

RGC Reference HKU3/CRF/11R
<i>please insert ref. above</i>

**The Research Grants Council of Hong Kong
Collaborative Research Fund Group Research Projects
Completion Report**

(for completed projects only)

Part A: The Project and Investigator(s)

1. Project Title

**Liver Transplantation Research Centre:
A Multidisciplinary Study for Liver Graft Injury**

2. Investigator(s) and Academic Department/Units Involved *(please highlight approved changes in the composition of the project team and quote the date when RGC granted approval of such changes)*

Research Team	Name/Post	Unit/Department/Institution	Average number of hours per week spent on this project in the current reporting period
Project Coordinator	Chung-Mau LO Chair Professor	Department of Surgery The University of Hong Kong	4
Co-Principal investigator(s)	Kwan MAN Professor	Department of Surgery HKU	8
	Xin-Yuan GUAN Professor	Department of Clinical Oncology, HKU	5
	Aimin XU Professor	Department of Medicine HKU	3
	Qi-Zhou LIAN Assistant Professor	Department of Ophthalmology HKU	4
	Nathalie WONG Professor	Department of Anatomical and Cellular Pathology, CUHK	2
	Jun YU Professor	Department of Medicine & Therapeutics, CUHK	6

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3. Project Duration

	Original	Revised	Date of RGC Approval (<i>must be quoted</i>)
Project Start Date	June 1, 2012		
Project Completion Date	May 31, 2015	Nov 30, 2015	April 20, 2016
Duration (<i>in month</i>)	36 months	42 months	
Deadline for Submission of Completion Report		Nov 30, 2016	

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Part B: The Final Report

5. Project Objectives

5.1 Objectives as per original application

1. To explore the biological implications of acute phase inflammatory response on the liver microenvironment and tumor behavior by investigating the circulating immune-cells in a series of in vivo and in vitro functional studies together with prospective clinical investigations.
2. To study the impact of acute phase liver graft injury on the induction of late phase chemoresistance after liver transplantation. Elucidation of cross-talks among inflammatory networking, endoplasmic reticulum stress and drug resistance will be carried out in a series of animal experiments and findings on mechanistic actions will be validated in clinical studies.
3. To characterize the cellular signaling pathways involved in fatty liver graft injury with liver regeneration impairment, nonalcoholic steatohepatitis (NASH) development and late phase liver fibrosis in various animal models and clinical series.
4. To define circulating markers including microRNA signatures associated with acute phase inflammatory injury and prediction of tumor recurrence and metastasis after liver transplantation.
5. To investigate the potentials of stem cell (hiPSCs-MSCs) therapies both for tissue repair during liver regeneration and for anti-inflammation together with anti-tumor recurrence as a novel pro-drug vehicle (MSCs-GPx3) to attenuate acute phase liver graft injury and prevent late phase tumor recurrence.

5.2 Revised objectives

Date of approval from the RGC: March 2012

Reasons for the change: Since more than 50% of the proposed budget has been cut, we have to remove the original objective 2 from the proposal. There will be numbers of animal models and in vitro functional experiments involved in the study of acute phase liver graft injury inducing late phase chemoresistance after liver transplantation. It will be difficult to achieve this objective using current budget. We would like to seek other funding source to conduct this part of the study.

Current Objectives:

1. To explore the biological implications of acute phase inflammatory response on the liver microenvironment and tumor behavior by investigating the circulating immune-cells in a series of in vivo and in vitro functional studies together with prospective clinical investigations.
2. To characterize the cellular signaling pathways involved in fatty liver graft injury with liver regeneration impairment, nonalcoholic steatohepatitis (NASH) development and late phase liver fibrosis in various animal models and clinical series.
3. To define circulating markers including microRNA signatures associated with acute phase inflammatory injury and prediction of tumor recurrence and metastasis after liver transplantation.
4. To investigate the potentials of stem cell (hiPSCs-MSCs) therapies both for tissue repair during liver regeneration and for anti-inflammation together with anti-tumor recurrence as a novel pro-drug vehicle (MSCs-GPx3) to attenuate acute phase liver graft injury and prevent late phase tumor recurrence.

6. Research Outcome

6.1 Major findings and research outcome

(maximum 1 page; please make reference to Part C where necessary)

1. The molecular signatures linked graft injury to tumor recurrence, induction of chemoresistance and NASH development

The molecular mechanisms of marginal liver graft regulating tumor recurrence, promoting chemoresistance and NASH development have been elucidated by a series of *in vivo* animal experiments and *in vitro* functional studies. Their clinical relevance has been also well validated in our clinical cohorts. We first reported that CXCL10/CXCR3 signaling mobilized circulating Tregs at early phase during liver graft injury promoted late phase tumor recurrence after transplantation (Li CX, et al., *J Hepatology* 2016; *Rising Star Award in ILTS2016*). We also demonstrated that M1 macrophages and Bregs play important roles for tumor growth and invasion (Shao et al., *Cancer Letter* 2015; Yeung et al., *J Hepatology* 2015). The up-regulation of CXCL10 in early-phase of liver transplantation can promote chemoresistance of HCC (Geng et al., *Oncotarget* 2016). We have also identified important mechanisms of carcinogenesis, metastasis and chemoresistance in liver cancer that will be valuable for development of effective therapeutic strategies to combat HCC recurrence (Chen et al., *Nature Medicine* 2013; Liu et al., *Hepatology*, 2013; Liu et al., *Gastroenterology*, 2014; Ng et al., *Mol Cancer Therapeutics* 2014; Qi et al., *Oncotarget* 2014). We have characterized the pathological mechanism and therapeutic potential of macrophages in NASH (Wu et al., *Expert Opin Ther Targets* 2016), the mechanism of CXCL10/CXCR3-mediated NASD development (Zhang et al., *J Hepatology* 2014; Zhang et al., *J Hepatology* 2016), and the mechanism of obesity-associated hepatocarcinogenesis (Shen et al., *Oncogene* 2016).

