BIOGRAPHICAL SKETCH

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NAME: Bihl, Ji Chen

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

POSITION TITLE: Associate Professor

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
Hengyang Medical College, South China University (Hunan, China)	M.D.	07/2005	Clinical Medicine
Medical Science Center, Peking University (Beijing, China)	Ph.D.	07/2010	Internal Medicine
Wright State University Boonshoft School of Medicine (Dayton, OH)	Post-doctor	06/2014	Pharmacology and Toxicology

A. Personal Statement

I have the training, expertise, motivation, and leadership necessary to supervise and collaborate with the current research project. I have a broad background in integrated basic and translational research projects, including the studies on the role of extracellular exosomes (EXs) and microvesicles (MVs), stem cell therapy, and the renin-angiotensin system in ischemic stroke, hemorrhagic stroke, and diabetic ischemic stroke. Several signal pathways such as PI3K/Akt/eNOS, oxidative stress, and microRNA mechanisms are actively investigated. My research approaches include using transgenic mouse models in combination with animal surgeries, such as telemetric probe implantation for recording blood pressure and heart rate, minipump/microinjection for chronic/acute drug administration, and animal modeling for MCAO-induced ischemic stroke. I have also been actively involved in translational studies by investigating the role of endothelial progenitor cells (EPCs) and MVs/EXs in stroke and diabetes patients. My laboratory is very well established to perform exosomal research, especially related to microRNA delivery. As a note, my publication history reflects my maiden name (Chen J) and I have been publishing under my married name (Bihl J) since 2014.

1. **Chen J**, Chen S, Chen Y, Zhang C, Wang J, Zhang W, Liu G, Zhao B, Chen Y, “Circulating endothelial progenitor cells and cellular membrane microparticles in db/db diabetic mouse: possible implications in cerebral ischemic damage,” *Am J Physiol Endocrinol Metab*, 2011, 301(1): E62-71. PMCID: PMC3129837.
2. **Chen J**, Xiao X, Chen S, Zhang C, Chen J, Yi D, Shenoy V, Raizada MK, Zhao B, Chen Y, “Angiotensin converting enzyme 2 priming enhances the function of endothelial progenitor cells and their therapeutic efficacy,” *Hypertension*, 2013, 61: 681-689. PMCID: PMC4011714.
3. Wang J, Zhong Y, Ma X, Xiao X, Cheng C, Chen Y, Iwuchukwu I, Gaines K, Zhao B, Liu S, Travers J, **Bihl J**[#], Chen Y[#], “Analyses of endothelial cells and endothelial progenitor cells released microvesicles by using microbead and Q-dot based nanoparticle tracking analysis,” *Sci Rep*, 2016, 6:24679. PMCID: PMC4837394.
4. Zhang C, Wang J, Ma X, Wang W, Zhao B, Chen Y, Chen C, **Bihl JC**, “ACE2-EPC-EXs protect ageing ECs against hypoxia/reoxygenation-induced injury through the miR-18a/Nox2/ROS pathway,” *J Cell Mol Med,* 2018, 22(3):1873-1882. PMCID: PMC5824419.

B. Positions and Honors

Positions and Employment:

2014. 6-2017.1: Research Assistant Professor, Department of Pharmacology & Toxicology, Wright State University Boonshoft School of Medicine, Dayton OH

2017.2-2020.12: Assistant Professor, Department of Pharmacology & Toxicology, Boonshoft School of Medicine, Wright State University, Dayton OH

2020.12-current: Associate Professor, Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington WV

Professional Society and Public Advisory Committees:

2010-2011: Member, Society for Neuroscience (SfN)
2011-current: Member, American Heart Association (AHA)
2013-current: Membership, WSU Graduate Faculty
2014-2016: Committee, National Postdoc Association (NPA)
2015-current: Member, American Diabetes Association (ADA)
2016-current: Member, International Society for Extracellular Vesicles (ISEV)

Honors and Awards:

2002: "Merit Student" Award, South China University School of Medicine, Hengyang, China
2003: "Outstanding Student" Award, South China University School of Medicine, Hengyang, China
2009: Young Scientist Travel Award, the 44th Annual Meeting of the European Association for the Study of the Liver
2009: "Merit Student" and "Outstanding Scholarship" Award, Peking University, Beijing, China
2010: Young Scientist Travel Award, the 45th Annual Meeting of the European Association for the Study of the Liver
2013: Young Scientist Travel Award, the XXVIth International Symposium on Cerebral Blood Flow, Metabolism and Function & XIth International Conference on Quantification of Brain Function with PET
2015: Faculty Research Incentive award, Wright State University (WSU), Dayton, OH
2016: Faculty Research Incentive award, Wright State University, Dayton, OH
2019: President's Awards for Excellence: Early Career Achievement Award, WSU, Dayton, OH

