BIOGRAPHICAL SKETCH

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NAME: Pei, Liming

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

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
University of Science & Technology of China, Hefei, China	B.S.	06/2000	Life Sciences
University of California, Los Angeles, CA	Ph.D.	06/2006	Cellular and Molecular Pathology
Salk Institute for Biological Studies, La Jolla, CA	Postdoctoral	03/2013	Molecular Biology

A. Personal Statement

My long-term research goal is to understand how different organs react to energy cues and communicate with each other to maintain whole-organism homeostasis in both physiological and pathological contexts. I have an extensive background in studying cellular metabolism, hormonal signaling and animal models of human disease. During my graduate training with Dr. Peter Tontonoz at UCLA, I identified NR4A nuclear receptors as important mediators of macrophage inflammatory response to oxidized lipids in the context of atherosclerosis, and as critical transcriptional regulators of hepatic gluconeogenesis that contributes to diabetes. I continued my postdoctoral training with Dr. Ronald Evans at the Salk Institute, studying the importance of transcriptional corepressor SMRT in mammalian development and ERR subfamily of nuclear receptors in metabolic regulation. Since establishing my independent research lab at the Children's Hospital of Philadelphia (CHOP) and University of Pennsylvania (UPenn), I have shown that ligand-modulated nuclear receptor ERRγ is an essential transcriptional regulator of cellular metabolism and mitochondrial function in the brain, heart and kidney. More recently I discovered that the heart secretes the TGFβ family protein Growth Differentiation Factor 15 (GDF15) as a hormone to regulate postnatal body growth. A series of studies from my lab revealed a unified endocrine mechanism that the heart employs to communicate with the rest of the body and opened an exciting new area which we termed cardiac endocrinology. I am actively expanding this new field by further understanding GDF15 biology, discovering other heart-derived hormones and studying their biological functions. I have also made significant discoveries using single-cell genomics to understand cardiac physiology and disease. We published one of the first massively parallel single-nucleus RNA-seq (snRNA-seq) studies in mammalian hearts. We are actively applying single-cell genomics to guide mechanistic understanding of cardiac and metabolic disease.

Ongoing and recent funded projects that I would like to highlight include:

Department of Defense HT9425-24-1-0268 Liming Pei (PI) 07/01/2024 – 06/30/2028
Elucidation of the cardiomyopathy of the mitochondrial disorder Friedreich ataxia
The major goal of this project is to obtain mechanistic insights into Friedreich ataxia cardiomyopathy.

Additional Ventures Liming Pei (PI) 03/01/2023 – 02/28/2026
Mechanistic understanding of Fontan associated liver disease with single-cell multiomics
The major goal of this project is to understand Fontan associated liver disease with single-cell multiomics.

NIH U54 HL165442 Kai Tan/Liming Pei/Jeffrey Moffitt (MPI) 08/01/2022 – 07/31/2026

Center for multidimensional atlas of the human heart
As part the NIH HuBMAP project, the major goal of this project is to perform spatial multi-omics study of the normal human heart at different ages.

American Heart Association 2022 AHA EIA 227477 Liming Pei (PI) 07/01/2022 – 06/30/2027
Heart-derived hormones in cardiovascular biology and disease
The major goal of this project is to use new animal models to identify and study the function of new heart-derived hormones.

Department of Defense W81XWH22-1-0561 Liming Pei (PI) 07/01/2022 – 03/31/2026
ANT1 gene therapy for the treatment of mitochondrial disease
The major goal of this project is to optimize an ANT1-based gene therapy to treat mitochondrial disease.

NIH U01 HL166058 Liming Pei/Douglas Wallace/Yi Xing (MPI) 07/01/2022 – 06/30/2026
Novel biological insights by utilizing mitochondrial genome information from HuBMAP resources
The major goal of this project is to demonstrate the value and use of mitochondrial genome data in HuBMAP datasets to obtain new biological insights.

Department of Defense W81XWH-22-1-0058 Liming Pei (PI) 04/01/2022 – 03/31/2025
Single-cell multiomics to understand mitochondrial disease
The major goal of this project is to use advanced single-cell multiomics to understand mitochondrial disease.

NIH R01 DK111495 Liming Pei (PI) 04/01/2017 – 03/31/2023
Coordinated regulation of mitochondrial and cellular functions by nuclear receptors
The major goal of this project is to determine mechanistically how nuclear receptors especially ERRγ coordinately regulate mitochondrial and cellular functions in kidney biology and disease.