2. Distinct mechanisms regulating acute phase fatty liver graft injury, regeneration impairment and development of graft fibrosis

The acute phase inflammatory signaling plays critical roles on marginal liver graft injury. We have identified several important molecular targets leading to acute phase fatty liver graft injury including Lcn2, AR and RAP1 (Cheng et al., *Ann Surg* 2014; Li et al., *Ann Surg* 2014; Li et al., *J Hepatology* 2016). Targeted inhibition of these targets could reduce the acute phase hepatic injury via suppression of immune response. We also demonstrated that microRNA-29b could prevent liver fibrosis through attenuating stellate cell activation (Wang et al., *Oncotarget* 2014). The role of oval cells in contributing to fibrogenesis of marginal liver grafts under dynamic regulation of aldose reductase and notch signaling was also explored (Liu et al., *J Hepatology*, under review).

3. Circulating biomarkers bridging inflammatory responses and tumor invasiveness

The potential circulating markers including microRNA profiling and protein marker associated with acute phase inflammatory injury and prediction of tumor recurrence and metastasis after liver transplantation have been identified. We identified post-liver transplantation early-phase circulating miR-1246 which is a novel indicator of early-phase hepatic injury and a significant predictor for late-phase HCC recurrence after liver transplantation (Ng et al., *Oncotarget* 2016). We also determined that plasma level of GPX3 can serve as a circulating biomarker for both small-for-size liver graft injury and HCC recurrence as well as survival of HCC recipients after liver transplantation (Qi et al., *Theranostics* 2016). We demonstrated that down-regulation of GPX3 after liver transplantation could be an important mechanism contributing to HCC invasiveness (Qi et al., *Theranostics* 2016). In addition, we identified that circulating fibroblast growth factor 21 is a sensitive biomarker for severe ischemia/reperfusion injury after liver transplantation (Ye et al., *Sci Report* 2016).

4. hiPSC-MSCs therapies for tissue repair during regeneration

We demonstrated the repair potential of hiPSC-MSCs in different cell types such as airway epithelial cells and myocardial cells (Li et al., *Am J Respir Cell Mol Biol.* 2014; Liang et al., *Cell Death Dis.* 2015; Zhang et al., *Stem Cell Reports.* 2016; Li et al., *J Cell Mol Med.* 2016). Importantly, we applied hiPSC-MSCs to deliver GPX3 protein in HCC cells that could specially overexpress GPX3 protein in HCC cells and significantly suppress HCC growth in *in vivo* animal model (Qi et al., *Oncotarget* 2014). We also demonstrated that hiPSC-MSCs can promote liver regeneration and repair through mediating cell proliferation and macrophage polarization (Ma et al., manuscript in preparation).

6.2 Potential for further development of the research and the proposed course of action
(maximum half a page)

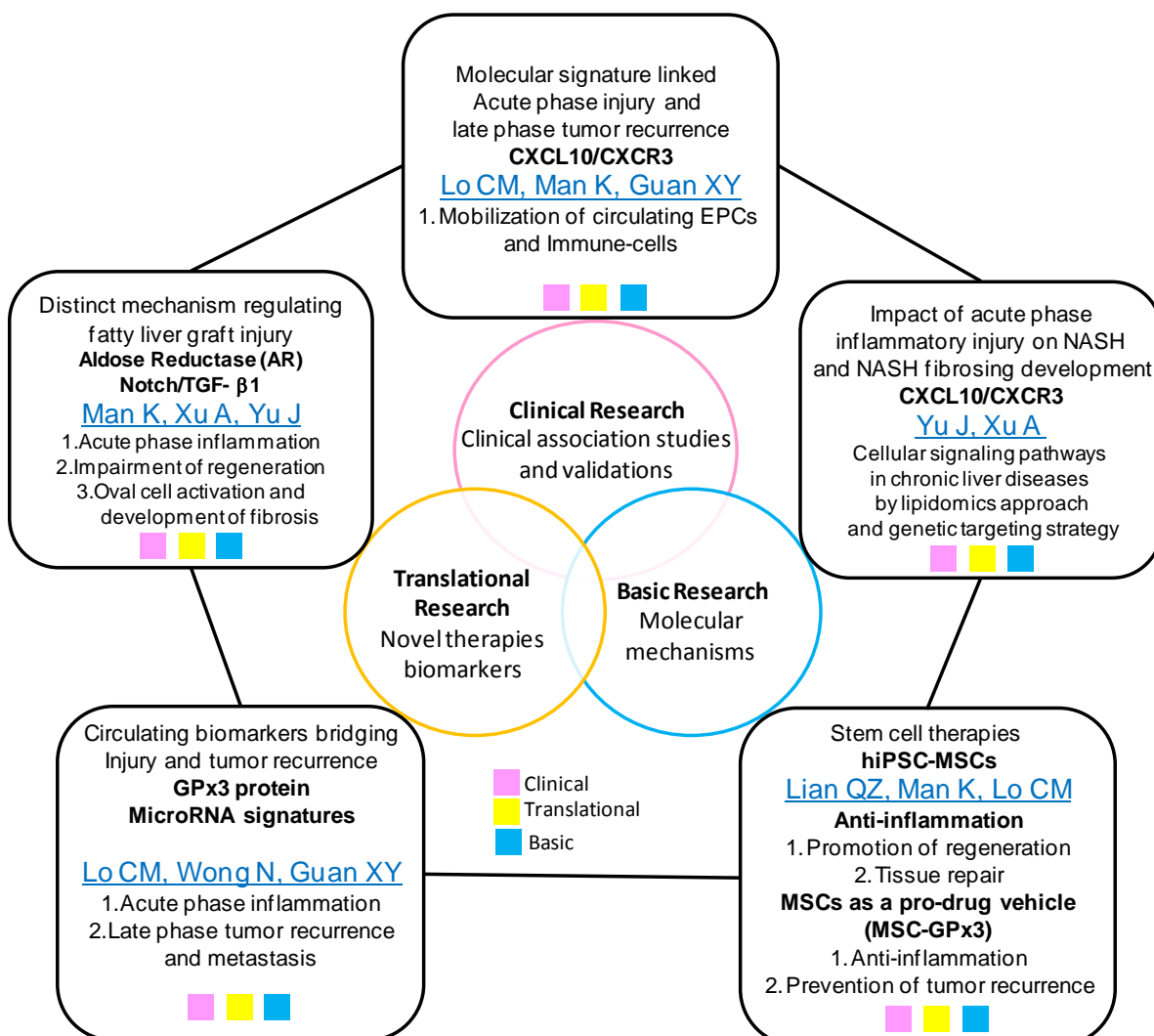
We would like to further develop the following research areas for liver transplantation:

1. To understand the role of regional specialization of immune system in tumor recurrence after liver transplantation by the approach of systems biology integrated with a series of clinical, basic and translational studies. The new concept of immunotherapies will be developed by educating the intragraft immune micro-environment to prevent tumor recurrence after liver transplantation.
2. To establish the novel therapeutics to overcome graft injury by using engineered cell therapy targeting for regional tissue repair and promoting functional liver regeneration.
3. To build a risk model for predicting patient outcomes after liver transplantation (graft injury, disease recurrence and patient survival) based on the molecular, immunological and biological features of the liver donors and recipients

- Proposed course of action: To apply for TBRS grant for the further developments.

