Jianxun Wang

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Education

Ph.D. in Pharmacology & Toxicology

University of Louisville, USA

M.S. in Genetics

Sun Yat-sen University, China

B.S. in Cell Biology

Lanzhou University, China

Data Science & Bioinformatics

Network Technology Academy Institute, USA

EXPERIENCES

Network Technology Academy Institute *Malden MA , 01/2023-08/2023*

- Employing the Random Forest machine learning algorithm and Bayesian inference, examine a diabetes dataset
- Using R codes and packages for a case study on breast cancer genetic heterogeneity by Next Generation Sequencing (NGS)
- Using R codes and packages for RNA-seq assay for knockdown of pyruvate kinase in HEK 293 cells by NGS

Massachusetts General Hospital & Harvard Medical School *Boston MA*

Department of Surgery, Center for Engineering in Medicine

Research Fellow **11/2018-03/2022**

Gastric bypass surgery (RYGB) on intestine and inflammatory bowel disease(IBD)

- Understanding the mechanisms underlying intestinal metabolic reprogramming following gastric bypass surgery (RYGB). Augmented intestinal glucose utilization plays a key role in the immediate improvement in glycemic control following the surgery, which could be probably from activation of PI3K/Akt/mTOR pathway induction of glut1 expression, and Notably, a significant accumulation of glut1-positive leukocytes within villi was observed as early as RYGB 3 days.
- Leading a project focused on unraveling the reasons behind increased energy expenditure post RYGB, we found a shift from M1 to M2 macrophages (CD206+ Arginase1+) in adipose tissue, which could influence insulin

sensitivity in white adipose tissues. Noteworthy was the elevated UCP-1 expression specifically in omental adipose tissues, not in subcutaneous and epididymal adipose tissues, indicating potential browning effects linked to the M1 to M2 macrophage shift.

- Creation of YAP-knockout and YAP-overexpression mice for stiffness- induced preferential differentiation of intestinal stem cells (ISCs) toward goblet cells in inflammatory bowel disease (IBD).
- Metabolites extracted from snake induced intestinal crypts proliferation and differentiation on a 3-dimensional hydrogel matrix .

Beth Israel Deaconess Medical Center (BIDMC) & Harvard Medical School *Boston MA*

Department of Cardiovascular

Research Fellow **07/2011-06/2018**

Using chemical compounds test against autoimmune lupus and hypertrophic heart in vivo

- Project 1, the compound 11a-1, Inhibition of SHP2, ameliorates the pathogenesis of systemic lupus erythematosus

1. Lupus T cells

Lupus presents a complex network of immune response dysregulation, encompassing abnormalities in T and B cells, as well as innate immunity involving dendritic cells, neutrophils, and macrophages. The interconnected nature of the innate and adaptive immune networks involves cytokines, complements, immune complexes, and intracellular machinery kinases/phosphatases.

This study specifically focused on inhibiting the activity of the SHP2 phosphatase by compound 11a-1, which branched off the T cell pathway from the complex network, leading to a significant reduction in lupus disease, where the numbers of double-negative T cells were decreased, ERK/MAPK signaling was normalized, and production of IFN-γ and IL-17A/F was reduced, in contrast, the B cell-related pathway remained unaffected, with the axis of spleen extrafollicular T helper cells-plasmablasts-plasma cells showing no impact. Levels of anti-dsDNA and total IgG antibodies were not reduced, and the PI3K/AKT pathway remained unnormalized. Consequently, targeting the SHP2 phosphatase-related T cell pathway branch emerges as a promising approach for treating lupus.

This work was published in the Journal of Clinical Investigation and a patent has been granted for compound 11a-1, along with its application in treating lupus through the SHP2 pathway.