Citations:

1. Wang T, Liu J, McDonald, C, Lupino K, Zhai X, Wilkins BJ, Hakonarson H, **Pei L** (2017). GDF15 is a heart-derived hormone that regulates body growth. EMBO Molecular Medicine *9*, 1150-1164. PMID: 28572090. PMCID: PMC5538424.
2. Zhao J, Lupino K, Wilkins BJ, Qiu C, Liu J, Omura Y, Allred AL, McDonald C, Susztak K, Barish GD, **Pei L**. (2018) Genomic integration of ERRγ-HNF1β regulates renal bioenergetics and prevents chronic kidney disease. Proceedings of National Academy of Sciences, E4910-E4919. PMID: 29735694. PMCID: PMC6003475.
3. Hu P, Liu J, Zhao J, Wilkins BJ, Lupino K, Wu H, **Pei L**. (2018). Single-nucleus transcriptomic survey of cell diversity and functional remodeling in the postnatal developing hearts. Genes & Development 32, 1344-1357. PMID: 30254108. PMCID: PMC6169839.
4. Hu P, Rychik J, Zhao J, Bai H, Bauer A, Yu W, Rand EB, Dodds KM, Goldberg DJ, Tan K, Wilkins BJ, **Pei L**. Single-cell multiomics guided mechanistic understanding of Fontan-associated liver disease. *Sci Transl Med* **16**, eadk6213 (2024). PMID: 38657025. PMCID: PMC11103255.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023–Present	Assistant Program Director & Steering Committee member, CHOP Cardiology T32, CHOP
2022–Present	Member and Vice Chair, Mid-Career Investigator (MCI) Committee, International Society of Heart Research, North American Section (ISHR-NAS)
2022–2024	Member, Medical Faculty Senate Steering Committee, Perelman School of Medicine, UPenn
2020–Present	co-Chair, Policies Working Group, NIH Human BioMolecular Atlas Program (HuBMAP)
2020–2022	Member, Scientific & Clinical Education Lifelong Learning Committee (SCILL), Council on Basic Cardiovascular Sciences (BCVS), American Heart Association (AHA)
2019–Present	Associate Professor, Children's Hospital of Philadelphia and University of Pennsylvania
2019–Present	co-Director, Academic Enrichment, Institute for Diabetes, Obesity and Metabolism, UPenn
2019–Present	Study section member of pre/postdoctoral fellowship, Career Development Award, and Established Investigator Award, American Heart Association

2019 Planning Committee member and Session Chair, the 9th Regional Translational Research in Mitochondrial, Aging, and Disease (TriMAD) Symposium. Philadelphia, PA.

2017–Present Member of Faculty Advisory Committee, Department of Veterinary Resources, CHOP

2017–2021 Study section member of Pre-MTD for IIRAs (Investigator-initiated Research Awards) and TTDAs (Technology/Therapeutic Development Awards), and Focused Program, Congressionally Directed Medical Research Program (CDMRP), US Department of Defense

2013–Present *Ad hoc* reviewer for Instituto de Salud Carlos III (Spain), Natural Sciences and Engineering Research Council of Canada, Barth Syndrome Foundation Grant Program (USA), Innovation and Technology Commission (Hong Kong), British Heart Foundation (UK), UK Research and Innovation (UK).

2013–2019 Assistant Professor, Children's Hospital of Philadelphia and University of Pennsylvania

2008–Present *Ad hoc* reviewer for *Proceedings of National Academy of Sciences, Circulation, Nature Communications, Journal of Clinical Investigation, JCI Insight, Advanced Science, Science Bulletin, Cell Report, Hepatology, EMBO Molecular Medicine*, *EMBO reports, Signal Transduction and Targeted Therapy, PLOS Genetics, Molecular and Cellular Biology, JACC: Basic to Translational Science*, *Molecular Metabolism, Scientific Bulletin*, *Journal of Molecular and Cellular Cardiology, Journal of the American Society of Nephrology*, *Kidney International*, *Breast Cancer Research, Oncogene*, *iScience*, *Theranostics, European Journal of Internal Medicine, Journal of Medical Genetics, FASEB Journal, FEBS Letters, BMC Genomics, BMC Nephrology, Molecular Neurobiology, Scientific Reports, PLOS One, Molecular and Cellular Biochemistry*, *FEBS Open Bio, Rejuvenation Research, Pediatric Obesity, Neuronal Signaling, Depression and Anxiety*, etc.