6.3 Research collaboration achieved (please give details on the achievement and its relevant impact)

The synergism and collaborations among the PC/Co-PIs



National Collaborations:

Research area: Artificial Organ Support

State Key Laboratory for Infection Diseases

Zhejiang University (ZJU)

China

- MOU signed between State Key Laboratory for Infection Diseases and Laboratory for Organ Transplantation and Regeneration
- Exchange students/fellows trained in HKU
- Scientific Symposiums/Congresses jointly organized by ZJU

Regional Collaboration:

Research area: Application of lipic metabolomic analysis in graft injury and cancer

State Key Laboratory of Quality Research in Chinese Medicine

Macau University of Science and Technology (MUST)

Macau, China

- Scientific Symposiums jointly organized by MUST and HKU

International Collaborations:

Established: International Liver Transplantation consortium

Research area: Transplantation and Cancer Immunology

Established: Collaborations with: INSERM UMR 1064-Center for Research in Transplantation and Immunology

- We have jointly held the International Symposium of Transplantation & Cancer Immunology (ISTC) in Hong Kong, 18-20 May, 2015.

Taken together, the established collaborations among local investigators and national, regional as well as international scholars will enable us to further develop the advance research in the field of organ transplantation.

7. The Layman's Summary

(describe in layman's language the nature, significance and value of the research project, in no more than 200 words)

Liver transplantation is a life-saving treatment for patients with end stage liver diseases including liver cancer. However, graft injury is the key issue, which may cause graft dysfunction and fibrosis and promote cancer recurrence. In current study, we have explored the cellular and molecular mechanisms of liver graft injury after transplantation. We have successfully identified the novel circulating biomarkers indicating acute phase graft injury and predicting late phase tumor recurrence and metastasis after transplantation. The potentials of stem cell therapy for graft regeneration have been also explored. The findings from this project will perfect the outcome of *liver transplantation* by addressing the issue of *graft injury* through integrated *clinical, basic* and *translational* research. It will be important to develop novel therapeutic strategies for clinical liver transplantation in near future.

Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project
(Please attach a copy of the publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.)

Summary of Output:

Publication

30 peer-reviewed international articles, total impact factor =241.347

Abstracts for international conferences

58 abstracts

Students

22 postgraduate student trained (20 PhD and 2 MPhil)

Awards (Total 44 Awards)

1. Awards of international conferences (Mentor-Mentee Awards, Rising Star Award, Young Investigator Awards, Best presentation Awards): 26
2. Achievement Awards for PIs (The Natural Science Awards (First Class), The Chinese Medical Technology Award (First Class), State Scientific and Technological Progress Award (Second Class)): 9
3. Achievement Awards for students (University Scholarships and Best Research Output Awards):9

The Latest Status of Publications				Author(s) <i>(denote the corresponding author with an asterisk*)</i>	Title and Journal/Book <i>(with the volume, pages and other necessary publishing details specified)</i>	Submitted to RGC <i>(indicate the year ending of the relevant progress report)</i>	Attached to this report <i>(Yes or No)</i>	Acknowledged the support of RGC <i>(Yes or No)</i>	Accessible from the institutional repository <i>(Yes or No)</i>
Year of publication	Year of Acceptance <i>(For paper accepted but not yet published)</i>	Under Review	Under Preparation <i>(optional)</i>						
2016				Qi X, Ng KT, Shao Y, Li CX, Geng W, Ling CC, Ma YY, Liu XB, Liu H, Liu J, Yeung WH, Lo CM , Man K* .	The Clinical Significance and Potential Therapeutic Role of GPx3 in Tumor Recurrence after Liver Transplantation. Theranostics 2016, 6(11):1934-46.	No	yes	yes	yes
2016				Li CX, Ling CC, Shao Y, Xu A, Li XC, Ng KT, Liu XB, Ma YY,	CXCL10/CXCR3 signaling mobilized-regulatory T cells promote liver	No	yes	yes	yes

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				Qi X, Liu H, Liu J, Yeung OW, Zhai Y, <u>Lo CM</u> , <u>Man K*</u> .	tumor recurrence after transplantation. <i>Journal of Hepatology</i> 2016, May 28. pii: S0168-8278(16)30244-6.				
2016				Ng KT, <u>Lo CM</u> , <u>Wong N</u> , Li CX, Qi X, Liu XB, Geng W, Yeung OW, Chan SC, <u>Man K*</u> .	Early-phase circulating miRNAs predict tumor recurrence and survival of hepatocellular carcinoma patients after liver transplantation. <i>Oncotarget</i> 2016, 7(15):19824-39.	No	yes	yes	yes
2016				Li CX, <u>Lo CM</u> , <u>Lian QZ</u> , Ng KT, Liu XB, Geng W, Ma YY, Qi X, Ling CC, Yeung OW, Shao Y, Cheng Q, <u>Man K*</u> .	Repressor and activator protein accelerates hepatic ischemia reperfusion injury by promoting neutrophil inflammatory response. <i>Oncotarget</i> 2016 7(19):27711-23	No	yes	yes	yes
2016				Ye D, Li H, Wang Y, Jia W, Zhou J, Fan J, <u>Man K</u> , Lo C, Wong C, Wang Y, Lam KS, <u>Xu A*</u>	Circulating Fibroblast Growth Factor 21 Is A Sensitive Biomarker for Severe Ischemia/reperfusion Injury in Patients with Liver Transplantation. <i>Sci Rep.</i> 2016 Jan 25;6:19776. doi: 10.1038/srep19776.	No	yes	yes	yes
2016				Zhang X, Han J, <u>Man K</u> , Li X, Du J, Chu ES,	CXC chemokine receptor 3 promotes steatohepatitis in	No	yes	yes	yes

