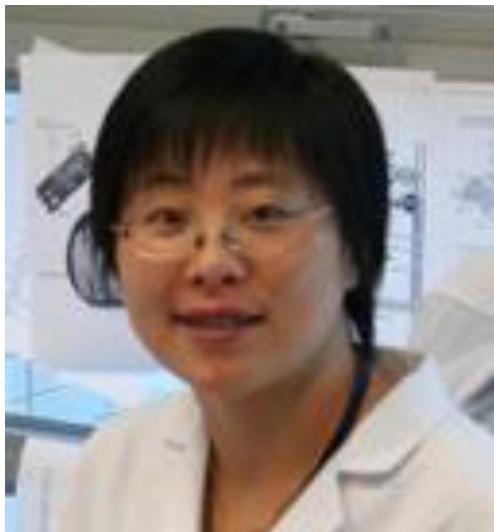


Endothelial SIRT1 as a drug target for vascular ageing-related diseases



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Ageing plays an important role in the alterations of vascular structure and function. Impaired endothelial function and increased arterial stiffness occur before the overt clinical manifestations such as hypertension and atherosclerosis. Sirtuin 1 (SIRT1), the mammalian ortholog of yeast longevity regulator Sir2, is a potent longevity regulator. Overexpression of SIRT1 in endothelium prevents cellular senescence, enhances vasodilatory responses, and attenuates ageing-induced vascular damages. Drugs targeting SIRT1 in endothelial cells represent promising therapeutics for vascular ageing-related diseases. The expression, regulation and signaling pathways of endothelial SIRT1 will be discussed in this seminar.

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Short Biography

Dr Yu Wang

NAME: Yu Wang

CURRENT POSITION: Associate Professor

DEPARTMENT: Pharmacology & Pharmacy

FACULTY: Li Ka Shing Faculty of Medicine, The University of Hong Kong

EDUCATIONAL QUALIFICATIONS: [Tertiary only]

2003 PhD in Biological Sciences, University of Auckland, New Zealand,

2000 MSc (First Class Honours) in Biological Sciences, University of Auckland, NZ

1992 MB ChB, Anhui Medical University, China

PREVIOUS APPOINTMENTS:

01/13 - present Associate Professor, Department of Pharmacology and Pharmacy, The University of Hong Kong

09/09 - present Visiting Professor, Guangzhou Institute of Biomedicine & Health, Chinese Academy of Sciences, China

05/08 - 12/12 Assistant Professor, Department of Pharmacology and Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong

10/04 - 04/08 Research Assistant Professor, Genome Research Center and Department of Biochemistry, The University of Hong Kong

10/03 - 09/04 Research Fellow, Maurice Wilkins Centre for Molecular Biodiscovery, The University of Auckland

01/00 - 09/03 Assistant Research Fellow (also as a PhD student), Proteomics and Biomedicine Laboratory, School of Biological Sciences, The University of Auckland

SIGNIFICANT DISTINCTIONS / AWARDS:

2016 Research Output Prize, LKS Faculty of Medicine, the University of Hong Kong

2014 National Science and Technology Awards of Advanced Individual, Shenzhen Virtual University Park

2012 Research Output Prize, the University of Hong Kong

2011 Universitas 21 Fellowship, the University of Hong Kong

2011 Outstanding Young Researcher Award, the University of Hong Kong

2010 Research Output Prize, the University of Hong Kong

2007 One of the best cancer-related papers in 2006-07 selected by "Cell Research"

2004 Best Doctoral Thesis Award, The University of Auckland

2003 REF Matthews Prize for the best paper publication in cellular and molecular biology, The University of Auckland

2000 Bright Futures Top Achiever Doctoral Scholarship, Foundation for Research, Science & Technology, New Zealand

2000 REF Matthews Prize for the best paper publication in cellular and molecular biology, The University of Auckland

2000 Dean of Science Prize for best MSc thesis, The University of Auckland

1999 Best Oral Presentation in the 1999 FAOSBMB symposium

PROFESSIONAL SOCIETIES / SERVICE / OTHER ACTIVITIES:

Memberships:

American Association for the Advancement of Science
American Chemical Society
American Diabetes Association Professional Section
American Heart Association Professional Section
American Society for Biochemistry and Molecular Biology
American Society for Pharmacology & Experimental Therapeutics
British Pharmacological Society
Hong Kong Pharmacology Society
New Zealand Society for Biochemistry and Molecular Biology

Editorships:

Jan 2014 – present Pharmacologia (Editorial Board member)
Nov 2013 – present Journal of Pharmaceutics & Pharmacology (Editorial Board member)
Jan 2013 – present Cardiovascular Pharmacology (Editorial Board member)
Dec 2012 – present World Journal of Diabetes (Editorial Board member)
Sep 2012 – present Journal of Integrated Omics (Associate Editor)
Apr 2012 – present International Scholarly Research Notices (previously ISRN Nutrition, Editorial Board member)
Jan 2011 – present American Journal of Translational Research (Senior Editor)
Jan 2011 – present PLoS One (Academic Editor)

Ad-hoc reviewers for journals:

Ageing; American Journal of Physiology - Regulatory, Integrative and Comparative Physiology; Antioxidants & Redox Signaling; Basic & Clinical Pharmacology and Toxicology; Biochemical Journal; Biochemistry; BMC Biochemistry; BMC Medical Genomics; British Journal of Dermatology; Cancer Research; Circulation Research; Clinical Biochemistry; Clinical Obesity; Diabetologia; Diabetology & Metabolic Syndrome; Endocrine-related Cancer; Expert Opinion On Therapeutic Targets; FEBS Letters; Hepatology Communications; International Journal of Molecular Sciences; Journal of Endocrinology, Journal of Hepatology; Journal of Molecular Endocrinology; The Journal of Investigative Medicine; The Journal of the American Society of Nephrology; The Journal of Pediatrics Proteomics; Laboratory Investigation, Liver Transplantation, Mini-reviews in Medicinal Chemistry, Molecular and Cellular Endocrinology, Pharmacist's/Prescriber's Letter Review; Pediatric Surgery International; Scandinavian Journal of Immunology; Thrombosis and Haemostasis

Invited speeches:

Endothelial overexpression of SIRT1 enhances vasodilatation via both eNOS-dependent and eNOS-independent signalling pathways. Mechanisms of Vasodilatation 12th International Symposium, November 7-9, 2016,

Adiponectin in regulating the lymphostromal interactions in thymus. Beijing Symposium on obesity and diabetes. April 9, 2016,

Anti-vascular ageing effects of endothelial SIRT1. Singapore Symposium on Metabolic Diseases, August 20-21, 2015,

Lipocalin-2 activation by deamidation causes endothelial dysfunction and hypertension 12, 2014,

Calorie restriction prevents adipose SIRT1 dysfunction-induced metabolic ageing. Seoul International Congress of Endocrinology and Metabolism & Asia-Pacific Diabetes and Obesity Study Group, May 16, 2014,

Deamidated lipocalin-2 induces endothelial dysfunction in dietary obese mice. Osaka Symposium on Obesity and Diabetes, March 29, 2014,

Adipokines – from discovery to therapeutic development. The 8th Leading Seminar, Hokkaido University, February 10, 2014,

Targeting endothelial senescence for atherosclerosis treatment: an approach based on SIRT1 modification. International Conference on Diabetes and Metabolism (ICDM) & the 5th Scientific Meeting of Asian Association for the Study of Diabetes (AASD), Seoul, Korea, November 6-9, 2013,

The vascular protective functions of SIRT1. Young-Honam Endocrinology and Metabolism Meeting, Muju, Korea, August 30, 2013,

Modulation of SIRT1 activity in adipose tissue – biotin versus caloric restriction. 2013 Summer Symposium by Vascular Cell Research Council in Korean Diabetes Association, Daegu, Korea, 2013,

Adipokines as biomarkers and drug targets for obesity-related cardiometabolic diseases. 2013 AAPS@China Symposium, August 17-18, 2013,

Modulation of SIRT1 Activity in Adipose Tissue: Biotin versus Caloric Restriction. 5th Singapore Symposium on Metabolic Diseases, August 1-2, 2013,

Targeting SIRT1 in adipose tissue as an effective approach for combating metabolic ageing. 2013 Hong Kong Symposium on Obesity and Diabetes, April 20, 2013

Anti-vascular aging effects of SIRT1. Eighth International Symposium on Healthy Aging "How to Age with Finesse", March 9-10, 2013,

Obesity-accelerated arterial aging: interplay between free fatty acids and lipocalin-2. EDHF2012 – 10th Anniversary Meeting, June 27-30, 2012,

The promise of SIRT1, a longevity regulator, in cardiometabolic syndrome. 10th Faculty Research Symposium, Frontiers in Biomedical Research, HKU, December 9, 2011,

