BIOGRAPHICAL SKETCH

NAME: Li, Wei

POSITION TITLE: Associate Professor of Biomedical Sciences

eRA COMMONS USER NAME: liwei4

EDUCATION/TRAINING:

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 and I have expertise in studying vascular biology, platelet biology and thrombosis. I received my medical education in China and got my Ph.D. training in a Cardiothoracic Surgery Department in Japan where I learned skills in Molecular Biology and Cell Biology. My research is mainly focusing on exploring the role of ***thymidine phosphorylase*** **(TYMP)**, also known as *platelet-derived endothelial cell growth factor (PD-ECGF)*, in cardiovascular diseases. We have found that TYMP promotes angiogenesis, while inhibiting vascular smooth muscle cell (VSMC) proliferation, suggesting that TYMP plays a complex role in the vascular system. TYMP is largely present in platelet; however, its role in platelet biology has never been studied. *My recent study published by Circulation Research revealed for the first time that TYMP is a signaling molecule and participates in platelet activation and enhances thrombosis.*

I have produced about 50 papers. Among them, 17 papers are related to platelet biology and thrombosis, and 8 papers are related to the role of TYMP in the vascular system. I am currently testing the hypotheses that through facilitating activation of components of platelet glycoprotein VI (GPVI) and G-protein coupled receptor (GPCR) signaling pathways, TYMP promotes platelet activation and thrombosis; and inhibition of TYMP in vivo will be a novel antithrombotic therapy without disrupting hemostasis. Therefore, I have the expertise and hold a unique position to explore the role of TYMP in cardiovascular diseases.

My lab has all the scientific and technical expertise, key instruments including intravital microscope and Chronolog aggregometer, mouse strains, mouse thrombosis models, potent TYMP inhibitors and other resources, which are unique, to successfully carryout this project.

1. Li W. (Corresponding author), Gigante A., Perez-Perez M.J., Yue H., Hirano M., McIntyre T.M., & Silverstein R.L. (2014). **Thymidine phosphorylase participates in platelet signaling and promotes thrombosis. *Circ Res***. 115:997-1006. PMCID: PMC4258140
   (This paper was highlighted by Ruth Williams, as “In This Issue”, *Circulation Research*. *2014; 115: 961)*
2. Ghosh A., Li W. (Co-First Author), Febbraio M., Espinola G.R., McCrae K.R., Cockrell E., & Silverstein R.L. (2008). Platelet CD36 mediates interactions with endothelial cell-derived microparticles and contributes to thrombosis in mice. *J Clin Invest.* 118:1934-43. PMCID: PMC2323190
3. Li W., Tanaka K., Morioka K., Uesaka T., Yamada N., Takamori A., Handa M., Tanabe S., & Ihaya A. (2005). Thymidine phosphorylase gene transfer inhibits vascular smooth muscle cell proliferation by upregulating heme oxygenase-1 and $p27^{KIP1}$. *Arteriosclerosis, Thrombosis and Vascular Biology,* 25:1370-5. PMID: 15879300
4. Li W (Corresponding author), Nieman M, and Sen Gupta A. Ferric chloride-induced murine thrombosis models. J. Vis. Exp. 2016; 115: e54479. doi:10.3791/54479. PMID: 27684194

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 Cellular and Molecular Medicine), 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 - *Associate Professor*, Deaprtment of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Other Experience and Professional Memberships

2000-2006: Member, The Japanese Association for Thoracic Surgery
2002-2006: Member, Japan Surgical Society
2003-2006: Member, The Japanese Society for Cardiovascular Surgery
2006- Member, American Heart Association
2009- American Society of Hematology
2010-2010 North American Vascular Biology Organization
2011-2014 Member, International Society on Thrombosis and Haemostasis
2011- Editorial Board of World Journal of Medical Genetics
2012-2015 Editorial Board member of *Circulation Research* (reviewed >80 papers)
2017- Editorial Board member of Frontiers in Medicine, section of Hematology
2017- Member of Peer Reviewer Committee for the American Heart Association
2002- Ad Hoc Reviewer for: Circulation Research; Frontiers, Thrombosis and Hemostasis, The Annals of Thoracic Surgery; Arterioscler Thromb Vasc Biol; Journal of Molecular and Cellular Cardiology; The American Journal of Physiology – Heart and Circulatory Physiology, The Journal of Gene Medicine; Journal of Molecular Histology; Expert Opinion on Therapeutic Patents, etc. Total > 200 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 Innovator Award of Cleveland Clinic (Thymidine phosphorylase promotes thrombosis)
2013 Circulation Research Top Reviewers Award
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)

C. Contribution to Science

1. Role of TYMP on angiogenesis and obstructive vascular diseases

My early research addressed the mechanistic role of transmyocardial laser revascularization (TMLR) on treating ischemic myocardium. TMLR reduces chest pain and improve the life quality of patients with coronary artery diseases, but the mechanism is not clear. We found that TMLR treatment significantly induced angiogenesis that was correlated with the upregulation of a pro-angiogenic factor, namely TYMP/PD-ECGF, as well as matrix metalloproteinase 2/9. Based on those findings, we conducted additional studies and found that direct injection of plasmid vector encoding human TYMP cDNA into the canine myocardium under acute and chronic ischemia dramatically reduced size of infarction and improved myocardial function. Similar therapeutic effect was found in rabbit hindlimb ischemic model. As the PI, I have successfully competed and received independent research grant [*Grant in Aid for Young Scientists (Category A)*] from the Ministry of Education, Culture, Sports, Science & Technology, Japan to support study regarding TYMP-mediated angiogenic therapy. Having demonstrated the pro-angiogenic effect of TYMP on myocardium, we continually examined its effect on

