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HUI-YAO LAN

07 INFLAMMATORY DISEASES

Research Progress Summary

The research team of Hui-yao Lan has been very productive with several important findings in year 2021.

Firstly, the team is continuous their research into the role and mechanisms of TGF- β /Smad signalling in acute and chronic kidney diseases by identifying that TGF- β is a master regulator of diabetic complications including cardiopathy and nephropathy. They discovered that TGF- β signals through its downstream mediator of Smad3 to mediate diabetic myocardopathy and nephropathy via a number of Smad3-dependent non-coding RNAs. They also found that latent form of TGF- β (inactive) and Smad7 are renal protective in diabetic nephropathy. Thus, targeting Smad3 or Smad3-dependent non-coding RNAs or overexpression of Smad7 may be a novel and specific therapeutic strategy for combating diabetic complications. All these findings have been published in internationally-well recognised journals as listed below. Specifically, they found that db/db lacking Smad3 are protected from diabetes and Smad3 deficiency promotes beta cell proliferation and function in db/db mice via restoring Pax6 expression (*Theranostics* 2021 Jan 1;11(6):2845-2859).

Secondly, they are continuously working on neuroimmune-related acute kidney and heart diseases by identifying that a neuron peptide Y (NPY) is produced by macrophages (CD68+NPY+) and protects against acute kidney and myocardial infarction by shifting proinflammatory M1 macrophages to reparative M2 macrophages. Results of "Neuropeptide Y (NPY) attenuates cardiac remodelling and deterioration of function following myocardial infarction" has been published in *Molecular Therapy* (2021 Oct 8;S1525-0016(21)00499-8). This is the first study to report that NPY is cardioprotective and is a novel therapeutic agent for acute myocardial infarction. This new finding may lead to develop as a novel therapy for acute myocardial infarction. Thus, this new discovery is highly significant both scientifically and clinically in cardiovascular medicine.

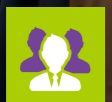
Thirdly, they have extended their previous discovery of macrophage-to-myofibroblast transition (MMT) in tissue fibrosis to cancer progression. They found that TGF- β 1 can activate its downstream molecule Smad3 to promote cancer by triggering tumour-associated macrophages (TAM) to become cancer-associated fibroblasts (CAF) via the macrophage-





Principal Investigator

Hui-yao Lan



Team members

Xiaoru Lan, Guangyu Lian, Thomas Mak, Biao Wei, Choilai Chung, Yuyan Qin, Huijun He, Jiaoyi Chen, Junzhe Chen, Qixia Shen, Yuchen Wang, Jiangchun Li, Liying Liang, Wenbiao Wang, Wenqian Xu, Wenjiang Wu, Yu Zhong

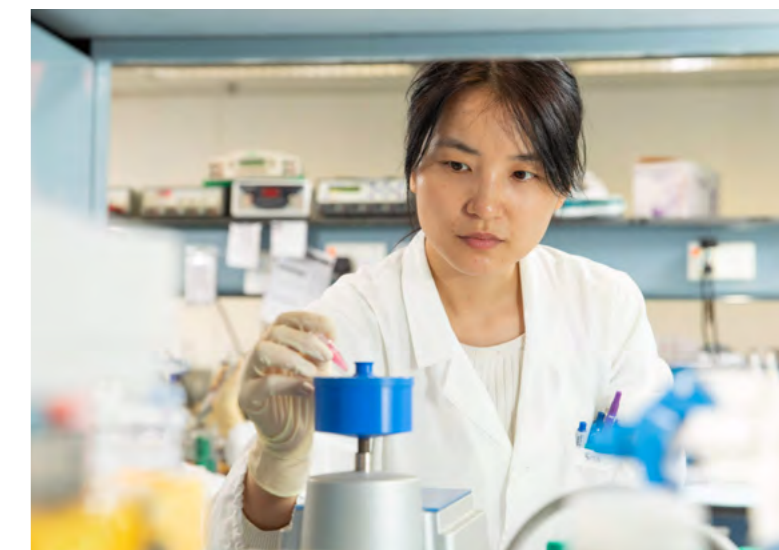
myofibroblast transition mechanism (MMT). These findings have been published in *Advanced Science* (2021 Nov17;e2101235) with a *Press Release* on 23 December, 2021.