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				Go MY, Sung JJ, <u>Yu J*</u>	mice through mediating inflammatory cytokines, macrophage and autophagy. <i>J Hepatol.</i> 2016 Jan;64(1):160-70.				
2016				Wu R, Nakatsu G, Zhang X, <u>Yu J*</u>	Pathophysiological mechanisms and therapeutic potentials of macrophages in non-alcoholic steatohepatitis. <i>Expert Opin Ther Targets.</i> 2016 Jan 22:1-12.	No	yes	yes	yes
2016				Shen J, Tsoi H, Liang Q, Chu ES, Liu D, Yu AC, Chan TF, Li X, Sung JJ, Wong VW*, <u>Yu J*</u>	Oncogenic mutations and dysregulated pathways in obesity-associated hepatocellular carcinoma. <i>Oncogene.</i> 2016 May 2. doi: 10.1038/onc.2016.162. [Epub ahead of print]	No	yes	yes	yes
2016				Li X, Zhang Y, Liang Y, Cui Y, Yeung SC, Ip MS, Tse HF, <u>Lian Q,</u> Mak JC	iPSC-derived mesenchymal stem cells exert SCF-dependent recovery of cigarette smoke-induced apoptosis/proliferation imbalance in airway cells. <i>J Cell Mol Med.</i> 2016 Sep 19. doi: 10.1111/jcmm.12962.	No	yes	yes	yes
2015				Geng W, <u>Lo CM,</u> Ng KT, Ling CC, Qi X, Li CX, Zhai Y, Liu XB, Ma YY, <u>Man K*</u>	Interferon-gamma Inducible Protein 10 up-regulated by acute-phase graft injury induced late-phase cisplatin resistance after	No	yes	yes	yes

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					liver transplantation. <i>Oncotarget</i> 2015, 6(29):28042-56.				
2015				Wang J, Liu M, Chen L, Chan TH, Jiang L, Yuan YF, Guan XY*	Overexpression of N-terminal kinase like gene promotes tumorigenicity of hepatocellular carcinoma by regulating cell cycle progression and cell motility. <i>Oncotarget</i> 2015;6(3):1618-30.	No	yes	yes	yes
2015				Jiang L, Kwong DL, Li Y, Liu M, Yuan YF, Li Y, Fu L, Guan XY*	HBP21, a chaperone of heat shock protein 70, functions as a tumor suppressor in hepatocellular carcinoma. <i>Carcinogenesis</i> 2015;36(10):1111-20.	No	yes	yes	yes
2015				Zhang Y, Yu Z, Jiang D, Liang X, Liao S, Zhang Z, Yue W, Li X, Chiu SM, Chai YH, Liang Y, Chow Y, Han S, Xu A , Tse HF, Lian Q*	iPSC-MSCs with High Intrinsic MIRO1 and Sensitivity to TNF- α Yield Efficacious Mitochondrial Transfer to Rescue Anthracycline-Induced Cardiomyopathy. <i>Stem Cell Reports</i> . 2016 Oct 11;7(4):749-763.	No	yes	yes	yes
2015				Liang X, Ding Y, Zhang Y, Chai YH, He J, Chiu SM, Gao F, Tse HF, Lian Q*	Activation of NRG1-ERBB4 signaling potentiates mesenchymal stem cell-mediated myocardial repairs following	No	yes	yes	yes

					myocardial infarction. <i>Cell Death Dis.</i> 2015 May 21;6:e1765. doi: 10.1038/cddis.2015.91.				
2014				Tang CM, Yau TO, Yu J*	Management of chronic hepatitis B infection: Current treatment guidelines, challenges, and new developments. <i>World J Gastroenterol.</i> 2014 May 28;20(20):6262-78.	No	yes	yes	yes
		Yes		Liu XB, Lo CM , CHENG Q, Ng KT, Shao Y, Li CX, Chung SK, Ng IO, Yu J , Man K* .	Oval cells contribute to fibrogenesis of marginal liver grafts under dynamic regulation of aldose reductase and notch signaling. <i>Journal of Hepatology</i>	No	yes	yes	yes
			Yes	Ma YY, Li CX, Geng W, Qi X, Ng KT, Yeung WH, Lian QZ , Lo CM , Man K* .	Human induced pluripotent stem cells derived mesenchymal stem cells promote liver regeneration and repair through mediating cell proliferation and macrophage polarization	No	yes	yes	yes
2015				Wang J, Chu ES, Chen HY, Man K , Go MY, Huang XR, Lan HY, Sung JJ, Yu J*	microRNA-29b prevents liver fibrosis by attenuating hepatic stellate cell activation and inducing apoptosis through targeting PI3K/AKT pathway.	2015	No	yes	yes

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					<i>Oncotarget.</i> 2014 Oct 22. pii: 2621. [Epub ahead of print]				
2015				Yeung OW, Lo CM , Ling CC, Li CX, Qi X, Ng KT, Geng W, Forbes S, Guan XY , Poon RT, Fan ST, Man K* .	Alternatively Activated (M2) Macrophages Promoted Tumor Growth and Invasiveness in Hepatocellular Carcinoma. <i>Journal of Hepatology</i> 2015, 62:607-616.	2015	No	yes	yes
2015				Ng KT, Xu A, Cheng Q, Guo DY, Lim ZX, Sun CK, Fung JH, Poon RT, Fan ST, Lo CM , Man K* .	Clinical relevance and therapeutic potential of angiopoietin-like protein 4 in hepatocellular carcinoma. <i>Molecular Cancer</i> 2014, 13(1):196-213.	2015	No	yes	yes
2015				Ng KT, Lo CM , Guo DY, Qi X, Li CX, Geng W, Li XB, Ling CC, Ma YY, Yeung WH, Shao Y, Poon RT, Fan ST, Man K* .	Identification of transmembrane protein 98 as a novel chemoresistance -conferring gene in hepatocellular carcinoma. <i>Molecular Cancer Therapeutics</i> 2014, 13(5):1285-1297	2015	No	yes	yes
2014				Qi X, Ng KT, Lian QZ , Liu XB, Li CX, Geng W, Ling CC, Ma YY, Yeung WH, Tu WW, Fan ST, Lo CM , Man K* .	Clinical significance and therapeutic value of Glutathione peroxidase 3 (GPx3) in hepatocellular carcinoma. <i>Oncotarget</i> 2014, 5(22):11103-111 20.	2015	No	yes	yes

