CRF 8G (Revised Sep 15)

RGC
Reference CUHK3/CRF/12R
please insert ref. above

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:
Macrophage-Myofibroblast-Transition in Organ Fibrosis: Molecular Mechanisms and Clinical Implications

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	Prof LAN Hui-yao	Medicine/CUHK	20
Co-Principal investigator(s)	Prof YU Cheuk-Man Prof HUI David SC Prof YU Jun Dr CHUNG Arthur CKDr LEUNG Joseph C	Medicine/CUHK Medicine/CUHK Medicine/CUHK LiHS/CUHK Medicine/HKU	5 5 10 10 10
Collaborators/ Others			

3. Project Duration

	Original	Revised	Date of RGC Approval *(must be quoted*)
Project Start Date	01/01/2013	01/06/2013	
Project Completion Date	31/12/2015	31/05/2016	
Duration (*in month*)	36	36	
Deadline for Submission of Completion Report		31/05/2017	

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Part B: The Final Report

5. Project Objectives

5.1 Objectives as per original application

1. To establish BM-derived MMT as a new, common, and major pathway of myofibroblast origin in patients and animal models of CVD, CKD, CLD, CPD, and PD.
2. To explore the role of MMT in organ scarring in CVD, CKD, CLD, CPD, and PD by conditionally deleting macrophages and by transferring with GFP^+ BM-macrophages or genetically-modified BM-macrophages.
3. To determine the mechanisms that drive MMT in five disease models in $GFP^+Smad3^{+/+}$ or $GFP^+Smad3^{-/-}$ BM chimeric mice and in BM-macrophages that lack Smad3, and to identify novel genes that drive MMT by using next-generation sequencing.
4. To develop novel therapies for CVD, CKD, CLD, CPD, and PD by targeting MMT with inhibitors to MIF and Smad3 or genetically-modified macrophages.

5.2 Revised objectives

Date of approval from the RGC:

Reasons for the change:

1.
2.
3. ....

6. Research Outcome

6.1 Major findings and research outcome
(maximum 1 page; please make reference to Part C where necessary)

In this CRF, a number of novel and significant findings have been achieved.

1) As expected, we found macrophages infiltrating the diseased tissues in both human and experimental models of kidney, heart, liver, lung, and peritoneal tissues are capable of converting into myofibroblast phenotype as demonstrated by co-expressing CD68 and α-SMA antigens. We thus first time described this new fibrogenic pathway as **m**acrophage-**m**yofibroblast **t**ransition (MMT) and named this fibrogenic macrophage phenotype as **MMT cells**. We also identified that the MMT cells are a major source of collagen-producing fibroblasts, accounting for 60-85% of total α-SMA+ cells. The discovery of MMT in chronic kidney transplantation has been published in *J Am Soc Nephrol* and was selected as a new discovery by the American Society of Nephrology

and a NEW was released to more than 450 media worldwide with great response, which is shown in **the Attachment 1 a**nd in a number of websites below: (https://medicalxpress.com/news/2017-02-discovery-tissue-scarring-transplanted-kidneys.html https://www.asn-online.org/about/press/releases/ASN_PR_20170216_JASN573LanFinalFeb16.pdf; https://medicalxpress.com/news/2017-02-discovery-tissue-scarring-transplanted-kidneys.html https://medicalxpress.com/news/2017-02-discovery-tissue-scarring-transplanted-kidneys.html https://scifeeds.com/news/discovery-may-help-prevent-tissue-scarring-and-rejection-of-transplanted-kidneys/ http://healthmedicinet.com/i2/discovery-may-help-prevent-tissue-scarring-and-rejection-of-transplanted-kidneys/). Thus, the major aim of this CRF to define MMT as a new and major source of myofibroblast origin during tissue fibrosis is fully established and received a worldwide reorganization.

2) We identified that MMT is derived from bone morrow macrophages as determined by using a number of cell-tracing studies including chimeric mice with Green Fluorescence Protein $(GFP)^+$ BM , adoptive transfer of GFP+ bone marrow-derived F4/80+ macrophages, and importantly, by using macrophage lineage tracing technique in LysM-Cre/Rosa-tdTomato mice. We found that more than 60% of α-SMA^+ myofibroblasts were shown to be donor BM-derived macrophages in models of obstructive nephropathy(CKD), ischemic cardiac remodeling (CVD), bleomycin-induced pulmonary disease(CPD), and peritoneal dialysis-related peritoneal fibrosis (PD). Macrophage depletion prevented MMT, substantially reduced the accumulation of α-SMA^+ myofibroblasts and collagen deposition in all five disease mouse models of CKD, CVD, CLD,CPD, and PD, revealing the functional importance of MMT in organ scarring.
3) We also discovered that MMT is regulated by a mechanism associated with TGF-β/Smad3 signaling. This is confirmed the findings that mice reconstituted with $GFP^+Smad3^{-/-}$ BM were protected against MMT and progressive fibrosis in CKD, CVD, CPD, and PD. In vitro, BM-derived macrophages lacking Smad3 were prevented from TGF-β1-induced MMT.
4) Finally, we also found that blockade of MMT by targeting the TGF-β/Smad3 signaling with a Smad3 inhibitor such as SIS3 and naringenin + Asiatic acid or by inactivating macrophages with a small molecule RPS19 that inhibits the binding of macrophage migration inhibitory factor (MIF) to its receptor CD74 were capable of inhibiting MIF-induced MMT in vitro and obstructive nephropathy in vivo. Thus, targeting the TGF-β/Smad3 signaling and the MMT pathway may represent a novel and specific therapeutic strategies for tissue fibrosis in chronic organ diseases. The research outcomes in renal fibrosis have received several scientific awards and a great asocial impact as described below (**Item 11. the other impact**) and the **Attachment 2**.
5) In addition, by using a single-cell-deep-sequencing, we further studied in-depth to explore the transcription regulation of MMT and found that a TGF-β/Smad3-dependent Src-centric regulatory network is responsible for MMT. Importantly, a neural transcription factor Pou4f1/Brn3a is essential transcription factor for MMT. This new discovery has resulted in a new ongoing research direction.

