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CELLULAR SIGNALLING

Principal Investigator

Professor William Wu

Team

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Research Progress Summary

In this reporting period, Professor William Wu and his team have developed two research approaches:

Pain research -

Previous animal and clinical studies showed that nitrous oxide may produce long-term analgesia. The team evaluated the effect of nitrous oxide in preventing chronic postsurgical pain and explored whether methylenetetrahydrofolate reductase gene polymorphisms (1298A>C, 667C>T) would enhance nitrous oxide analgesia. They found that nitrous oxide did not affect the rate of chronic postsurgical pain (11.8% nitrous oxide group; 12.5% no nitrous oxide group), relative risk (95% confidence intervals): 0.94 (0.75-1.17), P=0.57. However, in a planned subgroup analysis, nitrous oxide reduced the risk of chronic postsurgical pain in Asian patients, relative risk (95% confidence intervals): 0.70 (0.50-0.98), P=0.031. Patients who were homozygous for either gene polymorphism and who received nitrous oxide during surgery were less likely to report chronic postsurgical pain. In conclusion, nitrous oxide administration had no impact on chronic postsurgical pain, but benefits may still be possible in Asian patients and patients with variants in methylenetetrahydrofolate reductase gene.

Sepsis research -

Sepsis is a systemic host response to an infection leading to organ failure. This is associated with dynamic expression of non-coding RNAs and endogenous host defence peptides (e.g. cathelicidin). The former has crosstalk with JNK/NF-κB and other cellular pathways pertinent to innate immunity, mitochondrial function, and apoptosis whereas the latter regulates immune response and has crosstalk with pyroptosis and coagulation cascades. Dysregulation of these molecules is associated with septic morbidity and mortality. Modulation of autophagy, an innate immune defence mechanism against microbial challenges, also appears to be protective against multiple organ injuries in these murine sepsis models. This is achieved in part by preventing apoptosis, maintaining a balance between the productions of pro- and anti-inflammatory cytokines, and preserving mitochondrial functions.

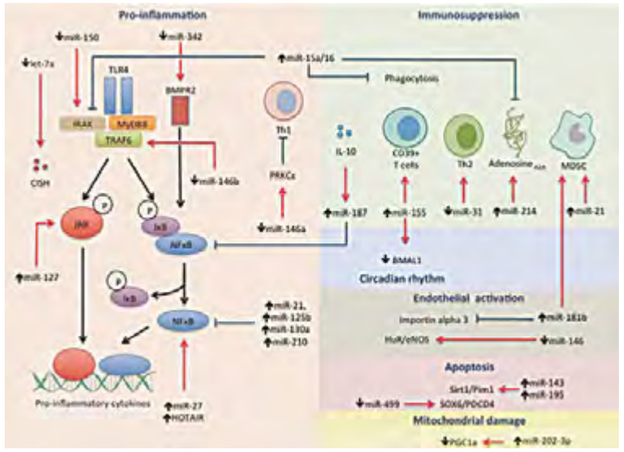
Recognitions

Awards and Fellowships

Member's Full Name	Details
William Wu	Second-class State Natural Science Award (2016) by the People's Republic of China