2. Lupus heart

In lupus hearts, focal patches of interstitial fibrosis were observed, accompanied by increased infiltrated CD11b+ leukocytes. These hearts exhibited reduced fractional shortening, enlarged chamber dimensions, and lower pY397-FAK activity, along with decreased p-ERK levels. Upon administration of the SHP2 inhibitor, there was a notable decrease in CD11b+ leukocyte numbers, a reduction in cardiac fibrosis, and a restoration of normal pY397-FAK and p-ERK activities

3. Methods used in vivo and in vitro for this compound test

In vivo. Flow cytometry, identifying immune cell subsets; Total cell isolation from tissues (kidney, spleen); Urinalysis for albumin and creatinine; Serum assay for cytokines, total IgG and anti-dsDNA IgG. Blood cell counts, determining numbers of WBC (neutrophil, lymphocytes, monocytes, eosinophil, and basophil), RBC, and platelets; Histology of kidney dysfunction by fibrosis; Immunoblots for AKT and ERK signaling and Immune complex PTP assays.

In vitro. Isolation, purification and culture of mouse and human T cells. T cell proliferation and viability assays, and related cytokine analyses

- Project2, the compound ARQ 092, AKT inhibitor, normalizes Noonan Syndrome with multiple lentigines-associated(NSML) hypertrophic heart

ARQ 092, an oral and selective allosteric AKT inhibitor currently in clinical trials for patients with PI3K/AKT-driven tumors or Proteus syndrome. Treatment of NSML mice with ARQ 092 normalized the hypertrophy in as early as 2 weeks following treatment, showing functional improvement of HCM. ARQ 092 specifically inhibited AKT activity, as well as its downstream effectors, PRAS and S6RP in NSML mice. Taken together, these data suggest ARQ 092 may be a promising novel therapy for treatment of hypertrophy in NSML patients.

University of Louisville *Louisville KY*

Department of Pharmacology & Toxicology

Graduate Student /Research Assistant **08/2005-06/2011**

Abnormal glucose metabolites and oxidized mitochondrial DNA on hearts

- Project1, reduction or increase of fructose-2,6-bisphosphate (F-2,6-P2) impact on cardiac hypertrophy and heart failure.

1. Establish a transaortic constriction (TAC) surgical model for induction of cardiac hypertrophy and heart failure.

An incision was made at the left second intercostal space to open the chest. A chest retractor was utilized to enhance visibility. The thymus was repositioned, and the transverse aorta was dissected from surrounding tissues. A 6–0 silk suture was threaded around the transverse aorta and tightened against a 26-G needle. The needle was promptly removed, creating a lumen with a stenotic aorta. After inflating the lungs, the chest cavity, muscles, and skin were closed sequentially using 6–0 silk sutures.

2. Reduction of fructose-2,6-bisphosphate (F-2,6-P_2) in mouse heart increased cardiac fibrosis by TAC

Hypertrophic biomarkers, including β-myosin heavy chain (MHC), α-MHC, atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP), were measured. Evaluation of cardiac fibrosis was conducted to assess histological changes, and cardiac function was appraised through echocardiography. Energy reserves were measured by calculating the ratio of phosphocreatine to ATP, while changes in redox status were determined by alterations in the content of pyridine nucleotides (NADH, NAD+ ratio) and oxidant status (NAPDH/NADP+).

- Project 2, Cardiac overexpression of 8-oxoguanine DNA glycosylase 1 (OGG1) protects mitochondrial DNA and reduces cardiac fibrosis following transaortic constriction (TAC)

1. Construction of mitochondrial target human OGG1 transgene in mouse heart from ground zero

Primers were designed to isolate mitochondrial isotype 2a of OGG1 from human fibroblasts. The purified OGG1 cDNA fragment was subcloned behind a 5.5-kb DNA fragment from the α-myosin heavy chain (MHC) promoter that produces transcription exclusively in cardiac myocytes and in front of a 500 bp of poly(A) DNA sequence derived from the rat insulin II gene. The transgene was released from the plasmid by Not I digestion and microinjected into single cell fertilized FVB mouse embryos by standard embryo microinjection procedures.

2. Protection of mitochondrial DNA and reduces cardiac fibrosis following TAC by overexpression of OGG1

The process involved the isolation and purification of mitochondrial DNA (mtDNA) from the entire heart. Subsequently, the measurement of 8-oxo-dG content on mitochondrial DNA was performed. Hypertrophic biomarkers, including β-myosin heavy chain (MHC), α-MHC, atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP), were

quantified. Additionally, the assessment of cardiac fibrosis was conducted to analyze histological changes, and cardiac function was evaluated through echocardiography.

