BIOGRAPHICAL SKETCH

NAME: Li, Wei

eRA COMMONS USER NAME (credential, e.g., agency login): liwei4

POSITION TITLE: Associate Professor of Biomedical Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
China Medical University, Shenyang, China	M.D.	07/1992	Medicine
Fukuoka International Academy, Fukuoka, Japan		03/1997	Japanese language
Fukui Medical University, Fukui, Japan	Ph.D.	03/2002	Physiology; Cardiovascular Surgery

A. Personal Statement

I am a cardiovascular biologist with expertise in the study of vascular biology, platelet biology, atherosclerosis, and thrombosis in addition to heart diseases. I received my medical education in China and my Ph.D. training in a cardiothoracic surgery department in Japan where I learned skills in molecular and cell biology as well as experimental medicine. I moved to the USA in 2006 to expand my training in cell biology and to establish an independent career in vascular cell biology. I was recruited by Dr. Roy L. Silverstein to the Cleveland Clinic as a Project Scientist (equivalent to research track Assistant Professor) with the goal of using my surgical skills on animals and my knowledge of vascular biology to develop mouse thrombosis models and study an NHLBI funded *SCCOR program in Arterial Thrombosis*. I was also given resources, including an independent lab, office space, and about 40-50% protected effort to develop my independent line of research and to continue the work I developed during my Ph.D. tenure: ***clarifying the role of thymidine phosphorylase (TYMP) in the cardiovascular system***. This experience has been very successful and I have made major contributions to the SCCOR program and have learned important new skills related to *in vivo* and *in vitro* assessment of platelet and vessel wall function, as well as the biology of signal transduction.

My laboratory primarily focuses on exploring the role of TYMP in the development of chronic diseases, including metabolic syndrome. We have found that TYMP promotes angiogenesis in ischemic heart and hind limb but prevents vascular smooth muscle cell (VSMC) proliferation. These data suggest that TYMP plays a complex role in the vascular system. Our recent study, for the first time, demonstrated that TYMP is a signaling molecule, participates in platelet activation, and enhances thrombosis. We also clarified that TYMP deficiency in mice or inhibition of TYMP with specific inhibitors dramatically inhibited thrombosis. These novel findings provide us a new direction and a new target for developing breakthrough anti-platelet and anti-thrombosis therapies. Our ongoing studies have been expanded to clarify the role of TYMP in metabolic disorders as well as in development of severe COVID-19.

My laboratory is well equipped for modern cellular and molecular biology and has expertise in studying thrombosis, atherosclerosis, and vascular biology using rodent models including diet-based animal models. We have advanced surgical skills in developing various animal models. We have all the key instruments including an intravital microscope, an Cellix flow chamber system, and a Chronolog aggregometer for *in vitro* and *in vivo* thrombosis studies, the leukocyte adhesion and rolling assay, and ATP assays. We also have unique mouse strains and potent TYMP inhibitors.

B. Positions and Honors

Positions/Employment:

1992–1996 *Surgeon*, Department of Thoracic Surgery, Ben Xi City Central Hospital, Liaoning, China

2002–2003 *Research Fellow*, Second Department of Surgery, Fukui Medical University, Fukui, Japan
2003–2006 *Assistant Professor*, Division of Cardiothoracic Surgery, Department of Surgery, Faculty of Medical Science, University of Fukui, Fukui, Japan
2006–2017 *Project Staff*, Department of Cell Biology (now as Department of Cardiovascular & Metabolic Sciences), Lerner Research Institute, Cleveland Clinic, Cleveland, OH
2010–2017 *Assistant Professor*, Department of Molecular Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH
2017–Present Associate Professor, Deaprtment of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Professional Memberships (all are active)

American Heart Association
American Society of Hematology
International Society on Thrombosis and Haemostasis
American Diabetes Association
Sigma Xi

Other Experience

2011 - 2019 Editorial Board of World Journal of Medical Genetics
2012 - 2015 Editorial Board member of ***Circulation Research*** (reviewed >80 papers)
2013 - AHA scientific Session Abstract reviewer (80-105 abstracts/year)
2017 - Editorial Board member of Frontiers in Medicine - Hematology
2021 - Associate Editor for Frontiers in Medicine – Hematology.
2021 - Editorial Board member of Frontiers in Medicine - Lipids in Cardiovascular Disease