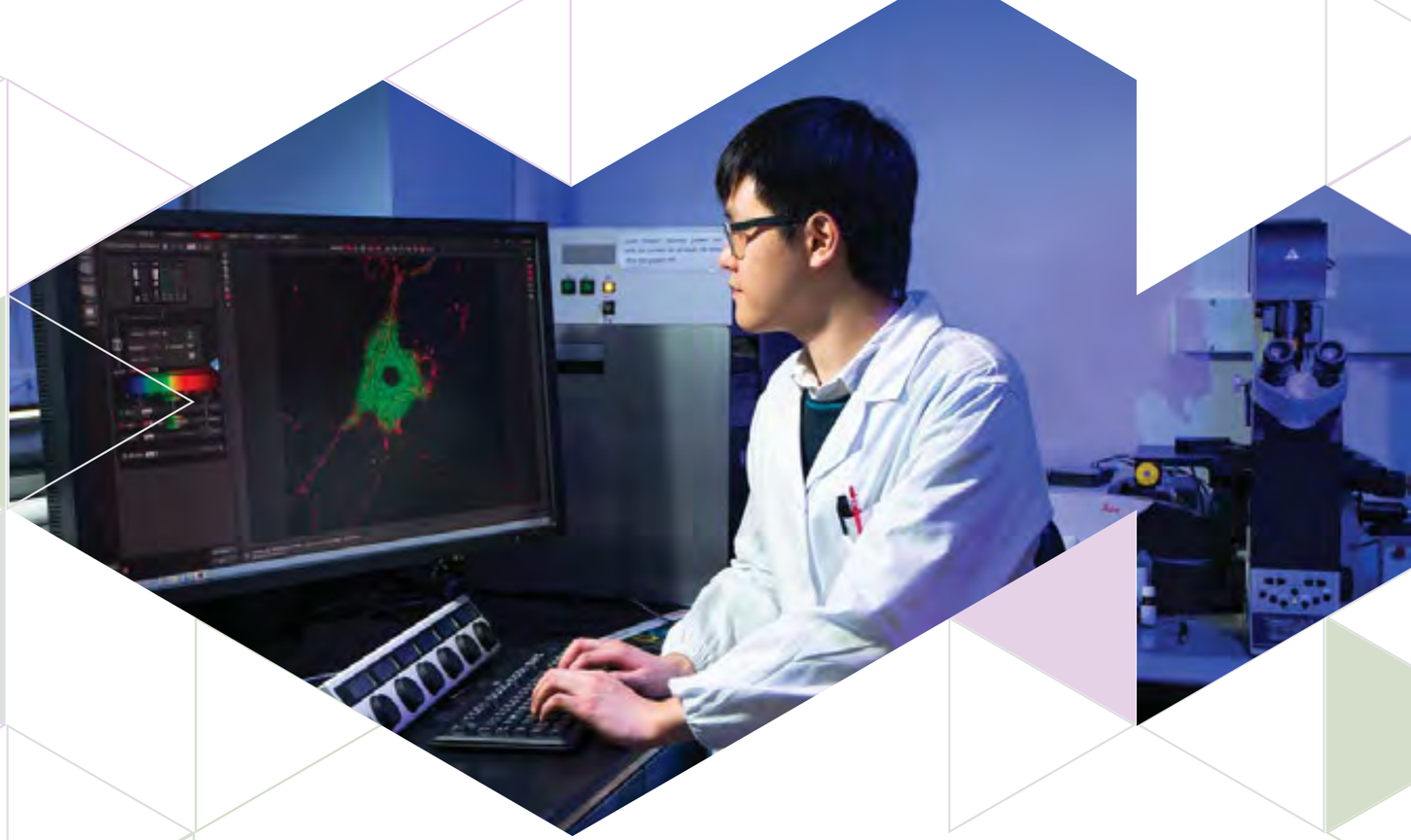
Grants and Consultancy

Full Name of PI	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
William Wu	Elucidating the Role of Autophagy in the Pathogenicity of *Clostridium difficile* Infection	Food and Health Bureau - Health and Medical Research Fund	10/09/2016	09/09/2018	1,199,040
William Wu	Targeting Defective Autophagy and its Molecular Sequelae in Non-alcoholic Fatty Liver Disease-related Hepatocellular Carcinoma	Research Grant Council – General Research Fund / Early Career Scheme	01/01/2016	31/12/2018	813,275
William Wu	The Role of Autophagy in CD24-Driven Colorectal Tumorigenesis	The Natural Science Foundation of Guangdong Province, Department of Science and Technology of Guangdong Province	01/08/2015	01/08/2018	RMB 100,000
William Wu	Therapeutic Potential of Autophagosomal-lysosomal Impairment in Non-alcoholic Fatty Liver Disease	Shenzhen Science and Technology Programme, Shenzhen Science and Technology Innovation Commission	6/11/2015	16/11/2017	RMB 200,000
William Wu	Detection and Characterization of Novel/ Unrecognized Microbial Pathogens Associated with Unexplained Severe Sepsis	Food and Health Bureau - Commissioned Research on Control of Infectious Diseases	01/04/2015	31/03/2017	300,000
William Wu	Association Study by Targeted Capture Sequencing of Autophagy-related Genes for Identification of New Susceptibility Loci in Asian Crohn's Disease Patients	Food and Health Bureau - Health and Medical Research Fund	01/02/2014	29/06/2014	999,379
Matthew Chan	Influence of Anesthetic Depth on Patient Outcome after Major Surgery: The BALANCED Anesthesia Trial	Research Grant Council - General Research Fund	01/01/2014	31/12/2016	952,636