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2014				Shao Y, <u>Lo CM</u> , Ling CC, Liu XB, Ng KT, Chu AC, Ma YY, Li CX, Fan ST, <u>Man K</u> *.	Regulatory B cells accelerate hepatocellular carcinoma progression via CD40/CD154 signaling pathway. <i>Cancer Letters</i> 2014, 355(2):264-272.	2015	No	yes	yes
2014				Ye D, Wang Y, Li H, Jia W, <u>Man K</u> , <u>Lo CM</u> , Wang Y, Lam KS, <u>Xu A</u> *	Fibroblast growth factor 21 protects against acetaminophen-induced hepatotoxicity by potentiating peroxisome proliferator-activated receptor coactivator protein-1 α -mediated antioxidant capacity in mice. <i>Hepatology</i> . 2014 Sep;60(3):977-89.	2015	No	yes	yes
2014				Liu M, Li Y, Chen L, Chan TH, Song Y, Fu L, Zeng TT, Dai YD, Zhu YH, Li Y, Chen J, Yuan YF, <u>Guan XY</u> *	Allele-specific imbalance of oxidative stress-induced growth inhibitor 1 associates with progression of hepatocellular carcinoma. <i>Gastroenterology</i> 2014;146(4):1084-96.	2015	No	yes	yes
2014				Zhang X, Shen J, <u>Man K</u> , Chu ES, Yau TO, Sung JC, Go MY, Deng J, Lu L, Wong VW, Sung JJ, Farrell G, <u>Yu J</u> *	CXCL10 plays a key role as an inflammatory mediator and a non-invasive biomarker of non-alcoholic steatohepatitis. <i>Journal of Hepatology</i> . 2014 Dec;61(6):1365-75.	2015	No	Yes	Yes

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2014				Li X, Zhang Y, Yeung SC, Liang Y, Liang X, Ding Y, Ip MS, Tse HF, Mak JC, <u>Lian Q*</u> .	Mitochondrial transfer of induced pluripotent stem cell-derived mesenchymal stem cells to airway epithelial cells attenuates cigarette smoke-induced damage. <i>Am J Respir Cell Mol Biol.</i> 2014 Sep;51(3):455-65	2015	No	Yes	Yes
2013				Ling CC, Ng KT, Shao Y, Geng W, Xiao JW, Lui H, Li CX, Liu XB, Ma YY, Yeung WH, Qi X, <u>Yu J, Wong N, Zhai Y, Chan SC, Poon RT, Fan ST, Lo CM*, Man K*</u> .	Post-transplant Endothelial Progenitor Cell Mobilization via CXCL10/CXCR3 Signaling Promotes Liver Tumor Growth. <i>Journal of Hepatology.</i> doi:pii: S0168-8278(13)00612-0.10.1016/j.jhep.2013.08.017	2013	No	Yes	yes
2013				Li CX, Ng KT, Shao Y, Liu XB, Ling CC, Ma YY, Geng W, Qi X, Cheng Q, Chung SK, <u>Lo CM, Man K*</u> .	The inhibition of aldose reductase attenuates hepatic ischemia reperfusion injury through reducing inflammatory response. <i>Annals of Surgery</i> 2014, 260:317-328.	2013	No	Yes	yes
2013				Cheng Q, Ng KT, <u>Xu A, Li CX, Liu XB, Guo DY, Poon RT, Fan ST, Lo CM, Man K.</u>	The roles of Lipocalin-2 in small-for-size fatty liver graft injury. <i>Annals of Surgery</i> 2014, 260(6): 1062-1072.	2013	No	Yes	yes
2013				Chen L, Li Y, Lin CH, Chan TH, Chow RK, Song Y, Liu	Recoding RNA editing of AZIN1 predisposes to hepatocellular	2013	No	Yes	yes

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				M, Yuan YF, Fu L, Kong KL, Qi L, Li Y, Zhang N, Tong AH, Kwong DL, <u>Man K, Lo CM, Lok S, Tenen DG, Guan XY*</u> .	carcinoma. <i>Nature Medicine</i> . 2013 Feb;19(2):209-16.				
2013				Liu L, Dai Y, Chen J, Zeng T, Li Y, Chen L, Zhu YH, Li J, Li Y, Xie D, Yuan YF, <u>Guan XY*</u>	Maelstrom promotes hepatocellular carcinoma metastasis by inducing epithelial-mesenchymal transition via Akt/GSK-3 β /snail signaling. <i>Hepatology</i> . 2013 Aug 8. doi: 10.1002/hep.26677. [Epub ahead of print]	2013	No	Yes	yes
2013				Cheung KF, Zhao J, Hao Y, Li X, Lowe AW, Cheng AS, Sung JJ, <u>Yu J*</u> .	CITED2 is a novel direct effector of peroxisome proliferator-activated receptor γ in suppressing hepatocellular carcinoma cell growth. <i>Cancer</i> 2013, 119:1217-26	2013	No	Yes	yes
2013				Wang J, Zhao J, Chu ES, Mok MT, Go MY, <u>Man K, Heuchel R, Lan HY, Chang Z, Sung JJ, Yu J*</u> .	Inhibitory role of Smad7 in hepatocarcinogenesis in mice and in vitro. <i>J Pathol</i> 2013; 230: 441-452	2013	No	Yes	yes

9. Recognized international conference(s) in which paper(s) related to this research project was/were delivered (Please attach a copy of each conference abstract)

Month /Year /place	Title	Conference Name	Submitted to RGC (indicate the year ending of the relevant progress report)	Attached to this report (Yes or No)	Acknowledged the support of RGC (Yes or No)	Accessible from the institutional repository (Yes or No)
August, 2016, Hong Kong	Up-regulation of GSTA2 at early-phase after liver transplantation increases the risk of late-phase hepatocellular carcinoma recurrence.	International Congress of TTS	No	Yes	Yes	Yes
August, 2016, Hong Kong	The clinical significance and potential therapeutic role of GPx3 in tumor recurrence after liver transplantation.	International Congress of TTS	No	Yes	Yes	Yes
August, 2016, Hong Kong	AMP-activated protein kinase attenuated marginal liver graft injury via promoting mitochondrial biogenesis and respiratory function.	International Congress of TTS	No	Yes	Yes	Yes
August, 2016, Hong Kong	Stem cell like memory B cells attenuate hepatitis B virus relapse in hepatocellular carcinoma patients post liver transplantation	International Congress of TTS	No	Yes	Yes	Yes
August, 2016, Hong Kong	Clinical significance of transforming growth factor beta receptor III (TGFβR3) with its suppressive role on tumor associated macrophages in HCC	International Congress of TTS	No	Yes	Yes	Yes