VSMC, as abnormal growth of VSMC contributes to development of atherosclerosis and obstructive vascular diseases. We found, in contrast to its chemotaxic role on endothelial cells, TYMP inhibits VSMC proliferation and migration and thus inhibits balloon injury induced neointimal hyperplasia. We also demonstrated that adventitial delivery of plasmid vector encoding TYMP gene dramatically prevented vein graft thickening and failure. Taken together, our studies implied that regulation of TYMP expression or activity may lead to develop new therapeutic strategy for ischemic cardiovascular diseases through promoting angiogenesis but inhibiting atherosclerosis. Following are representative publications regarding the above studies and "*****" indicates senior author papers.

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. PMID: 11167105

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. PMID: 18848756

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. PMID: 18196499

d.***** Yue H., Tanaka K., Furukawa T., Karnik S.S., & 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. PMID: 22668509

2. Mechanistic role of TYMP on thrombosis

TYMP is highly expressed in several systemic diseases including atherosclerosis, cancer, type II diabetes and HIV infection; all of these diseases have high risk of thrombotic complication. **By using *Tymp* null and deficient mice we demonstrated for the first time that TYMP plays important role in platelet activation and thrombosis**. TYMP facilitates multiple agonists induced platelet activation and aggregation; however, *Tymp* deletion or pharmacological inhibition does not cause bleeding, a severe side effect of current anti-platelet therapies. As mentioned in Section A, these exciting finding have been published by ***Circulation Research***, and also formed the foundation of this proposal. To the interest of this study, TYMP inhibitor, namely Tipiracil Hydrochloride, as a new drug component, has been approved by the U.S. FDA. These studies suggest that regulation of TYMP activity is safe. Therefore, clarification of the mechanistic role of TYMP in estrogen-associated platelet activation and thrombosis will be easily translated to clinical study, and lead to investigation of targeted TYMP-inhibition as a new and safer anti-thrombotic therapy 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
(This paper was highlighted by Ruth Williams, as "In This Issue", *Circulation Research*. *2014; 115: 961)*

3. Prothrombotic role of blood and vascular CD36

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

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

b. Li W., Febbraio M., Reddy S.P., Yu D.Y., Yamamoto M., & Silverstein R.L. (2010). CD36 participates in a signaling pathway that regulates ROS formation in murine VSMCs. *J Clin Invest.* 120:3996-4006. PMCID: PMC2964976

c. Chen K., Febbraio M., Li W., & Sivlerstein R.L. (2008). A specific CD36-dependent signalling pathway is required for platelet activation by oxidized low-density lipoprotein. *Circ Res*. 102:1512-9. PMCID: PMC2749986

d. Chen K., Li W., Major J., Rahaman S.O., Febbraio M., & Silverstein R.L. (2011). Vav guanine nucleotide exchange factors link hyperlipidemia and a prothrombotic state. *Blood*; 117:5744-50. PMCID: PMC3110031

4. Proteasome and exosome on platelet activation and thrombosis

From 2011, I joined Dr. McIntyre's group, and contributed to studies regarding proteasome and exosome on platelet activation and thrombosis. At same time, we also discovered that platelet-activating factor receptor affects life behavior.

a. Gupta N., Li W., Willard B., Silverstein R.L, & McIntyre T.M. (2014). Proteasome proteolysis supports stimulated platelet function and thrombosis. *Arterioscler Thromb Vasc Biol,* 34:160-8. PMCID: PMC4059534
b. Srikanthan S., Li W., Silverstein R.L., & McIntyre T.M. (2014). Exosome poly-ubiquitin inhibits platelet activation, downregulates CD36 and inhibits pro-atherothombotic cellular functions. *J Thromb Haemost*, 12:1906-17. PMCID: PMC4229405
c. Li. W. (Corresponding author), & McIntyre T.M. (2015). Platelet-activating factor receptor affects food intake and body weight. *Genes Dis.*, available online 24 June. doi:10.1016/j.gendis.2015.06.002
d. Gupta N, Li W. and McIntyre T.M. Deubiquitinases Modulate Platelet Proteome Ubiquitination, Aggregation, and Thrombosis. *Arterioscler Thromb Vasc Biol.* 2015;35:2657-66. PMCID: PMC4662625

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. Research Support

Ongoing Research Support

1. NIH R01HL129179 Anirban Sen Gupta (PI) 9/01/15-6/30/2020
   Title: Platelet-inspired Delivery System for Targeted Thrombolytic Therapy
   Role of Wei Li: I am a co-investigator and have 20% effort on this project. I conduct in vitro and in vivo studies to test nanovehicle-mediated, thrombus-targeted drug delivery on thrombolysis.
2. R01HL130090-01A1 Thomas M McIntyre (PI) 9/1/2016-5/31/2020
   Title: Dynamic Regulation of Thrombosis by the Platelet Proteome
   Role: I am a co-investigator and have 20% effort on this project. I will conduct in vivo studies to test HAUSP inhibitors in thrombosis.