Matthew Chan	Neurological Impact of Covert Strokes in Noncardiac Surgery: A Prospective Observational Cohort Study	Food and Health Bureau - Health and Medical Research Fund	01/03/2014	29/02/2016	920,372
Matthew Chan	Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia: A Randomized Controlled Trial for the Prevention of Chronic Pain after Major Abdominal Surgery	Food and Health Bureau - Health and Medical Research Fund	01/04/2014	30/09/2016	999,752
Matthew Chan	Vascular Events in Surgery Patients Cohort Evaluation (VISION) - Cardiac Surgery Study	Research Grant Council - General Research Fund	01/01/2015	31/12/2017	1,051,942
Matthew Chan	Pharmacokinetics of Oseltamivir in Critically Ill Patients with Severe Influenza	Food and Health Bureau - Commissioned Research on Control of Infectious Diseases	01/04/2015	31/03/2017	290,000
Matthew Chan	Re-designing Ventilation System for the Hospital Isolation Ward to Reduce Nosocomial Infection	Australian and New Zealand College of Anaesthetists - Research Grant	01/01/2016	31/12/2016	AUD 69,940
Matthew Chan	Targeting Anesthetic Depth to Prevent Postoperative Delirium: A Randomized Controlled Trial	Food and Health Bureau - Health and Medical Research Fund	01/07/2016	30/06/2018	1,194,448
Lin Zhang	A Link Between Bacterial Pathogen Host Tropism and Antimicrobial Peptides Resistance	University Grants Committee - Hong Kong - Scotland Partners of Post Doctoral Research, Hong Kong	28/06/2016	28/10/2016	41,667
Lin Zhang	The Mechanisms of Cathelicidin in *Fusobacterium nucleatum* induced Colon Cancer	The National Natural Science Foundation of China	01/01/2015	31/12/2017	259,900 (RMB 230,000)