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August, 2016, Hong Kong	Inflammasome exacerbated fatty graft injury with accumulation of myeloid-derived suppressor cells after living donor liver transplantation	International Congress of TTS	No	Yes	Yes	Yes
August, 2016, Hong Kong	Repressor and activator protein accelerates hepatic ischemia reperfusion injury by promoting neutrophil inflammatory response	International Congress of TTS	No	Yes	Yes	Yes
August, 2016, Hong Kong	Liver regeneration was attenuated by deletion of CXCL10 or its receptor CXCR3 via YAP1 signaling	International Congress of TTS	No	Yes	Yes	Yes
August, 2016, Hong Kong	Atg5/Atg7-independent macroautophagy mediates hepatic sinusoidal endothelial cells' response to ischemia-reperfusion injury	International Congress of TTS	No	Yes	Yes	Yes
May, 2016, Seoul	Early-phase up-regulation of glutathione S-transferase A2 promotes late-phase hepatocellular carcinoma recurrence after liver transplantation.	ILTS 22nd Annual International Congress	No	Yes	Yes	Yes
May, 2016, Seoul	A novel oxygen carrier sensitized Cisplatin based chemotherapy in hepatocellular carcinoma.	ILTS 22nd Annual International Congress	No	Yes	Yes	Yes
May, 2016, Seoul	AMP-activated protein kinase attenuated marginal liver graft injury via promoting mitochondrial biogenesis and respiratory function.	ILTS 22nd Annual International Congress	No	Yes	Yes	Yes

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May, 2016, Seoul	M2 macrophages activated by Toll like receptor 4 signaling accelerate tumor recurrence after liver transplantation.	ILTS 22nd Annual International Congress	No	Yes	Yes	Yes
May, 2015, Hong Kong	Regulatory B cells accelerate hepatocellular carcinoma pregression via CD40/CD154 signaling pathway.	International Symposium on Transplantation & Cancer Immunology	No	Yes	Yes	Yes
May, 2015, Hong Kong	The knockout of Rap1 accelerates liver regeneration after transplantation.	International Symposium on Transplantation & Cancer Immunology	No	Yes	Yes	Yes
May, 2015, Hong Kong	NLRP3 inflammasome induced graft injury regulated by telomere-independent repressor activator protein 1 (RAP1) / keratinocyte chemoattractant (KC) axis after LDLT.	International Symposium on Transplantation & Cancer Immunology	No	Yes	Yes	Yes
May, 2015, Hong Kong	Glutathione Peroxidase 3 (GPx3) suppressed HCC invasiveness through JNK-cJun-MMP2 signaling pathway	International Symposium on Transplantation & Cancer Immunology	No	Yes	Yes	Yes
May, 2015, Hong Kong	Increased tumor recurrence by M2 macrophages after liver transplantation	International Symposium on Transplantation & Cancer Immunology	No	Yes	Yes	Yes

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May, 2015, Hong Kong	Post-transplant Bregs promote the tumor recurrence via CXCL10/CXCR3 signaling	International Symposium on Transplantation & Cancer Immunology	No	Yes	Yes	Yes
May, 2015, Hong Kong	The roles of IP10 in liver regeneration and tissue repair are cell type dependent	International Symposium on Transplantation & Cancer Immunology	No	Yes	Yes	Yes
July, 2015, USA	Glutathione Peroxidase 3 (GPx3) suppressed HCC invasiveness through JNK-cJun-MMP2 signaling pathway - Application of in vivo real-time molecular imaging.	ILTS 21st Annual International Congress	No	Yes	Yes	Yes
Nov, 2014, Hong Kong	Clinical significance and therapeutic value of Glutathione Peroxidase 3 (GPx3) in Hepatocellular carcinoma	21st Hong Kong International Cancer Congress	No	Yes	Yes	Yes
Nov, 2014, Hong Kong	Regulatory B cells accelerate hepatocellular carcinoma progression via CD40/CD154 signaling pathway	22nd Hong Kong International Cancer Congress	No	Yes	Yes	Yes
May, 2014, USA	Mutations in Cel and Hras1 Are Associated With Obesity-Associated Hepatocellular Carcinoma.	Digestive Disease Week 2014	No	Yes	Yes	Yes
May, 2014, USA	Hepatic CXCR3 Promotes Non-Alcoholic Steatohepatitis Through Inflammation, Lipid Accumulation and Autophagy Deficiency.	Digestive Disease Week 2014	No	Yes	Yes	Yes

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May, 2014, USA	Decreased Lysosomal Function Impairs Autophagosome -Lysosome System in a Dietary Mice Model of Non-Alcoholic Fatty Liver Disease.	Digestive Disease Week 2014	No	Yes	Yes	Yes
May, 2014, USA	Inducible Macrophage Ablation Protects Mice From Non-Alcoholic Steatohepatitis.	Digestive Disease Week 2014	No	Yes	Yes	Yes
October, 2015, Spain	Role of Squalene Epoxidase (SQLE) in promoting fatty liver disease-associated liver cancer.	United European Gastroenterol J. 2015	No	Yes	Yes	Yes
October, 2015, Spain	Genomic mutations and pathways identified by whole-exome sequencing in NAFLD-associated hepatocellular carcinoma.	United European Gastroenterol J. 2015	No	Yes	Yes	Yes
October, 2015, Spain	O-GlcNAc transferase promotes fatty liver-associated liver cancer through activating JNK and NF-κB pathways.	United European Gastroenterol J. 2015	No	Yes	Yes	Yes
October, 2015, Spain	CXCL10 Mediates the Impairment of Autophagosome-lysosome System through Lysosome Dysfunction in Steatohepatitis.	United European Gastroenterol J. 2015	No	Yes	Yes	Yes
May, 2016, San Diego, CA, USA	CXC Chemokine Receptor 3 Causes Mitochondrial Dysfunction in the Development of Non-Alcoholic Steatohepatitis.	United European Gastroenterol J. 2015	No	Yes	Yes	Yes
May, 2016, USA	Bone Marrow-Derived Macrophage Contributes to Hepatic Nutritional Fibrosis Through Activating Hepatic Stellate Cells in Mice and <i>in vitro</i> .	United European Gastroenterol J. 2015	No	Yes	Yes	Yes