2006–Present Member, American Heart Association, Society of Chinese Bioscientists in America, International Society for Heart Research (ISHR), American Diabetes Association (ADA), Chinese American Diabetes Association (CADA), American Association for the Advancement of Science (AAAS).

2006–2013 Postdoctoral fellow, Salk Institute for Biological Studies, Howard Hughes Medical Institute

2000–2006 Graduate student researcher, University of California, Los Angeles

Honors

2021–Present Fellow, American Heart Association

2009–2012 Parker B. Francis Fellowship

2006 Sarkaria Award, UCLA Department of Pathology and Lab Medicine

2005 George J. Popjak Scholar, UCLA School of Medicine

2005 NIDDK Scholarship, Keystone Symposia "PPAR/LXR"

2000 Guo Moruo-President Scholarship (Highest honor for USTC undergraduate student), USTC

C. Contributions to Science

1. **I have made significant contributions to a new area of cardiac endocrinology, investigating the identities and roles of heart-derived hormones in physiology and disease.** A central question in physiology is how different organs communicate with each other to maintain whole-organism homeostasis. The classical endocrine system is well documented for its essential role in inter-organ communication. In addition, research in the past 20 years revealed that non-glandular organs such as adipose tissue, liver and skeletal muscle can secrete hormones that regulate whole-body metabolism. In contrast, little is known regarding heart-derived hormones save for ANP and BNP, each discovered almost 40 years ago. We discovered that the TGFβ family protein Growth Differentiation Factor 15 (GDF15) is a new heart-derived hormone. Circulating GDF15 acts on the liver to inhibit growth hormone signaling and body growth. Plasma GDF15 is increased in children with concomitant heart disease and FTT. Our results explain a well-established clinical observation that children with heart diseases often develop FTT. More importantly, these studies reveal a new endocrine mechanism by which the heart coordinates cardiac function and body growth. We further identified the key enzymes that process GDF15 precursors into the mature form of hormone. We then used single-nucleus RNA-Seq to identify the gene regulatory network that regulates GDF15 transcriptional induction in heart disease. These results and our follow up studies opened an exciting new area which we termed cardiac endocrinology. I am the PI in these studies.

   a. Wang T, Liu J, McDonald, C, Lupino K, Zhai X, Wilkins BJ, Hakonarson H, **Pei L** (2017). GDF15 is a heart-derived hormone that regulates body growth. EMBO Molecular Medicine *9*, 1150-1164. PMID: 28572090. PMCID: PMC5538424.

b. Li J, Liu J, Lupino K, Liu X, Zhang L, **Pei L** (2018). GDF15 maturation requires proteolytic cleavage by PCSK3, 5 and 6. Molecular and Cellular Biology. 38 (21). pii: e00249-18. PMID: 30104250. PMCID: PMC6189459.
c. Hu P, Liu J, Zhao J, Wilkins BJ, Lupino K, Wu H, **Pei L** (2018). Single-nucleus transcriptomic survey of cell diversity and functional remodeling in the postnatal developing hearts. Genes & Development 32, 1344-1357. PMID: 30254108. PMCID: PMC6169839.
d. Zhao, J, and **Pei, L** (2020). Cardiac Endocrinology: Heart-Derived Hormones in Physiology and Disease. JACC Basic Transl Sci *5*, 949-960. PMID: 33015416. PMCID: PMC7524786.

2. **I have made significant discoveries using single-cell genomics to understand cardiac physiology and disease.** We published one of the first massively parallel single-nucleus RNA-seq (snRNA-seq) studies in mammalian hearts. By profiling the transcriptome of ~24,000 nuclei, we identified major and rare cardiac cell types and revealed significant heterogeneity of cardiomyocytes, fibroblasts, and endothelial cells in postnatal developing hearts. When applied to a mouse model of pediatric mitochondrial cardiomyopathy, we uncovered profound cell type-specific modifications of the cardiac transcriptional landscape at single-nucleus resolution, including changes of subtype composition, maturation states, and functional remodeling of each cell type. Furthermore, we employed snRNA-seq to decipher the cardiac cell type-specific gene regulatory network (GRN) of GDF15, a heart-derived hormone and clinically important diagnostic biomarker of heart disease. Together, our results present a rich resource for studying cardiac biology and provide new insights into heart disease using an approach broadly applicable to many fields of biomedicine. We have since used single-cell genomics technology to study renal physiology and disease as well. I served as the PI or co-investigator in these studies.