Lastly, they also found that macrophages mediate crescent glomerulonephritis via TLR4-dependant mechanism as deletion of TLR4 from macrophages resulted in the shift from inflammatory macrophages to the anti-inflammatory macrophages. Such important findings have been published in *Cellular and Molecular Life Sciences* (2021 Oct;78(19-20):6721-6734).

More excitingly, the research team has been also studying COVID-19 associated acute kidney injury (AKI) because up to 45% of critically ill COVID-19 patients develop AKI with higher mortality secondary to the lung injury. They identified that one of SARS-CoV-2 proteins, SARS-CoV-2 N protein is a key mediator for AKI and induces AKI via the Smad3-dependent G1 cell cycle arrest mechanism. Targeting Smad3 with a Smad3 inhibitor can prevent SARS-CoV-2 N protein-induced AKI. These findings are highly significant both scientifically and clinically and may lead to the development of novel therapy for COVID-19 AKI with a patent

filled. These findings have been also published in an internationally high impact journal *Advanced Science* (2021 Nov 23;e2103248) with a *Press Release* on 29 November, 2021.

In summary, 2021 was a year worthy of the team's respect and memory. They are looking forward to achieving even greater goals in 2022.



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Hui-yao Lan Patrick Tang	Gold Medal with Congratulations of the Jury - 2021	The 2021 Special Edition of the Geneva International Exhibition of Inventions
Hui-yao Lan	Science and Technology Progress Award (3 rd Class) - 2021	Sichuan Provincial Government, China
	Distinguished Scientist Award	Chinese American Society of Nephrology

Academic Editorship

Member's Name	Details	
	Role	Journal
Hui-yao Lan	Editor-in Chief	Integrative Medicine in Nephrology and Andrology
	Editor	Clinical and Experimental Pharmacology and Physiology
	Executive Editor	International Journal of Biological Sciences
	Associate Editor	Journal of Clinical and Molecular Medicine
		Frontiers in Psychology
	Molecular Therapy	

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Hui-yao Lan	Reviewer	Journal of American Society of Nephrology
		Kidney International
		Scientific Reports
		Kidney Disease
		Diabetic Nephropathy

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK\$)
Hui-yao Lan	Regulatory Role of Smad3 in SARS-CoV-2 N Protein-induced Acute Kidney Injury in db/db Mice	Research Grants Council – General Research Fund	01/07/2021	31/12/2023	1,125,732
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	01/03/2019	28/02/2024	12,000
	Role of TGF-Beta/Smad3 Signaling in Lupus Nephritis	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,064,682
	Mechanism of Renal Inflammation: Role of Toll-like Receptor 4	Research Grants Council – Collaborative Research Fund	30/06/2017	29/06/2021	7,518,927
	Terminal Shortening Triggers the Molecular Regulation Mechanism of Neutrophil Capture in Acute Kidney Injury	Zhejiang University – Collaborative Research Fund	01/01/2019	31/12/2021	RMB 700,000
	Research Laboratory with Guangdong Province Hospital on Immunological and Genetic Kidney Diseases	Guangdong Provincial Department of Science and Technology, China	01/01/2020	31/01/2022	RMB 1,000,000
	Neuropeptide Y is a Novel Therapeutic Agent for Acute Myocardial Infarction	Food and Health Bureau – Health and Medical Research Fund	01/04/2020	31/03/2023	1,499,600
	Prevention and Treatment of Diabetes and Diabetic Complications by Targeting Smad3 with a Smad3 Inhibitor SIS3	Food and Health Bureau – Health and Medical Research Fund	01/04/2019	31/03/2022	1,500,000
	Regulatory Role and Mechanism of Smad3 in Immunosuppression of Neutrophil Anticancer Activities	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	1,151,040