In summary, as shown in the Research Output (Part C: Items 8 and 9), our research team members have produced **50 peer-reviewed publications** and total of **35 Abstracts** have been presented in local and International Scientific conferences. As shown in Items 10 and 11, total of **7 PhD students** have been trained and **43 Scientific Awards and scholarships** have been awarded to our students and research team members. **A worldwide patent** (WO2014/063660**)** that targets TGF-β/Smad signaling for tissue fibrosis has been filed. In addition, **5 international or regional collaborations** have been established through this CRF project as outlined in Item 6.3.

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

The identification of MMT as a new fibrogenic pathway during multiple organ fibrosis is highly significant both scientifically and clinically and may lead to the new development of specific and effective anti-fibrosis drugs for prevention and treatment of chronic diseases including heart, kidney, liver, lung and other tissues.

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

This CRF has not only largely enhanced the collaboration among the investigators and institutions locally but also promoted the collaboration internationally, which is described below.

1) This CRF has established the collaboration with Dr David Nikolic-Paterson at Monash University, Australia, on the MMT study in renal fibrosis. This collaboration has resulted in several high impact publications as described in the Research Output and a joint research grant entitled "***TGF-β/Smad signaling in macrophage-mediated renal fibrosis***" has been successfully awarded by NH&MRC in 2017 (**App1122073**).

2) We also collaborated with Professor Chen Jianghua research team from Zhejiang University to study the potential role of MMT in chronic kidney transplantation rejection. The results has been published in J Am Soc Nephrol and the discovery was selected as an international news release to more 450 media as described above (**Attachment #1**).

3) Data from this CRF has also resulted in a joint application of a 973 program from Mainland China with Professor Fan Fan Hou at the Southern China Medical University on "*Mechanisms of Chronic Kidney Disease"* with total of RMB 34,000,000 awarded and RMB5,040,000 allocated to this study at CUHK Shenzhen Institute under PI Professor Lan (**2012CB517705**).

4) As described in the Specific Aim 4, we have developed a collaborative study withProfessor Anping Xu from Sun Yat-sen University, Professors Jörg Klug and Andreas Meinhardt Justus Liebig University Giessen, Giessen, Germany; Dr Güter Fingerle-Rowson from University Hospital Cologne to block the MMT with a MIF inhibitor, which was reported in World Congress of Nephrology (April 21-25, 2017, Mexico City, Mexico) as described in **Abstract (A1)**.

5) We also developed a collaborative study with Professor Liu Bichen at Southeaster China Medical University to study the role of inflammatory macrophages on acute kidney injury. Results are also published in Kidney Int (*Lv LL, et al. 2017 Mar;91(3):587-602*), which was highlighted by an Editorial commentary (*Kidney Int. 2017 Mar;91(3):526-529.)*.

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)

Fibrosis or tissue scarring is the final common pathway leading to the end-stage organ diseases. However, mechanisms related to tissue fibrosis remain unclear ad no effective treatment against fibrosis is available. In this study we identified that macrophage-myofibroblast transition (MMT) is a new and major pathway leading to organ scarring and functional loss in a number of life-threatening diseases in heart, kidney, liver, and lung. MMT cells are from bone marrow macrophages, a common inflammatory cell type infiltrating the diseased tissues, and are induced by

a fibrogenic growth factor called transforming growth factor-beta 1 via a signaling protein Smad3.We also found that targeting this MMT pathway is able to effectively prevent or treat organ fibrosis of the heart, kidney, liver, and lung diseases. Thus, findings from this study are highly significant and meaningful both scientifically and clinically.

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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.)

The Latest Status of Publications				Author(s) *(denote the corresponding author with an asterisk*)*	Title and Journal/Book *(with the volume, pages and other necessary publishing details specified)*	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*
Year of publication	Year of Acceptance (For paper accepted but not yet published)	Under Review	Under Preparation (optional)						
		YES (revised)		Tang P, Zhou S, Li C, Liao J, Xiao J, Wang QM, Lian GY, Li J, Huang XR, To KF, NG QF, Chonge C, Ma R, Lee TL, **Lan HY***	Proto-oncogene Tyrosine Protein Kinase Src is Essential for Macrophage-Myofibroblast Transition during Tissue Scarring. ***Kidney Int***		YES	YES	No
		YES (revised)		Fu S, Tang Y, Huang XR, Feng M, Xu AP, **Lan HY***	Smad7 protects against Acute Kidney Injury by rescuing tubular epithel cells from the G1 cell cycle arrest. ***Cli Sci (revised)***		YES	YES	No
		YES (revised)		Liu Z, Huang XR, Chen HY, Liu J, **Lan HY***	Deletion of ACE2 Promotes Hypertensive Nephropathy by Targeting Smad7 for Ubiquitin Degradation. ***Hypertension (revised)***		YES	YES	No
2017				Tang Y, Fung E, Xu A, **Lan HY**	C-reactive protein and ageing. ***Clin Exp Pharmacol Physiol.*** 20 Apr 4. doi: 10.1111/1440-1681.127		YES	YES	YES