Role of microRNA and long non-coding RNA in sepsis

The figure was published by Critical Care 2016



Publications

A. Journal Papers

1. Ho J, Yu J, Wong SH, Zhang L, Liu X, Wong WT, Leung CC, Choi G, Wang MH, Gin T, Chan MT, Wu WK. Autophagy in sepsis: degradation into exhaustion? *Autophagy*. 2016; 12(7):1073-82. (Review)
2. Li X, Wu WK, Xing R, Wong SH, Liu Y, Fang X, Zhang Y, Wang M, Wang J, Li L, Zhou Y, Tang S, Peng S, Qiu K, Chen L, Chen K, Yang H, Zhang W, Chan MT, Lu Y, Sung JJ, Yu J. Distinct subtypes of gastric cancer defined by molecular characterization include novel mutational signatures with prognostic capability. *Cancer Research*. 2016; 76(7):1724-32.
3. Chan MT, Peyton PJ, Myles PS, Leslie K, Buckley N, Kasza J, Paech MJ, Beattie WS, Sessler DI, Forbes A, Wallace S, Chen Y, Tian Y, Wu WK, and the Australian and New Zealand College of Anaesthetists Clinical Trials Network for the ENIGMA-II investigators. Nitrous oxide and chronic postsurgical pain in the evaluation of nitrous oxide in the gas mixture for anesthesia (ENIGMA) – II Trial. *British Journal of Anaesthesia*. 2016; 117(6):801-11.
4. Tang S, Wu WK, Li X, Wong SH, Wong N, Chan MT, Sung JJ, Yu J. Stratification of digestive cancers with different pathological features and survival outcomes by MicroRNAs expression. *Scientific Reports*. 2016; 6:24466.
5. Zhang L, Wu WK, Gallo RL, Fang EF, Ling TK, Shen J, Chan RL, Lu L, Luo XM, Li MX, Chan KM, Yu J, Wong VW, Ng SC, Wong SH, Chan FK, Sung JJ, Chan MT, Cho CH. Critical role of antimicrobial peptide cathelicidin for controlling *Helicobacter pylori* survival and infection. *Journal of Immunology*. 2016; 196(4):1799-809.
6. Ho J, Chan H, Wong SH, Wang MH, Yu J, Xiao Z, Liu X, Choi G, Leung CC, Wong WT, Li Z, Gin T, Chan MT, Wu WK. The involvement of regulatory non-coding RNAs in sepsis: a systematic review. *Critical Care*. 2016; 20(1):383.
7. Lei D, Dong C, Wu WK, Dong A, Li T, Chan MT, Zhou X, Yuan H. Lentiviral delivery of small hairpin RNA targeting connective tissue growth factor blocks profibrotic signaling in Tenon's capsule fibroblasts. *Investigative Ophthalmology & Visual Science*. 2016; 57(13):5171-80.
8. Yu X, Li Z, Chan MT, Wu WK. Role of microRNAs in primary central nervous system lymphomas. *Cell Proliferation*. 2016; 49(2):147-53. (Review)
9. Xin Y, Li Z, Shen J, Chan MT, Wu WK. CCAT1: a pivotal oncogenic long non-coding RNA in human cancers. *Cell Proliferation*. 2016; 49(3):255-60. (Review)
10. Li Z, Shen J, Chan MT, Wu WK. TUG1: a pivotal oncogenic long non-coding RNA in human cancers. *Cell Proliferation*. 2016; 49(4):471-5. (Review)
11. Xin Y, Li Z, Chan MT, Wu WK. Circulating epigenetic biomarkers in melanoma. *Tumor Biology*. 2016; 37(2):1487-92. (Review)
12. Yu X, Li Z, Chan MT, Wu WK. The roles of microRNAs in Wilms' tumors. *Tumor Biology*. 2016; 37(2):1445- 50. (Review)
13. Li Z, Wong SH, Shen J, Chan MT, Wu WK. The role of microRNAs in ankylosing spondylitis. *Medicine (Baltimore)*. 2016; 95(14):e3325.
14. Xu L, Li X, Cai M, Chen J, Li X, Wu WK, Kang W, Tong J, To KF, Guan XY, Sung JJ, Chan FK, Yu J. Increased expression of Solute carrier family 12 member 5 via gene amplification contributes to tumour progression and metastasis and associates with poor survival in colorectal cancer. *Gut*. 2016; 65(4):635-46.
15. Yu J, Wu WK, Liang Q, Zhang N, He J, Li X, Zhang X, Xu L, Chan MT, Ng SS, Sung JJ. Disruption of NCOA2 by recurrent fusion with LACTB2 in colorectal cancer. *Oncogene*. 2016; 35(2):187-95.
16. Yu L, Wu WK, Gu C, Zhong D, Kong Y, Zhao X, Lin Q, Chan MT, Zhou Z, Liu S. Obatocalx impairs lysosomal function to block autophagy in cisplatin-sensitive and -resistant esophageal cancer cells. *Oncotarget*. 2016; 7(12):14693-707.
17. Wong SH, Ip M, Hawkey PM, Lo N, Hardy KJ, Manzoor S, Hui W, Choi KW, Wong R, Yung I, Cheung C, Lam K, Kwong T, Wu WK, Chan FK, Ng SC, Wu JC, Sung JJ, Lee N. High morbidity and mortality of *Clostridium difficile* infection and its associations with ribotype 002 in Hong Kong. *Journal of Infection*. 2016; 73(2):115-22.