Publications

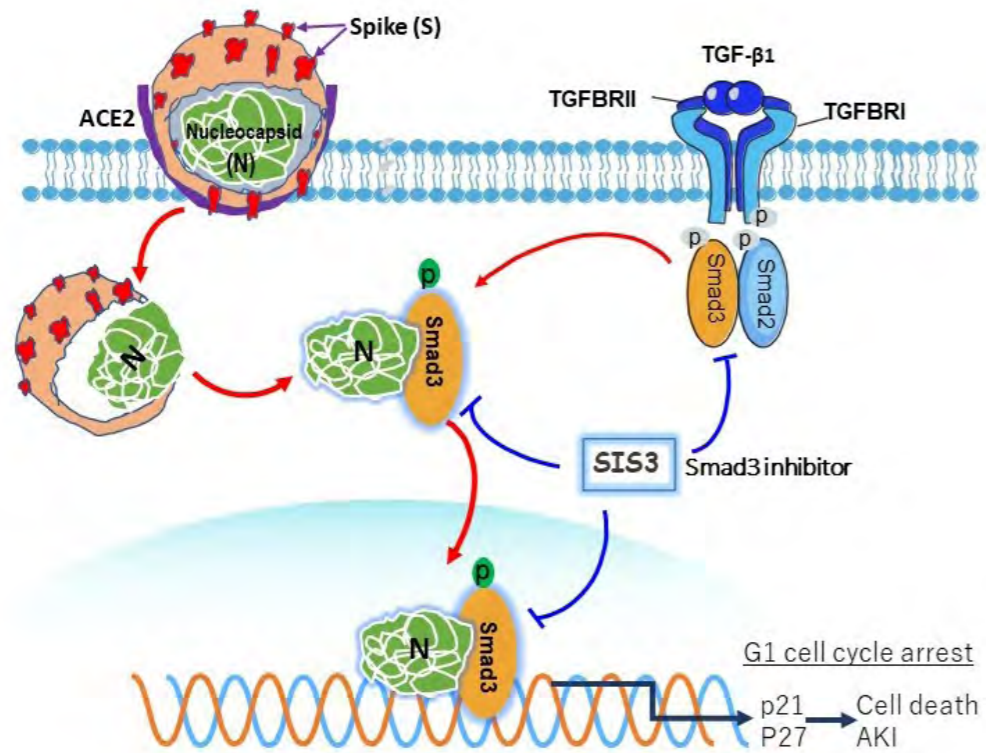
A. Journal Papers

1. Wang W, Chen J, Hu D, Pan P, Liang L, Wu W, Tang Y, Huang XR, Yu X, Wu J, Lan HY. SARS-CoV-2 N protein induces acute kidney injury via Smad3-dependent G1 cell cycle arrest mechanism. *Advanced Science*. Published online 2021:2103248. doi:10.1002/advs.202103248. (Epub ahead of print)
2. Tang PCT, Chung JYF, Xue VWW, Xiao J, Meng XM, Huang XR, Zhou S, Chan ASW, Tsang ACM, Cheng ASL, Lee TL, Leung KT, Lam EWF, To KF, Tang PMK, Lan HY. Smad3 promotes cancer-associated fibroblasts generation via macrophage–myofibroblast transition. *Advanced Science*. Published online 2021:2101235. doi:10.1002/advs.202101235. (Epub ahead of print)
3. Qin YY, Huang XR, Zhang J, Wu W, Chen J, Wan S, Yu XY, Lan HY. Neuropeptide Y attenuates cardiac remodeling and deterioration of function following myocardial infarction. *Molecular Therapy*. Published online 2021. doi:10.1016/j.ymthe.2021.10.005. (Epub ahead of print)
4. You YK, Wu WF, Huang XR, Li H Di, Ren YP, Zeng JC, Chen H, Lan HY. Deletion of Smad3 protects against C-reactive protein-induced renal fibrosis and inflammation in obstructive nephropathy. *International Journal of Biological Sciences*. 2021;17(14):3911-3922. doi:10.7150/ijbs.62929.
5. Xue VW, Chung JYF, Tang PCT, Chan ASW, To THW, Chung JSY, Mussal F, Lam EWF, Li C, To KF, Leung KT, Lan HY, Tang PMK. USMB-shMincle: A virus-free gene therapy for blocking M1/M2 polarization of tumor-associated macrophages. *Molecular Therapy - Oncolytics*. 2021;23:26-37. doi:10.1016/J.OMTO.2021.08.010.
6. Yang F, Chen J, Huang XR, Yiu WH, Yu X, Tang SCW, Lan HY. Regulatory role and mechanisms of myeloid TLR4 in anti-GBM glomerulonephritis. *Cellular and Molecular Life Sciences*. 2021;78(19-20):6721-6734. doi:10.1007/s00018-021-03936-1.
7. Chung JYF, Chan MKK, Tang PCT, Chan ASW, Chung JSY, Meng XM, To KF, Lan HY, Leung KT, Tang PMK. AANG: A natural compound formula for overcoming multidrug resistance via synergistic rebalancing the TGF- β /Smad signalling in hepatocellular carcinoma. *Journal of Cellular and Molecular Medicine*. 2021;25(20):9805-9813. doi:10.1111/jcmm.16928.
8. Lv LL, Wang C, Li ZL, Cao JY, Zhong X, Feng Y, Chen J, Tang TT, Ni HF, Wu QL, Wang B, Lan HY, Liu BC. SAP130 released by damaged tubule drives necroinflammation via miRNA-219c/Mincle signaling in acute kidney injury. *Cell Death & Disease*. 2021;12(10). doi:10.1038/S41419-021-04131-7. (In press, Epub ahead of print)
9. Yang Q, Gao L, Hu X, Wang J, Zhang Y, Dong Y, Lan HY, Meng X. Smad3-targeted therapy protects against cisplatin-induced AKI by attenuating programmed cell death and inflammation via a NOX4-dependent mechanism. *Kidney Diseases*. 2021;7(5):372-390. doi:10.1159/000512986. (Epub ahead of print)
10. Wu W, Huang XR, You Y, Xue L, Wang XJ, Meng X, Lin X, Shen J, Yu X, Lan HY, Chen H. Latent TGF- β 1 protects against diabetic kidney disease via Arkadia/Smad7 signaling. *International Journal of Biological Sciences*. 2021;17(13):3583-3594. doi:10.7150/ijbs.61647.
11. Li Y, Yuan Y, Huang Z xing, Chen H, Lan R, Wang Z, Lai K, Chen H, Chen Z, Zou Z, Ma H bin, Lan HY, Mak TW, Xu Y. GSDME-mediated pyroptosis promotes inflammation and fibrosis in obstructive nephropathy. *Cell Death & Differentiation*. 2021;28(8):2333-2350. doi:10.1038/s41418-021-00755-6.