					8. [Epub ahead of print]				
2017				Yang C, Huang XR, Fung E, Liu HF, **Lan HY***.	The Regulatory T-cell Transcription Factor Foxp3 Protects against Crescentic Glomerulonephritis. ***Sci Rep.*** 2017 May 3;7(1):1481		YES	YES	YES
2017				Tang PM, Zhou S, Meng XM, Wang QM, Li CJ, Lian GY, Huang XR, Tang YJ, Guan XY, Yan BP, To KF, **Lan HY**.	Smad3 promotes cancer progression by inhibiting E4BP4-mediated NK cell development. ***Nat Commun.*** 2017 Mar 6;8:14677.		YES	YES	YES
2017				Wang YY, Jiang H, Pan J, Huang XR, Wang YC, Huang HF, To KF, Nikolic-Paterson DJ, **Lan HY*,** Chen JH*.	Macrophage-to-myofibroblast transition contributes to interstitial fibrosis in chronic renal allograft injury. ***J Am Sco Nephrology*** 2017 Feb 16. pii: ASN.2016050573. doi: 10.1681/ASN.201605057 [Epub ahead of print]		YES	YES	YES
2017				Lv LL, Tang PM, Li CJ, You YK, Li J, Huang XR, Ni J, Feng M, Liu BC, **Lan HY***.	The pattern recognition receptor, Mincle, is essential for maintaining the M1 macrophage phenotype acute renal inflammation. ***Kidney Int.*** 2017 Mar;91(3):587-602		YES	YES	YES
2016				Shen J, Tsoi H, Liang Q, Chu ES, Liu D, Yu AC, Chan TF, Li X, Sung JJ, Wong VW*, **Yu J***	Oncogenic mutations and dysregulated pathways in obesity-associated hepatocellular carcinoma. ***Oncogene.*** 2016 ;35(49):6271-6280.		YES	YES	YES
2016				Wu R, Nakatsu G, Zhang X, **Yu J***	Pathophysiological mechanisms and therapeutic potentials of macrophages in non-alcoholic steatohepatitis. ***Expert Opin Ther Targets***. 2016 Jan 22:1-12		YES	YES	YES
2016				Zhang X, Han J,	CXC chemokine		YES	YES	YES

				Man K, Li X, Du J, Chu ES, Go MY, Sung JJ, **Yu J***	receptor 3 promotes steatohepatitis in mice through mediating inflammatory cytokines macrophage and autophagy. ***J Hepatol***. 2016;64(1):160-70.				
2016				Meng XM, Wang S, Huang XR, Yang C, Xiao J, Zhang Y, To KF, Nikolic-Paterson DJ, **Lan HY***.	Inflammatory macrophages can transdifferentiate into myofibroblasts during renal fibrosis. ***Cell Death Dis.*** 2016 Dec 1;7(12):e2495.		YES	YES	YES
2016				Lai W, Tang Y, Huang XR, Ming-Kuen Tang P, Xu A, Szalai AJ, Lou TQ, **Lan HY***	C-reactive protein promotes acute kidney injury via Smad3-dependent inhibition of CDK2/cyclin E. ***Kidney Int***. 2016 Sep;90(3):610-26.		YES	YES	YES
2016				You YK, Huang XR, Chen HY, Lyu XF, Liu HF, **Lan HY*.**	C-Reactive Protein Promotes Diabetic Kidney Disease in db/db Mice via the CD32b-Smad3-mTOR signaling Pathway. ***Sci Rep. 2***016 May 25;6:26740.		YES	YES	YES
2016				Meng XM, Nikolic-Paterson DJ, **Lan HY***.	TGF-β: the master regulator of fibrosis. ***Nat Rev Nephrol***. 2016 Jun;12(6):325-38		YES	YES	YES
2016				Dai XY, Huang XR, Zhou L, Zhang L, Fu P, Manthey C, Nikolic-Paterson DJ, **Lan HY***.	Targeting c-fms kinase attenuates chronic aristolochic acid nephropathy in mice. ***Oncotarget***. 2016 Mar 8;7(10):10841-56.		YES	YES	YES
2016				Zhao T, Sun S, Zhang H, Huang X, Yan M, Dong X, Wen Y, Wang H, **Lan HY**, Li P*.	Therapeutic Effects of Tangshen Formula on Diabetic Nephropathy in Rats. ***PLoS One***. 2016 Jan 25;11(1):e0147693.		YES	YES	YES
2016				Wang S, Meng XM, Ng YY, Ma FY, Zhou S, Zhang Y, Yang C, Huang XR,	TGF-β/Smad3 signalling regulates the transition of bone marrow-derived macrophages into		YES	YES	YES

				Xiao J, Wang YY, Ka SM, Tang YJ, Chung AC, To KF, Nikolic-Paterson DJ, **Lan HY*.**	myofibroblasts during tissue fibrosis. ***Oncotarge***t. 2016 Feb 23;7(8):8809-22.				
2015				Zhou Q, Xiong Y, Huang XR, Tang P, Yu X, **Lan HY***	Identification of Genes Associated with Smad3-dependent Renal Injury by RNA-seq-based Transcriptome Analysis ***Sci Rep.*** 2015 Dec 9;5:17901. doi: 10.1038/srep17901		YES	YES	YES
2015				Meng XM, Tang PM, Li J, **Lan HY***	Macrophage Phenotype in Kidney Injury and Repair. ***Kidney Dis*** (Basel). 2015 Sep;1(2):138-46		YES	YES	YES
2015				Meng XM, Zhang Y, Huang XR, Ren GL, Li J, **Lan HY*.**	Treatment of renal fibrosis by rebalancing TGF-β/Smad signaling with the combination of asiatic acid and naringenin. ***Oncotarget.*** 2015 Nov 10;6(35):36984-97.		YES	YES	YES
2015				Wang YY, Jiang H, Wang YC, Huang XR, Pan J, Yang C, Shou ZF, Xiang SL, Chen DJ, **Lan HY*,** Chen JH*.	Deletion of Smad3 improves cardiac allograft rejection in mice. ***Oncotarget.*** 2015 Jul 10;6(19):17016-30		YES	YES	YES
2015				Dai XY, Zhou L, Huang XR, Fu P, **Lan HY***.	Smad7 protects against chronic aristolochic acid nephropathy in mice. ***Oncotarget.*** 2015 May 20;6(14):11930-44.		YES	YES	YES
2015				Sun SF, Zhao TT, Zhang HJ, Huang XR, Zhang WK, Zhang L, Yan MH, Dong X, Wang H, Wen YM, Pan XP, **Lan HY**, Li P*	Renoprotective effect of berberine on type 2 diabetic nephropathy in rats. ***Clin Exp Pharmacol Physiol.*** 20 Jun;42(6):662-70		YES	YES	YES
2015				Zhang Y, Liu J, Luo JY, Tian XY,	Upregulation of Angiotensin		YES	YES	YES