   a. Hu P, Liu J, Zhao J, Wilkins BJ, Lupino K, Wu H, **Pei L** (2018). Single-nucleus transcriptomic survey of cell diversity and functional remodeling in the postnatal developing hearts. Genes & Development 32, 1344-1357. PMID: 30254108. PMCID: PMC6169839.
   b. Chung KW, Dhillon P, Huang S, Sheng X, Shrestha R, Qiu C, Kaufman BA, Park J, **Pei L**, Baur J, Palmer M, Susztak K (2019). Mitochondrial Damage and Activation of the STING Pathway Lead to Renal Inflammation and Fibrosis. Cell Metabolism 30, 784-799. PMID: 31474566. PMCID: PMC7054893.
   c. Dhillon P, Park J, Hurtado Del Pozo C, Li L, Doke T, Huang S, Zhao J, Kang HM, Shrestra R, Balzer MS, Chatterjee S, Prado P, Han SY, Liu H, Sheng X, Dierickx P, Batmanov K, Romero JP, Prosper F, Li M, **Pei L**, Kim J, Montserrat N, Susztak K. (2021). The Nuclear Receptor ESRRA Protects from Kidney Disease by Coupling Metabolism and Differentiation. Cell Metabolism 33, 379-394. PMID: 33301705. PMCID: PMC9259369.
   d. Hu P, Rychik J, Zhao J, Bai H, Bauer A, Yu W, Rand EB, Dodds KM, Goldberg DJ, Tan K, Wilkins BJ, **Pei L**. Single-cell multiomics guided mechanistic understanding of Fontan-associated liver disease. *Sci Transl Med* **16**, eadk6213 (2024). PMID: 38657025.

3. **Work in my lab has identified the ERR subfamily of nuclear receptors as essential transcriptional regulators of cellular metabolism and functions in multiple organs.** I pioneered the studies leading to the finding that ERRγ is a key regulator of neuronal metabolism and the ERRγ pathway is essential for hippocampal neuron function and learning and memory. This is the first study, to our knowledge, that links transcriptional control of neuronal metabolism to specific animal behavior, i.e., hippocampus-dependent spatial learning and memory. This work was published and featured as the cover of the 2015 April issue of *Cell Metabolism*. In addition, my lab generated mice lacking both ERRα and ERRγ in the heart. These mice exhibited typical features of human cardiomyopathy and heart failure, including severe mitochondrial dysfunction, defective myocardial metabolism, contraction and conduction, and these mice died within the first month of life. This work establishes unambiguously the essential role of ERRα and ERRγ in cardiac metabolism and functions. Most recently we discovered that ERRγ is also essential for maintaining normal kidney function and preventing kidney disease. ERRγ directly regulates mitochondrial metabolism but cooperatively controls renal reabsorption via convergent binding with HNF1β. Deletion of ERRγ in renal epithelial cells (RECs), in which it is highly and specifically expressed, results in severe renal energetic and reabsorptive dysfunction and progressive renal failure that recapitulates phenotypes of animals and patients with HNF1β loss-of-function gene mutations. Moreover, ERRγ expression positively correlates with renal function and is decreased in patients with chronic kidney disease. Together these studies demonstrate that ERRγ is a crucial transcriptional coordinator and mitochondrial and cell type-specific functions. I served as the PI or co-investigator in these studies.

a. Zhao J, Lupino K, Wilkins BJ, Qiu C, Liu J, Omura Y, Allred AL, McDonald C, Susztak K, Barish GD, **Pei L**. (2018) Genomic integration of ERRγ-HNF1β regulates renal bioenergetics and prevents chronic kidney disease. Proceedings of National Academy of Sciences, E4910-E4919. PMID: 29735694. PMCID: PMC6003475.
b. **Pei L***, Mu Y, Leblanc M, Alaynick W, Barish GD, Pankratz M, Tseng TW, Kaufman S, Liddle C, Yu RT, Downes M, Pfaff SL, Auwerx J, Gage FH, Evans RM* (2015). Dependence of hippocampal function on ERRγ regulated mitochondrial metabolism. Cell Metabolism *21*, 628-636 (* co-corresponding author, featured in cover). PMID: 25863252. PMCID: PMC4393848.
c. Wang T, McDonald C, Petrenko NB, Leblanc M, Giguere V, Evans RM, Patel VV, **Pei L** (2015). ERRalpha and ERRgamma are essential coordinators of cardiac metabolism and function. Molecular and Cellular Biology *35*, 1281-1298. PMID: 25624346. PMCID: PMC4355525.
d. Berry R, Harewood L, **Pei L**, Fisher M, Brownstein D, Ross A, Alaynick WA, Moss J, Hastie ND, Hohenstein P, Davies JA, Evans RM, FitzPatrick DR (2011). Esrrg functions in early branch generation of the ureteric bud and is essential for normal development of the renal papilla. Human Molecular Genetics *20*, 917-926. PMID: 21138943. PMCID: PMC3033182.