University of Louisville *Louisville KY*

Department of Medicine, Division of Gastroenterology& Hepatology

Research Associate **05/2003-07/2005**

Diabetic hearts

- Diabetes, induced in mice through a single streptozotocin injection, triggers cardiac dysfunction via elevated glucose and hyperlipidemia, escalating oxidant stress and resulting in nitrotyrosine damage. This detrimental effect can be alleviated by zinc supplements, which induce the expression of metallothionein (MT).

In vivo, diabetes was induced by a single streptozotocin injection in mice, followed by intraperitoneal administration of zinc supplements. Serum lipid peroxidation, triglyceride level and creatine phosphokinase (CPK) activity were measured, while cardiac morphological impairment, fibrosis, and dysfunction were assessed.

In vitro, primary neonatal cardiomyocytes and H9C2 cells were cultured and high glucose (HG) along with free fatty acid (palmitate) treatment was employed to mimic diabetes conditions. Cell viability was determined by a short-term microculture tetrazolium (MTT) assay. MT small-interfering RNA (siRNA) was utilized to knock down MT expression. MT mRNA was detected by Northern Blotting. Zinc and low-dose cadmium (Cd) served as MT inducers. Urate and Mn(111) tetrakis 1-methyl 4-pyridyl porphyrin pentachloride (MnTMPyP), acting as a peroxynitrite-specific scavenger and a superoxide dismutase mimic, were introduced to inhibit the formation of superoxide and 3-nitrotyrosine (3-NT), respectively.

University of Louisville *Louisville KY*

Department of Medicine, Division of Cardiology

Research Associate **10/2000-4/2003**

Ischemic preconditioning (PC) heart against myocardial infarction

- A significant discovery was made regarding the involvement of neural nitric oxide synthase (nNOS) in PC 72-hour protection against cardiac infarction. Ischemic preconditioning is an intrinsic protective mechanism in which sublethal ischemic episodes enhance myocardial resistance to subsequent ischemic stress. The late phase of ischemic PC (late PC) is a cardioprotective state that becomes evident 12 to 24 hours after the PC stimulus and persists until 72 hours.

Through Immunoblots, it was first time to reveal an upregulation of nNOS expression in the late PC 72h period. Histological staining of the heart involved immunostaining for inducible nitric oxide synthase (iNOS) and Cox-2, along with in situ RNA expression in cardiomyocytes of heart. NOS activities were assessed by measuring myocardial nitrite and nitrate, while COX-2 enzymatic activities were evaluated through measurements of myocardial 6-keto-PGF1α and PGE2.

Guangdong Medical College *Guangdong China*

First Affiliated Hospital, Department of Central Laboratory

Instructor **07/1994 – 10/2000**

Genetic instability study from clinical human tumor samples

- Total 128 clinical human tumor samples representing five different types of tumors were analyzed. Random Amplified Polymorphic DNA (RAPD) PCR was employed, utilizing nine 10-base arbitrary primers. The aim was to detect DNA instabilities and screen for new molecular markers linked to potential or unidentified oncogenes and tumor suppressor genes. Notably, a short sequence exhibiting allelic losses in gastric and colon cancers was identified as a potential biomarker (GeneBank Accession Number AF151005).

Skills and Techniques

Techniques:

Metabolites assay in tissues: lactate; pyruvate; glycogen; ATP; phosphocreatine; Fru-2,6-P2; pyridine nucleotides (NADH; NADPH; NAD; NADP);6-keto-PGF1α; PGE2; nitrite and nitrate

Multicolor Flow cytometry; Isolation and culture of immune cells from mouse and human; ELISA

Extraction of Protein; RNA; nuclei DNA and mitochondrial DNA;

Western blot; Northern blot and Southern blot;

Gene array; siRNA; RPA; EMSA; Immunoprecipitation;

Designing primers; PCR; RT-PCR and Cloning;

Cryostat sections; In situ hybridization and Immunohistochemistry/immunofluorescence;