				Cheang WS, Xu J, Lau CW, Wang L, Wong WT, Wong CM, **Lan HY**, Yao X, Raizada MK, **Huang Y*.**	(1-7)-Mediated Signaling Preserves Endothelial Function Through Reducing Oxidative Stress in Diabetes. ***Antioxid Redox Signal.*** 2015 Oct 10;23(11):880-92				
2015				Meng XM, Tang PM, Li J, **Lan HY*.**	TGF- β /Smad signaling in renal fibrosis. ***Front Physiol.*** 2015 Mar 19;6:82.		YES	YES	YES
2015				Zhou Q, Huang XR, Yu J, Yu X, **Lan HY***	Long Noncoding RNA Arid2-IR Is a Novel Therapeutic Target for Renal Inflammation. ***Mol Ther.*** 2015 Jun;23(6):1034-43.		YES	YES	YES
2015				Chen D, Xia M, Hayford C, Tham el-L, Semik V, Hurst S, Chen Y, Tam HH, Pan J, Wang Y, Tan X, Lan HY, Shen H, Kakkar VV, Xu Q, McVey JH, **Dorling A***	Expression of human tissue factor pathway inhibitor on vascular smooth muscle cells inhibits secretion of macrophage migration inhibitory factor and attenuates atherosclerosis in ApoE-/- mice. ***Circulation***. 2015 Apr 14;131(15):1350-60		YES	YES	YES
2014				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. ***Oncotarget.*** 2014;6(9):7325-38.		YES	YES	YES
				Below items were	submitted in Mid-Term Report in 2014				
2014				Nikolic-Paterson D J , Wang S, **Lan HY***	Macrophages promote renal fibrosis through direct and indirect mechanisms ***Kidney Int.,*** Suppl. 2014; 4: 34-38;	2014	No	YES	YES
2014				Meng XM, Nikolic-Paterson DJ, **Lan HY*.**	Inflammatory processes in renal fibrosis.	2014	No	YES	YES

					Nat Rev Nephrol. 2014;10:493-503.				
2014				Duan WJ, Yu X, Huang XR, Yu JW, **Lan HY***	Opposing Roles for Smad2 and Smad3 in Peritoneal Fibrosis in Vivo and in Vitro. ***Am J Pathol.*** 2014 Aug;184(8):2275-84	2014	No	YES	YES
2014				Tang YJ, Xiao J, Huang XR, Zhang Y, Yang C, Meng XM, Feng YL, Wang XJ, Hui DS, Yu CM, **Lan HY***	Latent TGF-β1 Protects Against Bleomycin-Induced Lung Injury in Mice. ***Am J Respir Cell Mol Biol.*** 2014 Dec;51(6):761-71	2014	No	YES	YES
2014				Zhang Y, Meng XM, Huang XR, Wang XJ, Yang L, **Lan HY***	TGF-β1 mediates psoriasis-like lesions via a Smad3-dependent mechanism in mice. ***Clin Exp Pharmacol Physiol.*** 2014 Nov;41(11):921-32	2014	No	YES	YES
2014				Zhang Y, Huang XR, Wei LH, **Chung** AC, Yu CM, **Lan HY**.	miR-29b as a therapeutic agent for angiotensin II-induced cardiac fibrosis by targeting TGF-β/Smad3 signaling. ***Mol Ther.*** 2014 May;22(5):974-85.	2014	No	YES	YES
2014				Li R, **Chung AC*,** Yu X, Lan HY.	MicroRNAs in Diabetic Kidney Disease. ***Int J Endocrinol.*** 2014;2014:593956.	2014	No	YES	YES
2014				Chen HY, Zhong X, Huang XR, Meng XM, You Y, Chung AC, **Lan HY*.**	MicroRNA-29b inhibits diabetic nephropathy in db/db mice. ***Mol Ther.*** **2**014 Apr;22(4):842-53.	2014	No	YES	YES
2014				Zhao TT, Zhang HJ, Lu XG, Huang XR, Zhang WK, Wang H, **Lan HY*, Li P*.**	Chaihuang-Yishen granule inhibits diabetic kidney disease in rats through blocking TGF-β/Smad3 signaling. ***PLoS One***. 2014 Mar 19;9(3):e90807	2014	No	YES	YES