Professional Service:

Reviewer for grant: the Portuguese Foundation for Science and Technology (FCT), Diabetes UK

Reviewer for journals: Scientific Reports, Clinical and Experimental Pharmacology and Physiology, Experimental Physiology, Inflammation Research, Cellular and Molecular Neurobiology, Toxicology Science, Stem Cell International, Medical Science Monitor, Life Sciences, Methods in Pharmacology and Toxicology, Scientific Reports, Molecular Brain, Circulation, Journal of Extracellular Vesicles, JACC: Basic to Translational Science, Drug Delivery, Molecular Therapy - Nucleic Acids, Microvascular Research, Cell and Tissue Research, Journal of Cellular Physiology, Molecular Medicine Reports.

Editorial Board: Oxidative Medicine and Cellular Longevity

Thesis committee member for Master and Ph.D students: Hala Mustafa Ammar, 2012-2014; Mahesh Kodali, 2013-2015; Ashvin Iyer, 2013-2015; Abdelfatah S. Abou Issa, 2013-2015; Langni Liu, 2013-2015; Ravina M. Ashtaputre, 2014-2016; Sayali Dharmadhikari, 2014-2016; Katherine Fahy, 2015-2017; Azeezat Afolake Awoyemi, 2016-2018; Lannig Liu, 2015-2020, Qinmao Ye, 2016-2018; Manasi Halurkar, 2017-2019; Venkata Sai Usha Sri Polaki, 2018-2020; Sri Meghana Yerrapragada, 2019-2021.

C. Contribution to Science

1. One of my research areas is to address that endothelial progenitor cells (EPCs) can alleviate injury and promote recovery for ischemic stroke in diabetes. Diabetes mellitus is a risk factor for ischemic stroke, which is the nation's second leading cause of death and the leading cause of long-term disability. Ischemic cerebral damage is exaggerated and the outcome is poor in diabetic patients because of the combinations of impaired

endothelial dysfunction, increased inflammation and decreased angiogenesis. Hence, there is an urgent need to discover why diabetics are susceptible and to design new treatments that specifically protect vascular integrity/function, reduce pathologic vascular inflammation and improve neurological function after stroke. These publications found that the ischemic stroke injury is enlarged in diabetic mice and the circulating EPCs are decreased in number and impaired in functions; therefore, I started a project to improve EPC function by modifying gene expression in EPCs. Firstly, I focused on the CXCR4/SDF-1 pathway which plays an important role in EPC migration and homing; and demonstrated that over-expression of CXCR4 could improve the dysfunction of EPCs from diabetic mice and enhance EPC-based therapy for ischemic stroke.

a. **Chen J**, Chen J, Chen S, Zhang C, Zhang L, Xiao X, Das A, Zhao Y, Yuan B, Morris M, Zhao B, Chen Y, "Transfusion of CXCR4-primed endothelial progenitor cells reduces cerebral ischemic damage and promotes repair in db/db diabetic mice," *PloS ONE*, 2012, 7(11): e50105. PMCID: PMC3503762.
b. Wang J, Chen Y, Yang Y, Xiao X, Chen S, Zhang C, Jacobs B, Zhao B, **Bihl J**[#], Chen Y[#], "Endothelial progenitor cells and neural progenitor cells synergistically protect cerebral endothelial cells from hypoxia/reoxygenation-induced injury via activating the PI3K/Akt pathway," *Mol Brain*, 2016, 9(1):12. PMCID: PMC4738765.
c. Wu K, Yang Y, Zhong Y, Zhang P, Guo R, Liu H, Cheng C, Koroscil TM, Chen Y, Liu S, **Bihl J**, "The effects of microvesicles on endothelial progenitor cells are compromised in type 2 diabetic patients via downregulation of miR-126/VEGFR2 pathway," *Am J Physiol Endocrinol Metab*, 2016, 310:E828-30. PMCID: PMC4895450.
d. Ma C, Wang J, Liu H, Chen Y, Ma X, Chen S, Chen Y, **Bih JC**[#], Yang Y[#], "Moderate exercise enhances endothelial progenitor cell exosomes released and function," *Med Sci Sports Exerc*, 2018, 50(10):2024-2032. PMID: 30222687

