BIOGRAPHICAL SKETCH

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NAME: Yibing Qyang, PhD

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

POSITION TITLE: Associate Professor of Medicine (Cardiology) and of Pathology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Nanjing University, Nanjing, China	B.S.	1988-1992	Biochemistry
Institute of Microbiology, CAS, Beijing, China	M.S.	1992-1995	Microbiology
University of Texas M.D. Anderson Cancer Center, Houston, TX	M.S.	1995-1999	Molecular Genetics
University of Texas M.D. Anderson Cancer Center, Houston, TX	Ph.D.	1999-2002	Molecular Genetics

A. Personal Statement

The Qyang laboratory is interested in employing induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), and tissue engineering to develop novel experimental models of human genetic diseases for the purpose of elucidating causative mechanisms and identifying potential therapeutic interventions to treat these diseases. As a postdoctoral fellow at The Harvard Stem Cell Institute, I isolated and characterized ISL1 cardiovascular progenitor cells (ISL1-CPCs) from primary heart tissues and embryonic stem cells. Furthermore, I discovered that the Wnt/β-catenin pathway promotes the self-renewal of these progenitor cells while inhibiting their cardiac differentiation. This research was published in a Cell Press Journal *Cell Stem Cell 2007*.

At Yale cardiology and Yale Stem Cell Center as an independent PI, I leverage my expertise in stem cell and developmental biology to derive and characterize vascular smooth muscle cells, endothelial cells, and cardiomyocytes from human ESCs and iPSCs in order to identify novel therapeutic strategies to treat cardiovascular diseases. Towards iPSC-based vascular disease modeling and tissue engineering, we have published several high-impact manuscripts including *Circulation 2012*, *Stem Cell Reports 2016*, *Biomaterials 2016*, *Biomaterials 2017*, *Cell Stem Cell 2020*, and *Circulation Research* 2022. Regarding cardiac biology and cardiac tissue engineering, we were the first group to report the use of small molecule Wnt inhibitors IWP1 or IWP4 for robust cardiac differentiation of human ESCs and iPSCs. Our exciting work led to impactful publications in *J Mol Cell Cardiol 2011*, *PLoS One 2014*, *JCI Insight 2016*, *JCI Insight 2019*, *Acta Biomater. 2020*, and *Circulation* 2022.

Besides making progress in scientific research, I have successfully administered the projects (e.g. mentoring 19 postdoctoral scientists, of whom 5 have become faculties and 5 industrial leaders, 8 graduate students, 2 medical students, 5 visiting scholars, and 5 undergraduate students). Using a multidisciplinary approach to the study of stem cell biology, tissue engineering, cardiovascular development, cardiac physiology, and small molecule screening, we hope to contribute to the understanding of cardiovascular disease mechanisms as well as the development of novel therapeutic interventions for these diseases.

Below are selected research articles from our laboratory I would like to highlight:

1. X. Ge, Y. Ren, Z. Yue, K. Kim, M. Lee, W. Li, P. Amos, E. Bozkulak, W. Zheng, H. Zhao, K. Martin, D. Kotton, G. Tellides, I. Park, L. Yue, **Y. Qyang** (2012). Modeling Supravalvular Aortic Stenosis Syndrome Using Human Induced Pluripotent Stem Cells. ***Circulation*** 126 (14):1695-1704. PMC3586776
2. Jiesi Luo, Lingfeng Qin, Liping Zhao, Liqiong Gui, Matthew W. Ellis, Yan Huang, Mehmet H Kural, J. Alexander Clark, Shun Ono, Juan Wang, Yifan Yuan, Shang-Min Zhang, Xiaoqiang Cong, Guangxin Li, Muhammad Riaz, Colleen Lopez, Akitsu Hotta, Stuart Campbell, George Tellides, Alan Dardik, Laura E Niklason, **Yibing Qyang** (2020). Tissue-Engineered Vascular Grafts with Advanced Mechanical

Strength from Human iPSCs. ***Cell Stem Cell*** 26:251-261. PMID:31956039. PMC7021512