2014				Chen H, Lan HY, Roukos DH, **Cho WC***.	Application of microRNAs in diabetes mellitus. ***J Endocrinol***. 2014l;222(1):R1-R10	2014	No	YES	YES
2014				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. ***Oncotarget.*** 2015;6(9):7325-38.	2014	No	YES	YES
2014				Wang J, Dong L, Xu L, Chu ES, Chen Y, Shen J, Li X, Wong CC, J Sung JJ, **Yu J***	B cell CLL/lymphoma 6 member B inhibits hepatocellular carcino ma metastases in vitro and in mice. ***Cancer Letters.*** 2014; 335(2): 192-200	2014	No	YES	YES
2014				Zhang N, Chu ES, Zhang J, Li X, Liang Q, Chen J, Chen M, Teoh N, Farrell G, Sung JJ, **Yu J***	Peroxisome proliferator activated receptor alpha inhibits hepatocarcinogenesis through mediating NF-κB signaling pathway. ***Oncotarget.*** 2014; 5(18): 8830-40	2014	No	YES	YES
2014				Jiang L, Yang YD, Fu L, Xu W, Liu D, Liang Q, Zhang X, Xu L, Guan XY, Wu B, Sung JJ, **Yu J***	CLDN3 inhibits cancer aggressiveness via Wnt-EMT signaling and is a potential prognostic biomarker for hepatocellular carcinoma. ***Oncotarget.*** 2014; 5(17): 7663-76.	2014	No	YES	YES
2014				Zhang X, Shen J, Man K, Chu ES, Yau TO, Sung JC, Go MY, Deng J, Lu L, Wong VW, Sung JJ, Farrell G, **Yu J***	CXCL10 plays a key role as an inflammatory mediator and a non-invasive biomarker of non-alcoholic steatohepatitis. ***J Hepatol.*** 2014 Jul 15.	2014	No	YES	YES

2013				Wang J, Zhao J, Chu ES, Mok MT, Go MY, Man K, Heuchel R, Lan HY, Chang Z, Sung JJ, **Yu J*.**	Inhibitory role of Smad7 in hepatocarcinogenesis in mice and in vitro. ***J Pathol.*** 2013;230(4):441-52.	2014	No	YES	YES
2013				Cheung KF, Zhao J, Hao Y, Li X, Lowe AW, Cheng AS, Sung JJ, **Yu J*.**	CITED2 is a novel direct effector of peroxisome proliferator-activated receptor γ in suppressing hepatocellular carcinoma cell growth. ***Cancer.*** 2013;119(6):1217-26.	2014	No	YES	YES
2013				Zhou Q, Yang M, Lan HY, Yu X*.	MiR-30a negatively regulates TGF-β-induced epithelial-mesenchymal transition and peritoneal fibrosis by targeting Snai1. ***Am J Pathol***. 2013 Sep;183(3):808-19.	2014	No	YES	YES
2013				Zhou Q, Chung AC, Huang XR, Dong Y, Yu X, **Lan HY***.	Identification of novel long noncoding RNAs associated with TGF-β/Smad3-mediated renal inflammation and fibrosis by RNA sequencing. ***Am J Pathol.*** 2014 Feb;184(2):409-17	2014	No	YES	YES
2013				Tang Y, Huang XR, Lv J, Chung AC, Zhang Y, Chen JZ, Szalai AJ, Xu A, **Lan HY***.	C-reactive protein promotes acute kidney injury by impairing G1/S-dependent tubular epithelium cell regeneration. ***Clin Sci (Lond).***	2014	No	YES	YES

					2014 May;126(9):645-59.				
2013				Chung AC, Yu X, **Lan HY***.	MicroRNA and nephropathy: emerging concepts. ***Int J Nephrol Renovasc Dis.*** 2013 Sep 25;6:169-79.	2014	No	YES	YES
2013				Li R, **Chung AC***, Dong Y, Yang W, Zhong X, Lan HY.	The microRNA miR-433 promotes renal fibrosis by amplifying the TGF-β/Smad3-Azin 1 pathway. ***Kidney Int.*** 2013 Dec;84(6):1129-44.	2014	No	YES	YES
2013				Wei LH, Huang XR, Zhang Y, Li YQ, Chen HY, Heuchel R, Yan BP, Yu CM, **Lan HY*.**	Deficiency of Smad7 enhances cardiac remodeling induced by angiotensin II infusion in a mouse model of hypertension. ***PLoS One.*** 2013;8(7):e70195.	2014	No	YES	YES
2013				Wei LH, Huang XR, Zhang Y, Li YQ, Chen HY, Yan BP, Yu CM, **Lan HY*.**	Smad7 inhibits angiotensin II-induced hypertensive cardiac remodelling. ***Cardiovasc Res.*** 2013 Sep 1;99(4):665-73.	2014	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)*

21-25/04/ 2017, Mexico City, Mexico	Macrophage migration inhibitory factor is a novel biomarker, mediator, and therapeutic target for acute kidney injury	World Congress of Nephrology		YES	YES	No
21-25/04/ 2017, Mexico City, Mexico	Impaired TGF-β/ Smad3 signaling exacerbates lupus nephritis by imbalancing Th17/Treg immunity.	World Congress of Nephrology		YES	YES	No
13-15/12/2 015, Hong Kong	Macrophage migration inhibitory factor promotes acute kidney injury by amplifying NF-κB-dependent inflammation	The 1st International Congress of Chinese Nephrology		YES	YES	No
13-15/12/2 015, Hong Kong	Long Noncoding RNA-7949 Regulates Macrophage Activation in Renal Inflammation via the TLR4/NF-kB Pathway	The 1st International Congress of Chinese Nephrology		YES	YES	No
13-15/12/2 015, Hong Kong	Long Non-coding RNA_5318 is A Novel Therapeutic Target For Renal Fibrosis in Obstructive Nephropathy	The 1st International Congress of Chinese Nephrology		YES	YES	No
13-15/12/2 015, Hong Kong	Protective Role of Smad7 in Acute Kidney Injury (AKI)	The 1st International Congress of Chinese Nephrology		YES	YES	No
13-15/12/2 015, Hong Kong	Macrophage Myofibroblast Transition Contributes to Renal Fibrosis in Allograft Rejection	The 1st International Congress of Chinese Nephrology		YES	YES	No
13-15/12/2 015, Hong Kong	A Novel Therapy for Type-2 Diabetic Nephropathy by Targeting Smad3-dependent lncRNA_5318	The 1st International Congress of Chinese Nephrology		YES	YES	No