12. Wang L, Wang HL, Liu TT, Lan HY. TGF-beta as a master regulator of diabetic nephropathy. *International Journal of Molecular Sciences*. 2021;22(15):7881. doi:10.3390/ijms22157881. (Review)
13. Chung JYF, Chan MKK, Li JSF, Chan ASW, Tang PCT, Leung KT, To KF, Lan HY, Tang PMK. TGF- β signaling: From tissue fibrosis to tumor microenvironment. *International Journal of Molecular Sciences*. 2021;22(14):7575. doi:10.3390/ijms22147575.
14. Chen XC, Li ZH, Yang C, Tang JX, Lan HY, Liu HF. Lysosome depletion-triggered autophagy impairment in progressive kidney injury. *Kidney Diseases*. 2021;7(4):254-267. doi:10.1159/000515035. (Review, Epub ahead of print)
15. Gu YY, Dou JY, Huang XR, Liu XS, Lan HY. Transforming growth factor- β and long non-coding RNA in renal inflammation and fibrosis. *Frontiers in Physiology*. 2021;12:572. doi:10.3389/fphys.2021.684236. (Review)
16. Dong L, Li JC, Hu ZJ, Huang XR, Wang L, Wang HL, Ma RCW, Lan HY, Yang SJ. Deletion of Smad3 protects against diabetic cardiomyopathy in db/db mice. *Journal of Cellular and Molecular Medicine*. 2021;25(10):4860-4869. doi:10.1111/jcmm.16464. (Review)
17. Chen J, Wang W, Tang Y, Huang XR, Yu X, Lan HY. Inflammatory stress in SARS-COV-2 associated acute kidney injury. *International Journal of Biological Sciences*. 2021;17(6):1497-1506. doi:10.7150/IJBS.58791. (Review)
18. Lian GY, Wang QM, Mak TSK, Huang XR, Yu XQ, Lan HY. Inhibition of tumor invasion and metastasis by targeting TGF- β -Smad-MMP2 pathway with Asiatic acid and Naringenin. *Molecular Therapy - Oncolytics*. 2021;20:277-289. doi:10.1016/j.omto.2021.01.006.
19. Cao JY, Wang B, Tang TT, Wen Y, Li ZL, Feng ST, Wu M, Liu D, Yin D, Ma KL, Tang RN, Wu QL, Lan HY, Lv LL, Liu BC. Exosomal miR-125b-5p deriving from mesenchymal stem cells promotes tubular repair by suppression of p53 in ischemic acute kidney injury. *Theranostics*. 2021;11(11):5248-5266. doi:10.7150/thno.54550.
20. Zhang P, Yu C, Yu J, Li Z, Lan HY, Zhou Q. Arid2-IR promotes NF- κ B-mediated renal inflammation by targeting NLRC5 transcription. *Cellular and Molecular Life Sciences*. 2021;78(5):2387-2404. doi:10.1007/s00018-020-03659-9.
21. Tang PCT, Chan ASW, Zhang CB, García Córdoba CA, Zhang YY, To KF, Leung KT, Lan HY, Tang PMK. TGF- β 1 signaling: Immune dynamics of chronic kidney diseases. *Frontiers in Medicine*. 2021;8:106. doi:10.3389/fmed.2021.628519. (Review)
22. Yiu WH, Li Y, Lok SWY, Chan KW, Chan LYY, Leung JCK, Lai KN, Tsu JHL, Chao J, Huang XR, Lan HY, Tang SCW. Protective role of kallistatin in renal fibrosis via modulation of Wnt/ β -catenin signaling. *Clinical Science*. 2021;135(3):429-446. doi:10.1042/CS20201161.
23. Zhou Q, Guo H, Yu C, Huang XR, Liang L, Zhang P, Yu J, Zhang J, Chan TF, Ma RCW, Lan HY. Identification of Smad3-related transcriptomes in type-2 diabetic nephropathy by whole transcriptome RNA sequencing. *Journal of Cellular and Molecular Medicine*. 2021;25(4):2052-2068. doi: 10.1111/jcmm.16133.
24. Gu YY, Lu FH, Huang XR, Zhang L, Mao W, Yu XQ, Liu XS, Lan HY. Non-coding RNAs as biomarkers and therapeutic targets for diabetic kidney disease. *Frontiers in Pharmacology*. 2021;11:2342. doi:10.3389/fphar.2020.583528. (Review)