2002 - Ad Hoc Reviewer for: Circulation Research; Frontiers; Thrombosis and Hemostasis; Journal of Thrombosis and Haemostasis; Arterioscler Thromb Vasc Biol; Thrombosis Research; Journal of Molecular and Cellular Cardiology; The Annals of Thoracic Surgery; The American Journal of Physiology – Heart and Circulatory Physiology; The Journal of Gene Medicine; Journal of Molecular Histology; Expert Opinion on Therapeutic Patents; Cellular Physiology and Biochemistry; Theranotiscs; PLOS ONE; Biomedicine & Pharmacotherapy, Aging, Biomedicines, Communications Biology, etc. Total reviewed > 300 papers.

Honors:

1999 Award for foreign student from Sasakawa Health Science Foundation
2002 & 2003 Yoneyama Doctor Course Scholarship from Rotary Yoneyama Memorial Foundation
2008 Elsa Albrecht RA/PS Award from Department of Cell Biology, Cleveland Clinic
2010 Elsa Albrecht RA/PS Award from Department of Cell Biology, Cleveland Clinic
2011 US new investigator travel award from International Society on Thrombosis and Haemostasis
2013 *Circulation Research Top Reviewers Award*
2013 Innovator Award of Cleveland Clinic (Thymidine phosphorylase promotes thrombosis)
2014 Best Poster Award, 2014 Cleveland Clinic Research Day (*Thymidine phosphorylase participates in platelet signaling and promotes thrombosis*)
2015 Cleveland Clinic Caregiver Excellence Award
2016 ACRE-CHAHA Federation, Chinese American Academy of Cardiology, Outstanding Young Investigator Award (11/12/2016, New Orleans, LA, USA)
2017 Fellow of American Heart Association (FAHA)
2017 Graduate faculty status

C. Contribution to Science

1. Mechanistic role of TYMP on thrombosis

TYMP expression is increased in several systemic diseases including atherosclerosis, cancer, type II diabetes, and HIV infection; all of these diseases have a high risk of thrombotic complications. *By using Tymp$^{-/-}$ and Tymp$^{+/-}$ mice, we demonstrated for the first time that TYMP plays an important role in platelet activation and thrombosis.* We found that TYMP facilitates multiple agonists, which target platelet adhesive receptors, e.g., glycoprotein VI (GPVI), or GPCR receptors, e.g., ADP and thrombin receptors, induced platelet activation,

leading to enhanced platelet aggregation and thrombosis. TYMP deletion or pharmacological inhibition does not cause bleeding, a severe side effect of the most current anti-platelet therapies. As mentioned in Section A, these exciting findings were published by ***Circulation Research*** and these studies provided rationales for us to continue to explore the role of TYMP in the cardiovascular system. To the interest of this project, a TYMP inhibitor, tipiracil hydrochloride (TPI), as an auxiliary component of a new anti-cancer drug, Lonsurf (TAS-102), has been approved by the U.S. FDA for clinical use, suggesting that regulation of TYMP activity is safe, and repositioning TPI for possible use as an anti-platelet, anti-thrombotic, or anti-atherosclerotic drug. Therefore, clarification of the mechanistic role of liver TYMP in development of obesity will help to translate our research to clinical study and lead to the investigation of targeted TYMP-inhibition as a new, safer therapy for patients with metabolic syndrome and high risk of atherothrombotic event in the future.