13-15/12/2015, Hong Kong	Deletion of Smad3 Prevents Renal Fibrosis and Inflammation in Type 2 Diabetes	The 1st International Congress of Chinese Nephrology		YES	YES	No
13-15/12/2015, Hong Kong	Targeting c-fms kinase attenuates Chronic Aristolochic Acid Nephropathy in mice	The 1st International Congress of Chinese Nephrology		YES	YES	No
13-15/12/2015, Hong Kong	C- Reactive Protein Exacerbates Diabetic Kidney Fibrosis by Enhancing CD32-Smad3-mTOR Signaling in Human CRP-Tg/db/db Mice	The 1st International Congress of Chinese Nephrology		YES	YES	No
22-25/10/2015, Shenzhen, China	TGF-beta/Smad signaling pathway in kidney and cardiovascular diseases	The ISN Forefronts Symposium 2015 "Immunomodulation of Cardio-Renal Function: A focus on cardio-renal pathophysiology and immunity		YES	YES	No
22-25/10/2015, Shenzhen, China	ACE2/Mas double deficiency promotes angiotensin II-induced renal fibrosis by enhancing the ERK1/2 MAPK- Smad3 crosstalk pathway	The ISN Forefronts Symposium 2015 "Immunomodulation of Cardio-Renal Function: A focus on cardio-renal pathophysiology and immunity		YES	YES	No
3-8/11/2015; San Diego, CA, USA	C-Reactive Protein Promotes renal fibrosis in Type 2 Diabetes via CD32-Smad3-mTOR Signaling pathway In Vivo and In Vitro	2015 Kidney Week, Am Soc Nephrol		YES	YES	No

3-8/11/2015; San Diego, CA, USA	C-Reactive Protein Promotes AKI By Impairing TEC Regeneration Via The CD32-Smad3-P27 Dependent Inhibition Of CKD2/Cyclin E Mechanism.	2015 Kidney Week, Am Soc Nephrol		YES	YES	No
21-24/05, 2016, San Diego, CA, USA	Bone Marrow-Derived Macrophage Contributes to Hepatic Nutritional Fibrosis Through Activating Hepatic Stellate Cells in Mice and *in vitro.*	United European Gastroenterol J. 2015		YES	YES (verbally in presentation)	No
24-28/10, 2015 Barcelona, Spain	CXC Chemokine Receptor 3 Causes Mitochondrial Dysfunction in the Development of Non-Alcoholic Steatohepatitis.	United European Gastroenterol J. 2015		YES	YES (verbally in presentation)	No
24-28/10, 2015 Barcelona, Spain	CXCL10 Mediates the Impairment of Autophagosome-lysosome System through Lysosome Dysfunction in Steatohepatitis.	United European Gastroenterol J. 2015		YES	YES (verbally in presentation)	No
24-28/10, 2015 Barcelona, Spain	O-GlcNAc transferase promotes fatty liver-associated liver cancer through activating JNK and NF-κB pathways.	United European Gastroenterol J. 2015		YES	YES (verbally in presentation)	No
24-28/10, 2015 Barcelona, Spain	Genomic mutations and pathways identified by whole-exome sequencing in NAFLD-associated hepatocellular carcinoma.	United European Gastroenterol J. 2015		YES	YES (verbally in presentation)	No
24-28/10, 2015 Barcelona, Spain	Role of Squalene Epoxidase (SQLE) in promoting fatty liver disease-associated liver cancer.	United European Gastroenterol J. 2015		YES	YES (verbally in presentation)	No

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	Items below submitted previously in 2014					
4-6/06/2013, Guangzhou, China	Macrophage-mesenchymal transition in renal fibrosis (invited lecture).	The WCN 2013 Satellite Symposium on "Renal fibrosis: New insights into the pathogenesis and therapeutics.	2014	No	YES	No
3-6/04/2014, Bergamo, Italy	SMAD 3 for fibrosis	2014 ISN Nexus Symposium "New era of drug discovery and clinical trials in kidney disease".	2014	No	YES	No
9-12/08/2013, Oxford, London, UK	CRP as an inflammatory factor promotes metabolic syndrome and diabetic complications (invited lecture).	18th EASD-HAGEDORN OXFORD WORKSHOP	2014	No	YES	No
9-12/09/2013，Lisbon, Portugal	Urinary TGF-beta as a biomarker for chronic kidney disease （Plenary lecture）	1st International Conference on Urine –OMICS，	2014	No	YES	No
14-18/08/2014, Harbin, China	Treatment of cardiac fibrosis by targeting Smad3 signaling	12th International Congress of Society for Heart Research Chinese Section	2014	No	YES	No
10-11/04/2014, Guangzhou, China	Specific Inhibitor (SIS3) is a Novel Therapeutic Agent for Angiotensin II–induced Hypertensive Cardiac Remodeling	16th SCICC basic and translational medicine symposium	2014	No	YES	No