Isolation of neonatal cardiomyocytes from mouse;

Cell culture including primary neonatal and adult mouse cardiomyocytes culture

Echocardiography

TAC surgery (Trans-aortic-constriction for induction of cardiac hypertrophy and heart failure);

RYGB surgery (Roux-en-Y gastric bypass for weight loss)

In vivo mouse handling:

Injection of drugs with iv, ip or sc;

Collecting peripheral blood for immune cell assay with flow cytometry and serum cytokine assay by ELISA;

Collecting urine for assaying kidney dysfunction;

Isolation & Assay of immune cells infiltrating in kidney and heart;

Monitoring heart functions with echocardiography for drug toxicity;

Surgery of trans-aortic-constriction for induction of heart failure to test drug protection;

Roux-en-Y gastric bypass for weight loss;

Pathological study of kidney and heart with H&E, immunohistochemistry and immunofluorescence.

Report of Local Teaching and Training

Laboratory and Research Supervisory and Training Responsibilities:

Formally Supervised Trainees:

Training Duration	Name	Current Position
November, 2018-present,	Peng lei,	Post doctor
	Ziheng	Intern
	Chijioke Chvkwvdr Chvkwvdi,	Post doctor
	Nasr Esfahani, Farid	Post doctor
February – May, 2016	Wini Zambrae	B.S. student in Boston University.
June 13-24, 2016	Nancy Shaw	High school student
June, 2017-07/2018	Shi Su	Ph.D. student at Boston University

Report of Technological and Other Scientific Innovations

Patents:

SHP2 INHIBITORS AND METHODS OF TREATING AUTOIMMUNE AND/OR GLOMERULONEPHRITIS-ASSOCIATED DISEASES USING SHP2 INHIBITORS (2014)	Pub. No.: WO/2015/003094 International , Application No.: PCT/US2014/045318 Publication Date: 08.01.2015 International Filing Date: 02.07.2014

Report of Scholarship

Original Peer Reviewed Articles:

1. **Wang J**, Wang Q, Ye F. Genetic instability in cancer tissues analyzed by random amplified polymorphic DNA PCR. *Chin Med J (Engl).* 2002 Mar;115(3):430-2

2. Wang Y, Guo Y, Zhang SX, Wu WJ, **Wang J**, Bao W, Bolli R. Ischemic preconditioning upregulates inducible nitric oxide synthase in cardiac myocyte*. J Mol Cell Cardiol*. 2002 Jan;34(1):5-15.

3. Wang Y, Kodani E**, Wang J**, Zhang SX, Takano H, Tang XL, Bolli R. Cardioprotection during the final stage of the late phase of ischemic preconditioning is mediated by neuronal NO synthase in concert with cyclooxygenase-2. *Circ Res.* 2004 Jul 9;95(1):84-91.

4. Cai L, **Wang J**, Li Y, Sun X, Wang L, Zhou Z, Kang YJ. Inhibition of superoxide generation and associated nitrosative damage is involved in metallothionein prevention of diabetic cardiomyopathy. *Diabetes.* 2005 Jun;54(6):1829-37.

5. Song Y, **Wang J***, Li Y, Du Y, Arteel GE, Saari JT, Kang YJ, Cai L. Cardiac metallothionein synthesis in streptozotocin-induced diabetic mice, and its protection against diabetes-induced cardiac injury. *Am J Pathol.* 2005 Jul;167(1):17-26. **(*, Co-first author**)

6. **Wang J**, Song Y, Elsherif L, Song Z, Zhou G, Prabhu SD, Saari JT, Cai L. Cardiac metallothionein induction plays the major role in the prevention of diabetic cardiomyopathy by zinc supplementation. *Circulation*. 2006 Jan 31;113(4):544-54. Epub 2006 Jan 23.