a) Li W (Corresponding author), Gigante A, Perez-Perez MJ, Yue H, Hirano M, McIntyre TM, Silverstein RL. (2014). Thymidine phosphorylase participates in platelet signaling and promotes thrombosis. *Circ Res,* 115:997-1006. **PMC4258140**

b) Li W (Corresponding author) and Yue H. (2018). Thymidine phosphorylase, a potential new target for treating cardiovascular diseases. *Trends Cardiovasc Med.* 28:157-171. **PMC5856583**

c) Belcher A, Zulfiker AHM, Li O, Yue H, Sen Gupta A, and Li W (Corresponding author). Targeting Thymidine Phosphorylase With Tipiracil Hydrochloride Attenuates Thrombosis Without Increasing Risk of Bleeding in Mice. *Arterioscler Thromb Vasc Biol*. 2021;41:668–682. **PMID: 33297751**

d) Li W (Corresponding author), Yue H. Thymidine Phosphorylase Is Increased in COVID-19 Patients in an Acuity-Dependent Manner. Front Med (Lausanne). 2021;8:653773. doi: 10.3389/fmed.2021.653773. eCollection 2021. **PMID: 33829029; PMCID: PMC8019714.**

2. Role of TYMP on angiogenesis and obstructive vascular diseases

My early research addressed the mechanistic role of transmyocardial laser revascularization (TMLR) in the treatment of ischemic myocardium. TMLR reduces chest pain and improves quality of life in patients with coronary artery disease, but the mechanism is not clear. We found that TMLR treatment significantly induces angiogenesis that was correlated with the upregulation of TYMP and matrix metalloproteinase 2/9. Based on those findings, we conducted additional studies and found that direct injection of a plasmid vector encoding human TYMP cDNA into canine myocardium under acute or chronic ischemia dramatically reduced the size of the infarction and improved myocardial function and regional blood flow. A similar therapeutic effect was found in a rabbit hindlimb ischemic model. As the PI, I have successfully competed and received an independent research grant [*Grant in Aid for Young Scientists (Category A), Project #: 16689023*] from the Ministry of Education, Culture, Sports, Science & Technology, Japan to support my study regarding TYMP-mediated angiogenic therapy.

Having demonstrated the pro-angiogenic effect of TYMP on myocardium, we continued to examine its effect on VSMC since VSMC dysfunction contributes to the development of atherosclerosis and obstructive vascular diseases. We found, in contrast to its chemotaxic effect on endothelial cells, TYMP overexpression inhibited VSMC proliferation and migration and thus inhibited balloon injury-induced neointimal hyperplasia. We also demonstrated that adventitial delivery of a plasmid vector encoding the *TYMP* gene dramatically prevented vein graft thickening and failure. Taken together, our studies imply that regulation of TYMP expression or activity may lead to the development of new therapeutic strategies for the treatment of ischemic cardiovascular diseases by promoting angiogenesis but inhibiting dysregulated VSMC proliferation-associated vessel wall thickening. The following are representative publications regarding these studies:

a. Li W (Corresponding author), Chiba Y, Kimura T, Morioka K, Uesaka T, Ihaya A, & Muraoka R. (2001). Transmyocardial laser revascularization induced angiogenesis correlated with the expression of matrix metalloproteinases and platelet-derived endothelial cell growth factor. *Eur J Cardiothorac Surg*, 19:156-63.

b. Handa M, Li W (Corresponding author), Morioka K, Takamori A, Yamada N, & Ihaya A. (2008). Adventitial delivery of platelet-derived endothelial cell growth factor gene prevented intimal hyperplasia of vein graft. *J Vas.Surg,* 48:1566-74.

c. Li W (Corresponding author), Tanaka K, Morioka K, Takamori A, Handa M, Yamada N & Ihaya A. (2008). Long-term effect of gene therapy for chronic myocardial ischemia using platelet-derived endothelial cell growth factor. *J Gene Med,* 10:412-20.

d. Yue H, Tanaka K, Furukawa T, Karnik SS, & Li W (Corresponding author). (2012) Thymidine phosphorylase inhibits rat vascular smooth muscle cell proliferation via unphosphorylated STAT3. *Biochim Biophys Acta-Molecular Cell Research,* 23:1316-23. **PMC4133185**