7-10/09/2014, Madrid, Spain	INCREASED ALTERNATIVELY ACTIVATED MACROPHAGES IN LONG-TERM PERITONEAL DIALYSIS PATIENTS	15th congress of the International Society for Peritoneal Dialysis	2014	No	YES	No
03-6/7, 2014, Yokohama, Japan	MicroRNA-29b inhibits peritoneal fibrosis in a mouse model of peritoneal dialysis	57th Annual Meeting of the Japanese Society of Nephrology	2014	No	YES	No
03-06/05/2014, Chicago, IL, USA	Decreased Lysosomal Function Impairs Autophagosome -Lysosome System in a Dietary Mice Model of Non-Alcoholic Fatty Liver Disease	Digestive Disease Week 2013	2014	No	YES	No
03-06/05/2014, Chicago, IL, USA	Inducible Macrophage Ablation Protects Mice From Non-Alcoholic Steatohepatitis.	Digestive Disease Week 2014	2014	No	YES	No
03-06/05/2014, Chicago, IL, USA	REC8, a Novel EBV-Associated Hypermethylated Gene, Contributes to the Pathogenesis of EBV-Associated Gastric Cancer. (Poster of Distinction)	Digestive Disease Week 2014	2014	No	YES	No
03-06/05/2014, Chicago, IL, USA	Mutations in Cel and Hras1 Are Associated With Obesity -Associated Hepatocellular Carcinoma. (Oral Presentation)	Digestive Disease Week 2014	2014	No	YES	No

03-06/05/2014, Chicago, IL, USA	Hepatic CXCR3 Promotes Non-Alcoholic Steatohepatitis Through Inflammation, Lipid Accumulation and Autophagy Deficiency. (Oral Presentation)	Digestive Disease Week 2014	2014	No	YES	No
03-06/05/2014, Chicago, IL, USA	Cholesterol Augments High Fat Diet in Accelerating Liver Carcinogenesis: Roles of NASH Oxidative Stress DNA Damage and Hepatocyte Proliferation. (Oral Presentation)	Digestive Disease Week 2014	2014	No	YES	No

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
Li Rong	PhD	2011-03-01	2013-12/2014-12
Jiayun Shen	PhD	01/08/2010	2013-08/2013-12
Xiang Zhang	PhD	01/08/2011	31/07/2014/2014-12
Jia Wang	PhD	01/08/2010	2013-08/2013-12
Chen Yang	PhD	01/08/2012	31-03-2016/12-2016
Yongke You	PhD	01/08/2013	30-08-2016/12-2016
Jinghong Li	PhD	01/08/2014	31-05-2016/12-2017

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

(1) Scientific Awards

With the support from the CRF grant and the best research outcomes obtained and postgraduate students trained, there are total of 16 awards to the students by internationally and locally.

1) Chen YANG (PhD student) received an **International Young Nephrologist Award** (Best Basic Science) on " The regulatory T cell transcriptional factor protects against crescentic glomerulonephritis" by International Society of Nephrology at World Congress of Nephrology 2013-May 31-June 4, Hong Kong.
2) Young Jianwen YU (PhD student) was awarded **a Travel Grant** for his invited Seminar entitled "MicroRNA-29b inhibits peritoneal fibrosis in a mouse model of peritoneal dialysis" in the 57th Annual Meeting of the Japanese Society of Nephrology and Asian Young Nephrologist Seminar, Yokohama, Japan (3-6/7, 2014)
3) Yonke You (PhD student) was awarded a **Travel Grant** by The European Association for the Study of Diabetes (EASD) for his presentation entitled "CRP as an inflammatory factor promotes metabolic syndrome and diabetic complications" in the 18th EASD Oxford Hagedorn Workshop to be held at Keble College, Oxford , UK (9-12/08/2013).

4) Jingxiu Meng (PDF) received **the Second Prize** for her oral presentation on " Specific Inhibitor (SIS3) is a Novel Therapeutic Agent for Angiotensin II–induced Hypertensive Cardiac Remodeling" in 16th SCICC Basic and Translational Medicine Symposium Guangzhou, China (10-11/04/2014).
5) Xiang Zhang (PhD student) was awarded **Yu To Sang and Yu Shing Keung Memorial Fund Scholarship 2012/2013;** issued by Senate Committee on University Scholarships, Hong Kong on July 17, 2013.
6) Lixia Xu (PhD student) was awarded **Poster of Distinction Award** for the project entitled "High dietary fat and cholesterol accelerate liver carcinogenesis by inducing DNA damage and promoting hepatocyte proliferation", Asian Pacific Association for The Study of the Liver (APASL), Brisbane 12 – 15 March 2014, Australia.
7) Lixia Xu (PhD student) was awarded **Reaching Out Award;** issued by Office of Admissions and Financial Aid, CUHK on April 15, 2014.
8) Lixia Xu (PhD student) was awarded **Yu To Sang and Yu Shing Keung Memorial Fund Scholarship 2013/2014;** issued by Senate Committee on University Scholarships, Hong Kong on May 5, 2014.
9) Kunning Wang (PhD candidate) was awarded **Poster of Distinction Award** for the project entitled "Promoter hypermethylation of a novel tumor suppressor MDGA2 predicts poor prognosis in gastric cancer", Digestive Disease Week (DDW) May 6 – May 12, 2014, Chicago.
10) Jia Wang (PhD student) was awarded **Poster of Distinction Award** for the project entitled "Promoter hypermethylation of a novel tumor suppressor MDGA2 predicts poor prognosis in gastric cancer", Digestive Disease Week (DDW) May 6 – May 12, 2014, Chicago.
11) Xiang Zhang (PhD student) was awarded **2nd prize at the CIGI Best Abstract Award** issued by The 2nd World Congress on CONTROVERSIES IN GASTROENTEROLOGY in Sep 12-14, 2014, Xi'an, China.
12) Lixia Xu (PhD student) was awarded **3rd prize at the CIGI Best Abstract Award** issued by The 2nd World Congress on CONTROVERSIES IN GASTROENTEROLOGY in Sep 12-14, 2014, Xi'an, China.
13) Shiyan Wang (PhD student) was awarded **Oral Free Paper Prize** for the project entitled "Colorectal cancer: Novel mechanism, novel targets", United European Gastroenterology Week (UEGW) 21 October 2014, Vienna, Austria.
14) Shiyan Wang (PhD student) was awarded **Travel grant** issued by the United European Gastroenterology Week (UEGW) 18-22 October 2014, Vienna, Austria.
15) Xiaojuan Wang (PhD candidate) was awarded **Travel grant** issued by the United European Gastroenterology Week (UEGW) 18-22 October 2014, Vienna, Austria.
16) Kunning Wang (PhD candidate) was awarded **Travel grant** issued by the United European Gastroenterology Week (UEGW) 18-22 October 2014, Vienna, Austria.
17) Jingwan Zhang (PhD candidate) was awarded **Yu To Sang and Yu Shing Keung Memorial Fund Scholarship 2014/2015** issued by Senate Committee on University Scholarships, Hong Kong on May 17, 2015.
18) Weiqi Xu (PhD candidate) was awarded **Travel grant** issued by the United European Gastroenterology Week (UEGW) 24-28 October 2015, Barcelona / Spain.
19) Dabin Liu (PhD candidate) was awarded **Travel grant** issued by the United European Gastroenterology Week (UEGW) 24-28 October 2015, Barcelona / Spain.
20) Xiang Zhang (post-doc fellow) was awarded **Travel grant** issued by the United European Gastroenterology Week (UEGW) 24-28 October 2015, Barcelona / Spain.
21) Xiangchun Li (PhD candidate) was awarded **Travel grant** issued by the United European Gastroenterology Week (UEGW) 24-28 October 2015, Barcelona / Spain.
22) Xiang Zhang (post-doc fellow) was awarded **National Scholar Award** issued by the United European Gastroenterology Week (UEGW) 24-28 October 2015, Barcelona / Spain.
23) Geicho Nakatsu (PhD candidate) was awarded **the Best Poster Presentation Award** issued by 2015 Probiotics, Prebiotics & Health Symposium, Hong Kong.
24) Yanquan Zhang (Post-doc fellow) was awarded **Scientific Accomplishement As An Early Stage**