4. **I have made significant contribution to understanding the NR4A subfamily of nuclear receptors as important transcriptional modulators of macrophage inflammatory response in atherosclerosis, as well as critical transcriptional regulators of hepatic gluconeogenesis that contributes to diabetes.** The presence and function of NR4A nuclear receptors in these areas was completely unknown prior to these studies. I served as the primary investigator or co-investigator in these studies.

a. **Pei L**, Waki H, Vaitheesvaran B, Wilpitz DC, Kurland IJ, Tontonoz P (2006). NR4A orphan nuclear receptors are transcriptional regulators of hepatic glucose metabolism. Nature Medicine *12*, 1048-1055. PMID: 16906154.
b. **Pei L**, Castrillo A, Chen M, Hoffmann A, Tontonoz P (2005). Induction of NR4A orphan nuclear receptor expression in macrophages in response to inflammatory stimuli. Journal of Biological Chemistry *280*, 29256-29262. PMID: 15964844.
c. **Pei L**, Castrillo A, Tontonoz P (2006). Regulation of macrophage inflammatory gene expression by the orphan nuclear receptor Nur77. Molecular Endocrinology *20*, 786-794. PMID: 16339277.
d. Chao LC, Wroblewski K, Zhang Z, **Pei L**, Vergnes L, Ilkayeva OR, Ding SY, Reue K, Watt MJ, Newgard CB, Pilch PF, Hevener AL, Tontonoz P (2009). Insulin resistance and altered systemic glucose metabolism in mice lacking Nur77. Diabetes *58*, 2788-2796. PMID: 19741162. PMCID: PMC2780886.

5. **I have made significant contributions to studies of LXR nuclear receptors in macrophage innate immune response, as well as discoveries that transcriptional corepressor SMRT is a critical regulator of thyroid hormone action *in vivo* and is critical for mammalian lung development and adipocyte functions.** I served as the primary investigator or co-investigator in these studies.

a. Joseph SB, McKilligin E, **Pei L**, Watson MA, Collins AR, Laffitte BA, Chen M, Noh G, Goodman J, Hagger GN, Tran J, Tippin TK, Wang X, Lusis AJ, Hsueh WA, Law RE, Collins JL, Willson TM, Tontonoz P (2002). Synthetic LXR ligand inhibits the development of atherosclerosis in mice. Proceedings of National Academy of Sciences *99*, 7604-7609. PMID: 12032330. PMCID: PMC124297.
b. Joseph SB, Bradley MN, Castrillo A, Bruhn KW, Mak PA, **Pei L**, Hogenesch J, O'Connell RM, Cheng G, Saez E, Miller JF, Tontonoz P (2004). LXR-dependent gene expression is important for macrophage survival and the innate immune response. Cell *119*, 299-309. PMID: 15479645.
c. Nofsinger RR, Li P, Hong SH, Jonker JW, Barish GD, Ying H, Cheng SY, Leblanc M, Xu W, **Pei L**, Kang YJ, Nelson M, Downes M, Yu RT, Olefsky JM, Lee CH, Evans RM (2008). SMRT repression of nuclear receptors controls the adipogenic set point and metabolic homeostasis. Proceedings of National Academy of Sciences *105*, 20021-20026. PMID: 19066220. PMCID: PMC2598729.
d. **Pei L**, Leblanc M, Barish G, Atkins A, Nofsinger R, Whyte J, Gold D, He M, Kawamura K, Li H, Downes M, Yu RT, Powell HC, Lingrel JB, Evans RM (2011). Thyroid hormone receptor repression is linked to type I pneumocyte associated respiratory distress syndrome. Nature Medicine *17,* 1466-1472. PMID: 22001906. PMCID: PMC3210920.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/liming.pei.1/bibliography/public