7. Wang Q, Donthi RV, **Wang J**, Lange AJ, Watson LJ, Jones SP, Epstein PN. Cardiac phosphatasedeficient 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase increases glycolysis, hypertrophy, and myocyte resistance to hypoxia. *Am J Physiol Heart Circ Physiol*. 2008 Jun;294(6):H2889-97

8. **Wang J**, Wang Q, Watson LJ, Jones SP, Epstein PN. Cardiac overexpression of 8-oxoguanine DNA glycosylase 1 protects mitochondrial DNA and reduces cardiac fibrosis following transaortic constriction. *Am J Physiol Heart Circ Physiol*. 2011 Nov;301(5):H2073-80.

9. **Wang J**, Xu J, Wang Q, Brainard RE, Watson LJ, Jones SP, Epstein PN. Reduced cardiac fructose 2,6 bisphosphate increases hypertrophy and decreases glycolysis following aortic constriction. *PLOS ONE*. 2013;8(1)

10. Lauriol J, Keith K, Jaffré F, Couvillon A, Saci A, Goonasekera SA, McCarthy JR, Kessinger CW, **Wang J**, Ke Q, Kang PM, Molkentin JD, Carpenter C, Kontaridis MI. RhoA signaling in cardiomyocytes protects against stress-induced heart failure but facilitates cardiac fibrosis. *Sci Signal*. 2014 Oct 21;7(348)

11. **Wang J**, Mizui M, Zeng LF, Bronson R, Finnell M, Terhorst C, Kyttaris VC, Tsokos GC, Zhang ZY, Kontaridis MI. Inhibition of SHP2 ameliorates the pathogenesis of systemic lupus erythematosus. *J Clin Invest.* 2016 May 16.

    Nat Rev Rheumatol. 2016 Jul;12(7):376. 10.1038/nrrheum.2016.94. Epub 2016 Jun 3
    Systemic lupus erythematosus: SHP2 inhibition ameliorates disease in lupus-prone mice.
    Shipman L. PMID: 27256710 DOI: 10.1038/nrrheum.2016.94

    Nat Rev Drug Discov. 2016 Jun 30;15(7):456. doi: 10.1038/nrd.2016.128.
    Autoimmune disease: Reversing systemic lupus erythematosus.
    Crunkhorn S. PMID: 27357019 DOI:10.1038/nrd.2016.128.

12**. Wang J,** Chandrasekhar V, Abbadessa G, Yu Y, Schwartz B, Kontaridis MI. In vivo efficacy of the AKT inhibitor ARQ 092 in Noonan Syndrome with multiple lentigines-associated hypertrophic cardiomyopathy *PLoS One.* 2017 Jun 5

13, Gibb AA, Epstein PN, Uchida S, Zheng Y, McNally LA, Obal D, Katragadda K, Trainor PJ, Conklin DJ, Brittian KR, Tseng MT, **Wang J**, Jones SP, Bhatnagar A, Hill BG. Exercise-Induced Changes in Glucose Metabolism Promote Physiologic Cardiac Growth. *Circulation*. 2017 Aug 31.

14, Pannu PR, Chukwudi C, **Wang J**, Yang PJ, Esfahani FN, Saeidi N. Physical properties of food or bile redirection do not contribute to the intestinal adaptations after Roux-en-Y Gastric Bypass in rats. Obes Sci Pract. 2022 Dec 8;9(3):274-284

15, He S, Lei P, Kang W, Cheung P, Xu T, Mana M, Park CY, Wang H, Imada S, Russell JO, **Wang J**, Wang R, Zhou Z, Chetal K, Stas E, Mohad V, Bruun-Rasmussen P, Sadreyev RI, Hodin RA, Zhang Y, Breault DT, Camargo FD, Yilmaz ÖH, Fredberg JJ, Saeidi N. Stiffness Restricts the Stemness of the Intestinal Stem Cells and Skews Their Differentiation Toward Goblet Cells. Gastroenterology. 2023 Jun;164(7):1137-1151.

Peer Reviewed Reviews:

14. **Wang J**, Song Y, Wang Q, Kralik PM, Epstein PN. Causes and characteristics of diabetic cardiomyopathy. Rev Diabet Stud. 2006 Fall;3(3):108-17.

15. Song Y, **Wang J**, Li XK, Cai L. Zinc and the diabetic heart. Biometals. 2005 Aug;18(4):325-32.