3. Pro-atherothrombotic role of blood and vascular CD36

I joined Dr. Silverstein's lab at the Cleveland Clinic in 2006 as a Project Scientist with the goal of using my skills in small animal vascular surgery and my knowledge of cardiovascular biology to study a NHLBI funded SCCOR program in Arterial Thrombosis. I refined the mouse thrombosis models and utilized creative approaches to dissect the function of scavenger receptor CD36 on thrombosis and VSMC-mediated vascular obstructive diseases, including using 2D-DIGE. This experience was very successful and we published several high impact papers:

a. Ghosh A, Li W (Co-First Author), Febbraio M, Espinola GR, McCrae KR, Cockrell E, & Silverstein RL. (2008). Platelet CD36 mediates interactions with endothelial cell-derived microparticles and contributes to thrombosis in mice. *J Clin Invest.* 118:1934-43. **PMC2323190**

b. Li W, Febbraio M, Reddy SP, Yu DY, Yamamoto M, & Silverstein RL. (2010). CD36 participates in a signaling pathway that regulates ROS formation in murine VSMCs. *J Clin Invest.* 120:3996-4006. **PMC2964976**

c. Yue H, Febbraio M, Klenotic PA, Kennedy DJ, Wu YH, Chen SX, Gohara AF, Li O, Belcher A, Kuang B, McIntyre TM, Silverstein RL, and Li W (Corresponding author). (2019). CD36 Enhances Vascular Smooth Muscle Cell Proliferation and Development of Neointimal Hyperplasia. *Arterioscler Thromb Vasc Biol.* 39:263-275. **PMC6345504**

d. Yang M, Li W, Harberg C, Chen WJ, Yue H, Ferreira RB, Wynia-Smith SL, Carroll KS, Zielonka J, Flaumenhaft R, Silverstein RL, and Smith BC. (2020) Cysteine Sulfenylation by CD36 Signaling Promotes Arterial Thrombosis in Dyslipidemia. *Blood Adv* 4(18):4494-4507. **PMC7509873**

4. Proteasome and exosome on platelet activation and thrombosis

I joined Dr. McIntyre's group in 2011 and contributed to studies regarding proteasomes and exosomes in platelet activation and thrombosis. These projects are supported by several R01 grants including the R01HL130090, in which I am a co-investigator and responsible for aim 2, testing the role of ubiquitin metabolism in *in vivo* thrombosis. At the same time, we also discovered that platelet-activating factor receptor affects behavior, while deletion of platelet-activating factor receptor increased food intake and induced weight gain, leading to obesity in mice.

a. Gupta N, Li W, Willard B, Silverstein RL, & McIntyre TM. (2014). Proteasome proteolysis supports stimulated platelet function and thrombosis. *Arterioscler Thromb Vasc Biol,* 34:160-8. **PMC4059534**

b. Srikanthan S, Li W, Silverstein RL, & McIntyre TM. (2014). Exosome poly-ubiquitin inhibits platelet activation, downregulates CD36 and inhibits pro-atherothombotic cellular functions. *J Thromb Haemost*, 12:1906-17. **PMC4229405**

c. Li W (Corresponding author), & McIntyre TM. (2015). Platelet-activating factor receptor affects food intake and body weight. *Genes Dis.*, 2: 255-260. **PMC5773056**

d. Gupta N, Li W and McIntyre TM. (2015) Deubiquitinases Modulate Platelet Proteome Ubiquitination, Aggregation, and Thrombosis. *Arterioscler Thromb Vasc Biol.*35:2657-66. **PMC4662625**

5. Thrombi-targeted drug delivery

The current antiplatelet and anti-coagulant drugs as well as the thrombolytic drug, tissue plasminogen activator (tPA), have severe side effects, especially bleeding, that can lead to a fatal event. In collaboration with Dr. Sen Gupta, we are developing a new therapeutic strategy with thrombi-targeted thrombolysis. My role is to extensively and rigorously test the proper thrombi-targeted nanovesicles using the *in vivo* mouse thrombosis model and assess potential side effects of those components on aggregation using an *in vitro* platelet aggregation assay, thus providing rationale and evidence for the Gupta laboratory to develop the proper growing thrombi-targeted nanoparticles. These nanovesicles are then used to formulate drug-encapsulating nanoparticles and are further tested in my lab to evaluate their therapeutic efficacy using both *in vivo* and *in vitro* studies; side effects are further evaluated using a tail-bleeding assay. This collaboration has been very fruitful and we have published several papers together, shown below:

a. Sun M, Miyazawa K, Pendekanti T, Razmi M, Firlar E, Yang S, Shokuhfar T, Li O, Li W, Sen Gupta. A Combination targeting of 'platelets + fibrin' enhances clot anchorage efficiency of nanoparticles for vascular drug delivery. *Nanoscale*, First published on 17 Sep 2020. https://doi.org/10.1039/D0NR03633A

b. Pawlowski CL, Li W, Sun M, Ravichandran K, Hickman D, Kos C, Kaur G, Sen Gupta A. (2017). Platelet microparticle-inspired clot-responsive nanomedicine for targeted fibrinolysis. *Biomaterials* 128:94-108. **PMID: 28314136**

c. Shukla M, Sekhon UD, Betapudi V, Li W, Hickman DA, Pawlowski CL, Dyer MR, Neal MD, McCrae KR, Sen Gupta A. (2017). In vitro characterization of SynthoPlate™ (synthetic platelet) technology and its in vivo evaluation in severely thrombocytopenic mice. *J Thromb Haemost*. 15:375-387. **PMC5445574**

d. Li W (Corresponding author), Nieman M, and Sen Gupta A. (2016). Ferric chloride-induced murine thrombosis models. *J. Vis. Exp.* 115: e54479. **PMC5091988**

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/46364725/?sort=date&direction=descending

https://scholar.google.com/citations?user=FCpL1akAAAAJ

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1. Marshall University---Institutional Start-up Fund (Wei Li) 4/1/2017-
   This fund is to support Dr. Wei Li to build his modern cellular and molecular biology laboratory at Marshall University Joan C. Edwards School of Medicine.

2. 1R15HL145573-01 Wei Li (PI) 2.4 calendar months 1/3/2019-12/31/2021
   Title: Thymidine Phosphorylase: a novel target of antiplatelet therapy.
   (**No overlapping with the current application**)

3. R01HL129179 Anirban Sen Gupta (PI) 9/01/15-4/30/2021
   Title: Platelet-inspired Delivery System for Targeted Thrombolytic Therapy
   Role: Co-investigator 2.4 calendar months
   I am conducting in vivo thrombosis studies to test nanoparticle-mediated, thrombus-targeted drug delivery on thrombolysis, as well as hemostasis.

4. R01HL130090-01A1 Thomas M McIntyre (PI) 9/1/2016-5/31/2021
   Title: Dynamic Regulation of Thrombosis by the Platelet Proteome
   Role: Co-investigator 2.4 calendar months
   I am a co-investigator and have 20% effort on this project. I am conducting in vivo studies to test HAUSP inhibitors as well as genetic ablation of platelet HAUSP in thrombosis.

5. West Virginia Clinical and Translational Science Institute- Pop-Up COVID-19 Funding Opportunity 7/1/2020-6/30/2021
   Role: Principal investigator
   Title: The mechanistic role of SARS-CoV-2 spike protein in COVID-19-associated thrombosis

6. NIH Bench-to-Bedside Program (PIs, Olga V. Fedorova and Komal Sodhi) 1/1/2021-12/31/2022
   Role: Co-investigator at Marshall University
   Title: Fibrosis markers in kidney disease associated with dementia in women vs men

Completed Research Support

1. Marshall University Schools of Medicine and Pharmacy team with Cabell Huntington Hospital on pilot grants program (PI: Wei Li) 1/1/2018-12/31/2018
   Title: Evaluation of transdermal delivery of thymidine phosphorylase inhibitor on inhibition of thrombosis

2. WV-INBRE NGS pilot grant (PI: Wei Li) 8/1/2018-731/2019
   Title: Role of Thymidine Phosphorylase in Development of Metabolic Syndrome

3. PI for NASA WVSGC Graduate Research Fellowship Program for Adam Belcher (PhD student) 6/1/2019-8/31/2020
   Title: Role of TYMP in type II diabetes-associated high risk of thrombosis