Investigator issued by Digestive Disease Week (DDW) 21–24 May, 2016, San Diego, CA, USA.

25) Jieting Tang (Post-doc fellow) was awarded **Scientific Accomplishement As An Early Stage Investigator** issued by Digestive Disease Week (DDW) 21–24 May, 2016, San Diego, CA, USA.
26) Akira Higashimori (Visiting Scholar) was awarded **Scientific Accomplishement As An Early Stage Investigator** issued by Digestive Disease Week (DDW) 21–24 May, 2016, San Diego, CA, USA.
27) Jinghua Du (PhD candidate) was awarded **Scientific Accomplishement As An Early Stage Investigator** issued by Digestive Disease Week (DDW) 21–24 May, 2016, San Diego, CA, USA.
28) Jinghua Du (PhD candidate) was awarded **Basic Research travel award (one out of 20 in total)** issued by Digestive Disease Week (DDW) May 21-24, 2016, San Diego, CA, USA.
29) Ni Jun (PDF): **Best Abstract prize** by Nat Rew Nephrol in ISN Forefronts Symposium, China, Oct 2015.
30) You Yong Ke (PhD)**: Best Abstract prize** by 17th Diabetes and Cardiovascular Risk Factors – East Meets West Symposium, Hong Kong, Oct 2015.
31) You Yong Ke (PhD): **Best Poster Award** by The 1St International Congress of Chinese Nephrologists, Hong Kong, Dec 2015.
32) Lv LinLi (PDF): **Young Investigator Award** by The 1St International Congress of Chinese Nephrologists, Hong Kong, Dec 2015.
33) Sun SiFan (PhD): **Best Abstract and Young Investigator Awards** by The 1St International Congress of Chinese Nephrologists, Hong Kong, Dec 2015.
34) Fu Sha（PhD): **Best Poster Award** by The 1St International Congress of Chinese Nephrologists, Hong Kong, Dec 2015.
35) Wang Ying Ying (PhD): **Young Investigator Award** by The 1St International Congress of Chinese Nephrologists, Hong Kong, Dec 2015.

(2) Other major awards

1) Professor Hui Yao Lan (PC) was awarded as **Raine Visiting Professorship-2014** by Raine Medical Research Foundation, University of Western Australia.
2) Professor Hui Yao Lan (PC) was awarded as **Chon-Ming Li Professor of Biomedical Sciences-**2014 by the Chinese University of Hong Kong.
3) Professor Jun Yu was awarded as **First-class Higher Education Outstanding Scientific Research Output Award (Natural Science Award) 2014** by Ministry of Education of the People's republic of China.
4) Professor Jun Yu was awarded as **Outstanding Fellow of the Faculty of Medicine** by the Chinese University of Hong Kong.
5) Professor Jun Yu was awarded as **Croucher Senior Research Fellowship** by Croucher foundation, Hong Kong.
6) Professor Hui Yao Lan was awarded as **The 2nd class Higher Education Outstanding Scientific Research Output Awards 2014** on " Role of TGF-β/Smad signaling in renal fibrosis. Mechanisms and therapeutic implications （2014-128）.
7) Professor Hui Yao Lan was awarded as **The First Prize of Chinese Medical Science and Technology Award 2015**（201501230P1502）"Mechanisms, Prevention, and treatment for progressive chronic kidney diseases"。
8) Professor Hui Yao Lan was awarded as **2016 State Sciences and Technologies Award (2nd Class)** on "Mechanisms, Prevention, and treatment for progressive chronic kidney diseases .

(3) Patent Awards

Combined Product for the Treatment of Tissue Fibrosis (US 61/719,107; PCT/CN2013/086058; WO2014/063660) has been invented by Professor Lan with the Chinese University of Hong Kong.

Project Coordinator

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