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July/2014 /USA	Hepatic Senescence Associated Down-regulation of Glutathione Peroxidase 3 (GPx3) Promoted Tumor Recurrence after Living Donor Liver Transplantation	World Transplant Congress	2015	No	Yes	Yes
July/2014 /USA	The knockout of Rap1 accelerates liver regeneration after transplantation	World Transplant Congress	2015	No	Yes	Yes
June/2014 /UK	Knockout of Telomere-independent Rap1 Attenuates Hepatic Ischemia Reperfusion Injury by Suppressing Neutrophil Activation.	The 2014 Joint International Congress of ILTS, ELITA & LICAGE	2015	No	Yes	Yes
June/2014 /UK	NLRP3 Inflammasome Regulated by Telomere-independent Repressor Activator Protein1(RAP1) Induced Graft Injury after LDLT	The 2014 Joint International Congress of ILTS, ELITA & LICAGE	2015	No	Yes	Yes
June/2014 /UK	The Role of RAP1 in Graft Injury Induced Cisplatin Resistance after Liver Transplantation.	The 2014 Joint International Congress of ILTS, ELITA & LICAGE	2015	No	Yes	Yes
June/2014 /UK	The Roles of IP10 in Liver Regeneration and Tissue Repair Are Cell Type Dependent	The 2014 Joint International Congress of ILTS, ELITA & LICAGE	2015	No	Yes	Yes
June/2013 /Singapore	Transplantation of human iPSC-derived MSC promotes liver regeneration and reduces inflammation attributed to paracrine actions-mediated macrophage depolarization .	The APASL Liver Week 2013	2015	No	Yes	Yes

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Nov/2013 /France	The knockout of telomere-independent Rap1 attenuates liver graft injury by suppressing macrophage activation	3 rd ESOT Basic Science Meeting & 13 th TTS Basic Science Symposium	2013	No	Yes	Yes
June / 2013/ Sydney, Australia	The role of Interferon-gamma Inducible Protein 10 (IP10) in acute phase graft injury induced cisplatin resistance after liver transplantation	ILTS 19 th Annual International Congress.	2013	No	Yes	Yes
June / 2013/ Sydney, Australia	Telomere-Independent Rap1 Accelerates Small-For-Size Liver Graft Injury by Enhancing Liver Inflammatory Responses.	ILTS 19 th Annual International Congress.	2013	No	Yes	Yes
June / 2013/ Sydney, Australia	Glutathione peroxidase 3 (GPx3) delivered by mesenchymal stem cells (MSC) ameliorates hepatic ischemia/reperfusion injuries.	ILTS 19 th Annual International Congress.	2013	No	Yes	Yes
June / 2013/France	M2 macrophages promote tumor growth and invasion in hepatocellular carcinoma	18th NAT 2013 conference	2013	No	Yes	Yes
May / 2012/USA	Acute phase circulating microRNAs predict tumor recurrence and survivals of hepatocellular carcinoma patients after liver transplantation.	ILTS 18 th Annual International Congress.	2013	No	Yes	Yes
May / 2012/USA	Novel mechanism for tissue repair of human induced pluripotent stem cells derived mesenchymal stem cells during liver regeneration	ILTS 18 th Annual International Congress.	2013	No	Yes	Yes
May / 2012/USA	Acute Phase Liver Graft Injury Mobilizes Regulating B cells after LDLT for HCC Patients Through TLR4/CXCL10/CXCR3 Signaling	ILTS 18 th Annual International Congress.	2013	No	Yes	Yes

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May / 2012/USA	Alternative activation of macrophages by liver graft injury promotes tumor recurrence after LDLT for HCC patients	ILTS 18 th Annual International Congress.	2013	No	Yes	Yes
July/2012 /Germany	Acute phase graft injury promotes tumor invasiveness through down-regulation of Glutathione Peroxidase 3 (GPx3) after liver transplantation	24 th International Congress of The Transplantation Society	2013	No	Yes	Yes
July/2012 /Germany	Acute Phase Graft Injury Mobilizes Regulating B cells after Living Donor Liver Transplantation for the Patients with Hepatocellular Carcinoma through TLR4/CXCL10/CXCR3 Signaling	24 th International Congress of The Transplantation Society	2013	No	Yes	Yes
May 19-22, 2013, Orlando, FL, USA	MicroRNA-29b Prevents Liver Fibrosis by Attenuating Hepatic Stellate Cell Activation and Inducing Apoptosis In Vitro and in Mice.	The Digestive Disease Week	2013	No	Yes	Yes
May 19-22, 2013, Orlando, FL, USA	Role of interferon- γ -inducible protein 10 in the pathogenesis of non-alcoholic steatohepatitis.	The Digestive Disease Week	2013	No	Yes	Yes
May 19-22, 2013, Orlando, FL, USA	CXCL10 induces hepatocyte apoptosis and autophagy in experimental non-alcoholic steatohepatitis	The Digestive Disease Week	2013	No	Yes	Yes
May 19-22, 2013, Orlando, FL, USA	Inhibitory Role of Peroxisome Proliferator-Activated Receptor Alpha in Hepatocarcinogenesis in Mice.	The Digestive Disease Week	2013	No	Yes	Yes
May 19-22, 2013, Orlando, FL, USA	BCL6B Inhibits Hepatocellular Carcinoma Metastases In Vitro and in Mice.	The Digestive Disease Week	2013	No	Yes	Yes

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May 19-22, 2013, Orlando, FL, USA	Epigenetic Inactivation of Claudin 3 in Hepatocellular Carcinoma and Its Functional Consequences.	The Digestive Disease Week	2013	No	Yes	Yes
June/2013/Singapore	Transplantation of human iPSC-derived MSC promotes liver regeneration and reduces inflammation attributed to paracrine actions-mediated macrophage depolarization	Asian Pacific Association for the Study of the Liver 2013	2013	No	Yes	Yes