2. My research also focuses on extracellular microvesicles (MVs). Extracellular MVs are small vesicles of cellular membrane released from almost all types of cells in response to physiological and pathological stimuli. MVs represent a novel way of cell-to-cell communication by transferring their molecular signatures (proteins and miRs) to target cells and tissues. Thus, extracellular MVs could be the novel therapeutic target or avenue for stroke; and could be the biomarkers for stroke patients. These studies emphasize the protective effects of MVs derived from EPCs (EPC-MVs) on vascular cells. These publications also discuss the function of MVs from different origins by carrying different molecular signatures.

a. Gu S*, Zhang W*, **Chen J***, Ma R, Xiao X, Ma X, Yao Z, Chen Y, "EPC-derived microvesicles protect cardiomyocytes from Ang II-induced hypertrophy and apoptosis," *PloS ONE*, 2014, 2; 9(1): e85396. PMCID: PMC3879348.
b. Xiao X, Bi K, Liu Y, Fan R, Zhao Y, Ma X, Wang J, Zhao B, Chen Y, **Chen J**, "Cellular membrane microparticles: potential targets of combinational therapy for vascular disease," *Curr Vasc Pharmacol*, 2015, 13: 449-58. PMCID: PMC25360845.
c. Wang J, Guo R, Yang Y, Jacobs B, Chen S, Iwuchukwu I, Gaines K, Chen Y, Simman R, Lv G, Wu K, **Bihl J**, "The novel methods for analysis of exosomes released from endothelial cells and endothelial progenitor cells," *Stem Cells Int*, 2016, 2016:2639728. PMCID: PMC4826946.
d. Ma X, Wang J, Li J, Ma C, Chen S, Lei W, Yang Y, Liu S, **Bihl J**[#], Chen C[#], "Loading miR-210 in endothelial progenitor cells derived exosomes boosts their beneficial effects on hypoxia/reoxygenation-induced human endothelial cells via protecting mitochondrial function," *Cell Physiol Biochem,* 2018, 46(2):664-675. PMID: 29621777.

3. In addition to the contribution described above, I also documented the protective role of ACE2/Ang-(1-7)/Mas in ischemic stroke by counteracting the effects of ACE/Ang II/AT1. The renin-angiotensin system (RAS) participants in the pathogenesis of stroke, primarily through the actions of the vasoactive peptide Ang II and its pathway ACE/Ang II/AT1. ACE2/Ang-(1-7)/Mas, a newly identified member of RAS, has been demonstrated to counteract the effects of ACE/Ang II/AT1. ACE2 is a homolog of ACE that is abundantly expressed in the cardiovascular-related areas of the brain and blood vessels. The primary function of ACE2 is to metabolize the deleterious Ang II into Ang-(1-7), a heptapeptide with vasoprotective actions. Therefore, activation of the ACE2/Ang-(1-7)/Mas pathway might represent a novel target and strategy for treating strokes. These publications demonstrate that ACE2 and Ang-(1-7) protects the brain form ischemic and hemorrhagic stroke. These studies also discuss the protective effects of ACE2 on EPC function and how ACE2 improves the therapeutic efficacy in ischemic stroke.

a. **Chen J**, Xiao X, Chen S, Zhang C, Chen J, Yi D, Shenoy V, Raizada MK, Zhao B, Chen Y, "Angiotensin converting enzyme 2 priming enhances the function of endothelial progenitor cells and their therapeutic efficacy," *Hypertension*, 2013, 61: 681-689. PMCID: PMC4011714.
b. **Chen J**, Zhao Y, Chen S, Wang J, Xiao X, Ma X, Penchikala M, Xia H, Lazartigues E, Zhao B, Chen Y, "Neuronal over-expression of ACE2 protects brain from ischemia-induced damage," *Neuropharmacology*, 2014, 79: 550-558. PMCID: PMC 3992949.
c. **Bihl J**, Zhang C, Zhao Y, Xiao X, Ma X, Chen Y, Chen S, Zhao B, Chen Y, "Angiotensin-(1-7) counteracts the effects of Ang II on vascular smooth muscle cells, vascular remodeling and hemorrhagic stroke: role of NFkB inflammation pathway," *Vascul Pharmacol*, 2015, 73: 115-23. PMCID: PMC4617528.
d. Zhang C, Wang J, Ma X, Wang W, Zhao B, Chen Y, Chen C, **Bihl JC**, "ACE2-EPC-EXs protect ageing ECs against hypoxia/reoxygenation-induced injury through the miR-18a/Nox2/ROS pathway," *J Cell Mol Med,* 2018, 22(3):1873-1882. PMCID: PMC5824419.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/ji.chen.1/bibliography/45427493/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