Adipokines – toward the molecular dissection of interactions between stromal adipocytes and breast cancer cells. 18th Hong Kong International Cancer Congress, November 3-5, 2011,

Adipokines: Friend or Foe? Department of Molecular Medicine and Pathology Seminar Series, University of Auckland, August 2, 2011,

SIRT1 and AMPK: the seesaw effect in regulating endothelial senescence. 10th International Symposium on Resistance Arteries, 8th-12th May, 2011,

Mitochondria dysfunction in metabolic syndrome and cardiovascular disease: role of adipokines. The Croucher Foundation-Advanced Study Institute on Mitochondrial Stress in Diabetes and Aging, September 3-7, 2011,

Causative role of lipocalin-2, an inflammatory adipokine, in obesity-related cardiometabolic syndrome. 14th Asia-Oceania Congress of Endocrinology, Seoul, October, 2010,

Hepatoprotective functions of adiponectin: Indispensible role of uncoupling protein-2. 8th International Diabetes Federation Western Pacific Region Congress, 2010,

Therapeutic potentials of adiponectin in fatty liver diseases. The 21st IUBMB and 12th FAOBMB International Congress of Biochemistry and Molecular Biology, 2009,

Protective roles of adiponectin in obesity-related fatty liver diseases: Mechanisms and Therapeutic Interventions. The International Society for Endocrinology meeting, 2008,

Structural mechanisms underlying the inhibitory effects of angiopoietin-like protein 4 on lipoprotein lipase activities. 4th Scientific Meeting of the Asia-Pacific Diabetes and Obesity Study Group, 2008,

Lipocalin-2, a small lipid binding protein as an important mediator at the crossroad of obesity, inflammation and metabolic syndrome. Annual Meeting of Korean Endocrine Society, 2008,

An integrated proteomic approach to characterize protein post-translational modifications and protein-protein interactions. The 3rd Hong Kong Medical Genetics Conference, 2005,

Adiponectin as a novel diagnostic marker and therapeutic agent for the treatment of diabetes, fatty liver diseases and other metabolic disorders. Australasian Paediatric Endocrine Group Annual Scientific Meeting, 2004.

RESEARCH SPECIALTIES / CAREER:

Summary Statement:

The aims of my research are to elucidate the molecular mechanisms underlying the development of ageing-related cardiovascular, metabolic and cancer diseases by focusing on a number of druggable protein targets, including adiponectin, lipocalin-2 and SIRT1. During the past ~20 years of my research and development, these molecules have been proven to play key roles in the pathogenesis of ageing and related diseases. In this regard, we are currently exploring different approaches of intervention based on the druggable properties of these three molecules.

Research Publications:

Total publications: 162

Peer-reviewed journal articles: 124

Book chapters: 8

Commentary: 2

Invited reviews: 28

H-index 56

i10-index 123

Scopus citation 7968 (Author ID: 34973733700)

Original research articles (*corresponding author)

1. Luo D, Guo Y, Cheng Y, Zhao J, Wang Y, Rong J. Natural product celastrol suppressed macrophage M1 polarization against inflammation in diet-induced obese mice via regulating Nrf2/HO-1, MAP kinase and NF- κ B pathways. *Aging (Albany NY)*. 2017 Oct 16;9(10):2069-2082. doi: 10.18632/aging.101302,
2. Hampe L, Xu C, Harris PW, Chen J, Ming L, Middleditch M, Radjainia M*, Wang Y*, and Mitra AK*. Obesity-related metabolic disorders mitigated by peptides designed to modulate adiponectin assembly. *British Journal of Pharmacology* 2017 DOI: 10.1111/bph.14050,
3. Huang Z, Zhong L, Lee JT, Zhang J, Wu D, Geng L, Wang Y, Wong CM* and Aimin Xu*. The FGF21-CCL11 axis mediates browning of white adipose tissues by coupling sympathetic nervous system to type 2 immunity. *Cell Metabolism* 2017 Sep 5;26(3):493-508.e4. doi: 10.1016/j.cmet.2017.08.003. Epub 2017 Aug 24. <http://dx.doi.org/10.1016/j.cmet.2017.08.003>,
4. Yang K, Deng HB, Man AW, Song E, Zhang J, Luo C, Cheung BM, Yuen KY, Jensen PS, Irmukhamedov A, Elie AG, Vanhoutte PM, Xu A, De Mey J, Wang Y*. Measuring non-polyaminated lipocalin-2 for cardiometabolic risk assessment. *ESC Heart Failure*. 2017 DOI: 10.1002/ehf2.12183,
5. Ying F, Cai Y, Cai Y, Wang Y, Tang EHC. Prostaglandin E receptor subtype 4 regulates lipid droplet size and mitochondrial activity in murine subcutaneous white adipose tissue. *FASEB J*. 2017 May 22. pii: fj.201700191R. doi:

- 10.1096/fj.201700191R. [Epub ahead of print],
6. Song E, Jahng JW, Chong LP, Sung HK, Han M, Luo C, Wu D, Boo S, Hinz B, Cooper MA, Robertson AA, Berger T, Mak TW, George I, Schulze PC, Wang Y, Xu A, Sweeney G. Lipocalin-2 induces NLRP3 inflammasome activation via HMGB1 induced TLR4 signaling in heart tissue of mice under pressure overload challenge. *Am J Transl Res.* 2017 Jun 15;9(6):2723-2735. eCollection 2017,
7. Mao L, Nie B, Nie T, Hui X, Gao X, Lin X, Liu X, Xu Y, Tang X, Yuan R, Li K, Li P, Ding K, Wang Y, Xu A, Fei J, Han W, Liu P, Madsen L, Kristiansen K, Zhou Z Ding S, Wu D. Visualization and Quantification of Browning Using a Ucp1-2A-Luciferase Knock-in Mouse Model. *Diabetes.* 2017 Feb;66(2):407-417. doi: 10.2337/db16-0343. Epub 2016 Nov 8,
8. Hui X, Zhang M, Gu P, Li K, Gao Y, Wu D, Wang Y*, Xu A*. Adipocyte SIRT1 controls systemic insulin sensitivity by modulating macrophages in adipose tissue. *EMBO Reports* 2017 Apr;18(4):645-657. doi: 10.15252/embr.201643184. Epub 2017 Mar 7,
9. Ye D, Yang K, Zang S, Lin Z, Chau HT, Wang Y, Zhang J, Shi J, Xu A, Lin S, Wang Y*. Lipocalin-2 mediates non-alcoholic steatohepatitis by promoting neutrophilmacrophage crosstalk via the induction of CXCR2. *Journal of Hepatology* 2016 Nov;65(5):988-997. doi: 10.1016/j.jhep.2016.05.041,
10. Herath TD, Darveau RP, Seneviratne CJ, Wang CY, Wang Y, Jin L. Heterogeneous Porphyromonas gingivalis LPS modulates immuno-inflammatory response, antioxidant defense and cytoskeletal dynamics in human gingival fibroblasts. *Scientific Report* 2016 Aug 19;6:29829. doi: 10.1038/srep29829,
11. Gong Q, Hu Z, Zhang F, Cui A, Chen X, Jiang H, Gao J, Chen X, Han Y, Liang Q, Ye D, Shi L, Eugene Chin Y, Wang Y, Xiao H, Guo F, Liu Y, Zang M, Xu A, Li Y. Fibroblast growth factor 21 improves hepatic insulin sensitivity by inhibiting mammalian target of rapamycin complex 1. *Hepatology* 2016 Aug;64(2):425-438. doi: 10.1002/hep.28523,
12. Bai B, Man AW, Yang K, Guo Y, Xu C, Tse HF, Han W, Bloksgaard M, De Mey JG, Vanhoutte P, Xu A, Wang Y*. Endothelial SIRT1 prevents arterial remodeling by facilitating HERC2-mediated degradation of acetylated LKB1. *Oncotarget* 2016 Jun 28;7(26):39065-39081. doi: 10.18632/oncotarget.9687,
13. Elie AG, Jensen PS, Nissen KD, Geraets IM, Xu A, Song E, Hansen ML, Irmukhamedov A, Rasmussen LM, Wang Y, De Mey JG. Adipokine imbalance in the pericardial cavity of cardiac and vascular disease patients. *PLoS One* 2016 May 3;11(5):e0154693. doi: 10.1371/journal.pone.0154693,
14. Ye D, Li H, Wang Y, Jia W, Zhou J, Fan J, Man K, Lo C, Wong C, Wang Y, Lam KS, Xu A. Circulating fibroblast growth factor 21 is a sensitive biomarker for severe ischemia/reperfusion injury in patients with liver transplantation. *Scientific Report* 2016 Jan 25;6:19776. doi: 10.1038/srep19776,
15. Cai Y, Ying F, Song E, Wang Y, Xu A, Vanhoutte PM, Tang EH. Mice lacking prostaglandin E receptor subtype 4 manifest disrupted lipid metabolism attributable to impaired triglyceride clearance. *The FASEB Journal* 2015 Dec;29(12):4924-4936. doi: 10.1096/fj.15-274597,
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19. Lin Z, Pan X, Wu F, Ye D, Zhang Y, Wang Y, Jin L, Lian Q, Huang Y, Ding H, Triggle C, Wang K, Li X, Xu A. Fibroblast Growth Factor 21 Prevents Atherosclerosis by Suppression of Hepatic Sterol Regulatory Element-Binding Protein-2 and Induction of Adiponectin in Mice. *Circulation* 2015 May 26;131:1861-1871. doi: 10.1161/CIRCULATIONAHA.115.015308,
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21. Wang N, Wang Z, Wang Y, Xie X, Shen J, Peng C, You J, Peng F, Tang H, Guan X, Chen J. Dietary compound isoliquiritigenin prevents mammary carcinogenesis by inhibiting breast cancer stem cells through WIF1 demethylation. *Oncotarget* 2015 Apr 30;6(12):9854-9876,
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26. Ye D, Wang Y, Li H, Jia W, Man K, Lo CM, Wang Y, Lam KS, Xu A. FGF21 protects against acetaminophen-induced hepatotoxicity by potentiating PGC-1 α -mediated antioxidant capacity in mice. *Hepatology* 2014 Sep;60(3):977-989. doi: 10.1002/hep.27060,
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28. Song E, Fan P, Huang B, Deng HB, Cheung BM, Féletalou M, Vilaine JP, Villeneuve N, Xu A, Vanhoutte PM and Wang Y*. Deamidated lipocalin-2 induces endothelial dysfunction and hypertension in dietary obese mice. *JAHA: Journal of the American Heart Association* 2014 Apr 10;3(2):e000837. doi: 10.1161/JAHA.114.000837,
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- Seneviratne CJ. In vitro and In vivo activity of a novel antifungal small molecule against *Candida* infections. *PLoS one* 2014 Jan 22;9(1):e85836. doi: 10.1371/journal.pone.0085836,
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32. Cheng KK, Lam KS, Wang Y, Wu D, Zhang M, Wang B, Li X, Hoo RL, Huang Z, Sweeney G, Xu A. TRAF6-mediated ubiquitination of APPL1 enhances hepatic actions of insulin by promoting the membrane translocation of Akt. *Biochemical Journal* 2013 Oct 15;455(2):207-216. doi: 10.1042/BJ20130760,
33. Liu J, Xu A, Lam KS, Wong NS, Chen J, Shepherd PR, Wang Y*. Cholesterolinduced mammary tumorigenesis is enhanced by adiponectin deficiency: role of LDL receptor upregulation. *Oncotarget* 2013 Oct;4(10):1804-1818,
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Fluconazole resistance in *Candida glabrata* is associated with increased bud formation and metallothionein production. *Journal of Medical Microbiology* 2013 Feb;62(Pt 2):303-318. doi: 10.1099/jmm.0.044123-0,