- 25. Gu YY, Zhang M, Cen H, Wu YF, Lu Z, Lu F, Liu XS, Lan HY. Quercetin as a potential treatment for COVID-19-induced acute kidney injury: Based on network pharmacology and molecular docking study. *PLOS ONE*. 2021;16(1):e0245209. doi:10.1371/journal.pone.0245209.
- 26. Tang PMK, Zhang YY, Hung JSC, Chung JYF, Huang XR, To KF, Lan HY. DPP4/CD32b/NF-kb circuit: A novel druggable target for inhibiting CRP-driven diabetic nephropathy. *Molecular Therapy*. 2021;29(1):365-375. doi:10.1016/j.ymthe.2020.08.017.
- 27. Sheng J, Wang L, Tang PMK, Wang HL, Li JC, Xu BH, Xue VW, Tan RZ, Jin N, Chan TF, Huang XR, Ma RCW, Lan HY. Smad3 deficiency promotes beta cell proliferation and function in db/db mice via restoring Pax6 expression. *Theranostics*. 2021;11(6):2845-2859. doi:10.7150/thno.51857.

B. Patents

- 1. Inventors: LAN Hui Yao, YU Xueqing
 Title: SMAD3 抑制劑治療 COVID-19 急性腎損傷
 Patent Application No. CN202110776692.9



SARS-CoV-2 N protein binds and activates Smad3-dependent cell death pathway.

Source: Hui-yao Lan's team