1 R01NS102720 Bihl (PI) 05/01/2018-04/30/2023
NIH NINDS
Exosomes from miR-primed endothelial progenitor cells for treating ischemic stroke
The major goal of this project is to determine the enhanced therapeutic effects of EPC-EXs-miR^{210} on IS by protecting the brain from ischemic injury and promoting neurological recovery. This project will provide important mechanistic insights into SDF-1α/CXCR4, and relevant miRs, such as miR-126 and miR-210.
Role: Principal investigator

2R01HL062996 Travers (PI) 01/01/2020-11/30/2023
NIH NHLBI
Platelet Activating Factor and Epidermal Cytoxicity.
The major goal of this project is to investigate the combinatorial impact of short-term ethanol exposure and thermal burn injury on platelet-activating factor and microvesicle particles in keratinocytes leading to multi-organ dysfunction.
Role: Co-investigator

IBX000853D Travers (PI) 01/01/2019-11/30/2029
VA Merit Grant
Oxidized lipids and UV immunosupperesion.
The major goal of this project is to investigate the impact of UVB exposure on platelet-activating factors and microvesicle particles in keratinocytes leading to immunosuppression.
Role: Collaborator

AMAG Pharmaceutical Research Grant Brown (PI) 12/01/2020-11/30/2021
VA Merit Grant
Placental exosomes induce pathophysiological symptoms of pre-eclampsia
The goal of this project is to advance our understanding of preeclampsia etiology and will identify a signaling mechanism integral to the generation of preeclampsia that could be utilized for the development of targeted, novel therapeutics to improve maternal and neonatal health.
Role: Co-investigator

Completed Research Support

1-17-IBS-187 Bihl (PI) 01/01/2017-12/31/2020
ADA Innovative Basic Science Award
Therapeutic role of miR-126 over-expressing EPC-MVs for ischemic stroke in diabetes

The goal of this project is to determine the therapeutic role of miR-126 over-expressing endothelial progenitor cell-released microvesicles for ischemic stroke in diabetes and the underlying mechanisms related to the miR-126 downstream pathway.
Role: Principal investigator

5 R21 AR071110 Bihl (PI) 08/10/2017-07/31/2020
NIH NIAMS
Microvesicles as a novel transmitter for UVB-induced bioactive products
The major goals of this project are to determine the involvement of PAF-PAFR signaling pathway in mediating UVB-induced MVP release and the effects of antioxidant on UVB-induced MVP release, and determine the bioactive agents in UVB-MVP.
Role: Principal investigator

16SDG26420078 Bihl (PI) 01/01/2016-06/30/2020
AHA Scientist Development Grant
Role of ACE2 over-expressing endothelial progenitor cells in cerebral hemorrhage
The goal of this project is to determine the preventive and therapeutic role of angiotensin converting enzyme 2 (ACE2) over-expressing endothelial progenitor cells (ACE2-EPCs) in hemorrhagic stroke animal model and determine the underlying mechanisms.
Role: Principal investigator

18POST33990433 Wang (PI) 07/01/2018-6/30/2020
AHA Post-doctoral Fellowship Award
Therapeutic role of miR-126 over-expressing EPC-MVs for ischemic stroke in diabetes
The major goal of this project is to determine the therapeutic role of miR-126-EPC-MVs in ischemic stroke in diabetes by protecting ECs/EPCs/neurons/astrocytes against ischemic and inflammatory injury and promoting angiogenic/neurogenic repair; and determine the predictive role of the levels of cEPC-MVs and their carried miR-126 for ischemic stroke outcomes in diabetic patients.
Role: Mentor

13POST14780018 Chen/Bihl (PI) 01/01/2013-12/31/2014
AHA Post-doctoral Fellowship Award
Role of Angiotensin II/Angiotensin (1-7) balance in intracerebral hemorrhagic stroke
The goal of this project is to investigate the role of Angiotensin II/Angiotensin (1-7) balance in EPC and EC function, and in the progress of intracerebral hemorrhagic stroke and examine the underlying mechanisms related to NFκB.
Role: Principal investigator