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(<http://globalmedicaldiscovery.com/key-scientific-articles/upregulation-of-ucp2-byadiponectin-the-involvement-of-mitochondrial-superoxide-and-hnrnp-k/>),

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Inventions and Patents:

1. Phosphoprotein target for insulin and insulin antagonists (US patent No 6,884,575)
2. Adiponectin and uses thereof (US Patent No 7,365,170)
3. FALP proteins (US 20050074756 A1)
4. Lipocalin-2 as a diagnostic marker and therapeutic target (US patent No 7,645,616)
5. Lipocalin-2 as a prognostic and diagnostic marker for heart and stroke risks (US patent No 8,030,097)
6. Lipocalin-2 antibodies for methods of treatment (US patent No 8,481,032 B2)
7. Treating cancer (e.g. cervical epithelioid carcinoma, hepatocellular carcinoma, breast carcinoma and/or lung carcinoma) comprises administering composition Form 01StdCV01 comprising new or known substituted gold(III) porphyrin complexes (EP2493897-B1)
8. Antifungal compound and uses thereof (CN105102441A, EP2928875A1, WO2014086285A1, US 20140155478 A1)
9. Non-polyaminated Lcn2 as a biomarker for diagnosis and treatment of cardiometabolic diseases (PCT/CN2016/103792)
10. Hydroxy-substituted gold(III) porphyrin complexes as histone deacetylase inhibitors (US8563712 B2/ WO2011050575 A1).