10. Student(s) trained (please attach a copy of the title page of the thesis)

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Chang Chun LING	PhD	Jan-08	Apr-12
Wei GENG	PhD	Sep-09	Dec-12
Oscar Wai Ho YEUNG	PhD	Jun-09	May-13
Ming LIU	PhD	Sep-09	Aug-13
Chang Xiang LI	PhD	May-12	Jul-16
Cindy Ka Yee CHEUNG	PhD	2009	2015
Xiang Qi	PhD	1-Jan-10	1-Dec-13
Wilson Wu	PhD	2008	2012
Junhong Zhao	PhD	2009	2012
Yujuan Dong	PhD	2009	2012
Jun He	PhD	2009	2013
Nana Zhu	PhD	2010	2013
Jia Wang	PhD	2010	2013
Jiayun Shen	PhD	2010	2013
Xiang Zhang	PhD	2011	2014
Lixia Xu	PhD	2011	2014
Xiaojuan Wang	PhD	2012	2015
Kunning Wang	PhD	2012	2015
Xue Xiao	PhD	2012	2015
Lingxi Jiang	PhD	Sep-12	Jun-16
Siu Ming Chiu	MPhil	Sep-11	Oct-13
Senwei Tang	Mphil	2013	2015

11. Other impact (*e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.*)

Recipient	Award	Year	Awarder
Lo Chung Mau	Mentor and Mentee Traval Award (Mentor)	2016	The Transplantation Society (TTS)
Man Kwan	Mentor and Mentee Traval Award (Mentor)	2016	The Transplantation Society (TTS)
Qi Xiang	Mentor and Mentee Traval Award (Mentee)	2016	The Transplantation Society (TTS)
Liu Jiang	Mentor and Mentee Traval Award (Mentee)	2016	The Transplantation Society (TTS)
Ng Kevin Tak Pan	Young Investigator Award	2016	The Transplantation Society (TTS)
Yeung Oscar Wai Ho	Young Investigator Award	2016	The Transplantation Society (TTS)
Liu Jiang	Young Investigator Award	2016	International Liver Transplantation Society (ILTS)
Li Chang Xiang	Rising Star Award	2016	International Liver Transplantation Society (ILTS)
Yu Jun	Croucher Senior Research Fellowship	2016	Croucher foundation, Hong Kong
Man Kwan	Mentor and Mentee Award (Mentor)	2015	The Transplantation Society (TTS)
Li Chang Xiang	Mentor and Mentee Award (Mentee)	2015	The Transplantation Society (TTS)
Qi Xiang	Young Investigator Award	2015	International Liver Transplantation Society (ILTS)
Shao Yan	Outstanding Presentation Award	2015	International Symposium on Transplantation & Cancer Immunology, Hong Kong
Qi Xiang	Outstanding Presentation Award	2015	International Symposium on Transplantation & Cancer Immunology, Hong Kong
Liu Hui	Outstanding Presentation Award	2015	International Symposium on Transplantation & Cancer Immunology, Hong Kong

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Li Chang Xiang	Outstanding Presentation Award	2015	International Symposium on Transplantation & Cancer Immunology, Hong Kong
Li Chang Xiang	YS and Christabel Lung Postgraduate Scholarship	2015	Faculty of Medicine, The University of Hong Kong
Yu Jun	Outstanding Fellow of the Faculty of Medicine	2015	The Chinese University of Hong Kong
Li Chang Xiang	Wong Ching Yee Medical Postgraduate Scholarship	2014	Faculty of Medicine, The University of Hong Kong
Li Chang Xiang	Mentor and Mentee Award (Mentee)	2014	TTS and ILTS
Man Kwan	Mentor and Mentee Award (Mentor)	2014	TTS and ILTS
Lo Chung Mau, Man Kwan, Ng Kevin Tak Pan, Li Chang Xiang, Geng Wei, Liu Xiao Bing	The Chinese Medical Technology Award, First Class	2014	The Chinese Medical Association, China
Lo Chung Mau, Man Kwan, Ng Kevin Tak Pan	The Natural Science Award, First Class	2014	Ministry of Education, China
Qi Xiang	Poster Award	2014	Hong Kong International Cancer Congress
Yu Jun	The Natural Science Award, First Class	2014	Ministry of Education, China
Yeung Oscar Wai Ho	Best Research Output Award	2014	Department of Surgery, The University of Hong Kong
Chang Chung Ling	Best Research Output Award	2013	Department of Surgery, The University of Hong Kong
Yu Jun	State Scientific and Technological Progress Award, Second Class	2012	Ministry of Science and Technology of the People's Republic of China
Yu Jun	Science and Technology Progress Award, First Class	2012	Ministry of Education, China
Man Kwan	TTS Basic Science Mentor and Mentee Travel Award (Mentor)	2013	The Transplantation Society (TTS)

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Man Kwan	TTS Basic Science Mentor and Mentee Travel Award (Mentor)	2012	The Transplantation Society (TTS)
Li Chang Xian	TTS Basic Science Mentor and Mentee Travel Award (Mentee)	2013	The Transplantation Society (TTS)
Ma Yuen Yuen	The Young Investigator Award	2012	International Liver Transplantation Society (ILTS)
Ng Kevin Tak Pan	The Young Investigator Award	2012	International Liver Transplantation Society (ILTS)
Yeung Oscar Wai Ho	Travel Award	2013	18th NAT 2013 conference
Qi Xiang	TTS Basic Science Mentor and Mentee Travel Award (Mentee)	2012	The Transplantation Society (TTS)
Guan Xin-Yuan	Outstanding Researcher Award	2011-2012	The University of Hong Kong
Li Yan	Li Ka Shing Prizes	2011-2012	The University of Hong Kong
Liu Ming	Mary Sun Medical Scholarship (Postgraduate)	2011-2012	The University of Hong Kong
Liu Ming	YS and Christabel Lung Postgraduate Scholarship	2011-2012	The University of Hong Kong
Liu Ming	Joseph Shuk-Cho Lung Memorial Scholarship	2011-2012	The University of Hong Kong
Liu Ming	Yu To Sang and Yu Shing Keung Memorial Fund Scholarship	2011-2012	The University of Hong Kong

Project Coordinator

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