, X.Y., and Lung, M.L., Chromosome 14 transfer and functional studies identify a candidate tumor suppressor gene, mirror image polydactyly 1, in nasopharyngeal carcinoma. *Proc Natl Acad Sci U S A*, 2009. 106(34): p. 14478-83.
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43. **Ko, J.M.Y.**, Cheung, M.H., Kwan, M.W., Wong, C.M., Lau, K.W., Tang, C.M., and Lung, M.L., Genomic instability and alterations in Apc, Mcc and Dcc in Hong Kong patients with colorectal carcinoma. *Int J Cancer*, 1999. 84(4): p. 404-9.
44. **Ko, J.M.Y.**, Cheung, M.H., Wong, C.M., Lau, K.W., Tang, C.M., Kwan, M.W., and Lung, M.L., K-ras codon 12 point mutational activation in Hong Kong colorectal carcinoma patients. *Cancer Lett*, 1998. 134(2): p. 169-76.

## **Book Chapters**

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1. Lung M.L., Dai W. and **Ko J.M.Y.** NPC Genetics and Genomics, Nasopharyngeal Carcinoma: from Etiology to Clinical Practice, Anne Lee, Maria Lung, WT Ng, Elsevier, 17-44, (2019)
2. Chen H., Ji M.F., Zong J.F., **Ko J.M.Y.**, Dai W. and Lung M.L. Conventional and novel diagnostic biomarkers and approaches for detection of NPC, Nasopharyngeal carcinoma: from Etiology to Clinical Practice, Anne Lee, Maria Lung, WT Ng, Elsevier, 129-154 (2019)
3. Cheung A.K.L., PHOON Y.P., Lung H.L., **Ko J.M.Y.**, Cheng Y. and Lung M.L. Roles of Tumor Suppressor Signaling on Reprogramming and Stemness Transition in Somatic Cells, Future Aspects of Tumor Suppressor Gene, Yue Cheng, InTech, 75-96, (2013)

## **On Line Protocol**

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**J.M.Y. Ko** and M.L. Lung. In vitro Human Umbilical Vein Endothelial Cells (HUVEC) Tube-formation Assay. Vol 2, Iss 18, September 20, 2012. DOI: 10.21769/BioProtoc.260

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## **Statement of research interests and vision**

My primary research interest is elucidation of the underlying molecular genetic basis of three cancers, namely colorectal cancer (CRC), esophageal squamous cell carcinoma (ESCC) and nasopharyngeal carcinoma (NPC) that are important to Hong Kong.

With my aim to understand the underlying genetic basis of ESCC pathogenesis, genomic studies of ESCC was initiated to elucidate the underlying familial genetic susceptibility and diagnostic biomarkers. Utilizing WES strategies to systematically and more comprehensively search for the genes associated with genetic risk, we subsequently obtained evidence that higher risk of ESCC is associated with patients with loss-of-function *BRCA2*. I am now focusing on the genomic and functional study of rare deleterious germline mutations in candidate genes associated with familial risk for ESCC.

I pioneered the establishment of needed approaches to study genetic susceptibility utilizing the high density SNP array and the next-generation sequencing (NGS) approaches for identification of the genetic alterations in both ESCC and NPC. My collaborative efforts in the big team of AoE facilitated the identification of host genetic elements in the HLA regions, DNA repair genes, *TERT* at 5p15.33, and showed for the first time that telomere length biology associates with NPC risk. The long-term goals of these studies are to identify individuals with high ESCC or NPC risk for earlier detection of cancer and provide new insights for therapeutic options. This knowledge is expected to translate into improved survival.

I am also interested in identification of biomarkers for early detection of cancer, metastatic relapse and prognosis. The suboptimal peripheral blood telomere length is independently associated with poorer survival in the late stage NPC patients.

The tumor biopsy is the gold standard for evaluation of treatment response. This traditional practise imposes limitations for precise personalized medicine due to the tumor heterogeneity and dynamically changes in clonal evolution upon treatment. I am currently establishing translational research focusing primarily on the clinical utility of liquid biopsy, i.e. circulating DNA (cfDNA) and CTC analysis, for non-invasive real-time monitoring for

early relapse and the molecular evolution of drug resistance. The long-term goal of these studies is to identify key genetic alterations that accompany disease progression to guide treatment with target therapy for personalized medicine and enhance clinical management to benefit the patient treatment outcomes.

My PhD study focused on the identification of putative tumor suppressor genes (TSGs) in ESCC using a functional complementation approach, microcell-mediated chromosome transfer (MMCT) and subsequently led the way to identifying harbored candidate TSGs at 3p14.2 (*ADAMTS9*), 13q14 (*THSD1*), and 14q32, *LTBP2*. These studies provided novel insights for the TSG molecular genetic basis and suggested the role of angiogenesis and extracellular matrix involved in ESCC carcinogenesis. This training strengthens my future research interests focusing on cancer biology and cancer microenvironment. It is hypothesized that the tumor progression to metastasis and drug resistance is related to the epithelial-mesenchymal transition (EMT) and chronic inflammation, which is induced by the tumor microenvironment (TME), including the immune cells, tumor-associated fibroblasts, bone marrow-derived inflammatory cells and lymphocyte infiltration. The cytokines and signaling molecules secreted by the tumors and cellular components in the TME may be the driving force for tumor heterogeneity arising during clonal selection upon disease progression. One focus of my research on the TME and immunology is to understand their roles in tumor metastasis and tumor heterogeneity with the aim to translate the findings to clinical benefits for the cancer patients.

In summary, I focus on three cancers of particular importance in Hong Kong: CRC, ESCC, and NPC. CRC is ranked at the top in incidence. NPC is the top cancer in young males. Survival rates for ESCC are dismal. There is a need for biomarkers that are useful for the early identification of the cancer and early relapse. I aim to focus on the translational studies of liquid biopsy for the identification of molecular markers that will be useful for disease risk stratification. Most cancer patients die from metastasis and elucidation of the mechanistic basis is important for identification of novel therapeutic insights. My long-term goal is translation of laboratory findings in cancer biology into clinical practice to enable precise personalized medicine.