3. Jiesi Luo, Lingfeng Qin, Jinkyu Park, Mehmet H Kural, Yan Huang, Xiangyu Shi, Muhammad Riaz, Juan Wang, Matthew W. Ellis, Christopher W. Anderson, Yifan Yuan, Yongming Ren, Mervin C Yoder, George Tellides, Laura E Niklason, **Yibing Qyang** (2022). Readily Available Tissue-Engineered Vascular Grafts Derived from Human iPSCs. ***Circulation Research*** 130:925-927. PMC9113663
4. Muhammad Riaz, Jinkyu Park, Lorenzo R. Sewanan, Yongming Ren, Jonas Schwan, Subhash K. Das, Pawel T. Pomianowski, Yan Huang, Matthew W. Ellis, Jiesi Luo, Juli Liu, Loujin Song, I-Ping Chen, Caihong Qiu, Masayuki Yazawa, George Tellides, John Hwa, Lawrence H. Young, Lei Yang, Charles C. Marboe, Daniel L. Jacoby, Stuart G. Campbell, and **Yibing Qyang** (2022). Muscle LIM Protein Force-Sensing Mediates Sarcomeric Biomechanical Signaling in Human Familial Hypertrophic Cardiomyopathy. ***Circulation*** 145(16):1238-1253. PMC9109819

Selected, ongoing funded projects I would like to highlight:

1R01HL164783: Qyang (PI) - 07/01/2022 – 06/30/2026
NIH/NHLBI
Modulation of heart function by Muscle LIM protein-mediated mechanotransduction
The goal of this research proposal is to elucidate the molecular mechanisms that mediate the repression of calcineurin/NFAT by MLP as well as MLP protein degradation by stretch-sensing in familial hypertrophic cardiomyopathy caused by sarcomeric mutations.

1R01HL155411: Qyang (PI) - 07/01/2021 – 06/30/2025
NIH/NHLBI
Development of HLA engineered universal vascular grafts from human iPSCs
This proposal is aimed at investigating the interactions between a hypoimmunogenic, universal endothelium derived from human pluripotent stem cells and a mechanically robust, cell-produced extracellular matrix scaffold in order to produce endothelialized, small diameter (2-4 mm) tissue-engineered vascular grafts.

1R01HL150352: Qyang (PI) - 07/01/2020 – 06/30/2024
NIH/NHLBI
Readily Available Stem Cell-Based Vascular Grafts for Emergent Surgical Care
The goal of this project is to develop readily available tissue-engineered vascular grafts using vascular cells derived from wild type pluripotent stem cells for testing in immune deficient rats and immune-suppressed pigs, setting the stage for treating patients with urgent need for endothelialized small caliber vascular grafts.

W81XWH1910557: Qyang (PI) - 08/15/2019 – 08/14/2023
Department of Defense
Human Tissue Engineered Pulsatile Conduits for Treatment of Single Ventricle Congenital Heart Defect
This proposal is aimed at producing a tissue engineered pulsatile conduit (TEPC) for the Fontan procedure, which is used as a clinical intervention for children born with single ventricle congenital heart defect (SVCHD).

B. Positions, Scientific Appointments, and Honors

Positions and Employment

9/16-present	Associate Professor of Pathology, Yale University School of Medicine, New Haven, CT
7/16-present	Associate Professor of Medicine, Section of Cardiovascular Medicine, Dept. of Internal Medicine, Yale University School of Medicine, New Haven, CT
9/15-present	Co-Director of Yale Myocardial Biology Seminar Series
7/10-6/16	Assistant Professor of Medicine, Section of Cardiovascular Medicine, Dept. of Internal Medicine, Yale University School of Medicine, New Haven, CT
3/10-present	Director of Yale Stem Cell Research Forum, Yale Stem Cell Center
10/08-6/10	Instructor, Section of Cardiovascular Medicine, Dept. of Internal Medicine, Yale Stem Cell Center, Yale University School of Medicine, New Haven, CT
8/05-9/08	Research Fellow, Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, Harvard Stem Cell Institute, Boston, MA, with Dr. Kenneth R. Chien.
8/03-8/05	Postdoctoral, Institute of Molecular Medicine, University of California, San Diego, with Dr. Kenneth R. Chien.
8/02-8/03	Postdoctoral, Huffington Center on Aging, Baylor College of Medicine, Houston.

Other Experience, Appointments, and Professional Membership

2022 Reviewer for NIH Integrative Myocardial Physiology/Pathophysiology B (MPPB) Study Section
2021 Reviewer for NHLBI Program Project Grant (P01)
2020-present Section/Associate Editor, JACC*:* Basic to Translational Science
2020 Reviewer for NHLBI Program Project Grant (P01)
2020 Reviewer for NIH Director's Transformative Research Award Program
2019-present Editorial Board Member, Circulation Research
2019 Reviewer for British Medical Research Council, England.
2019 Reviewer for NIH Regenerative Medicine Innovation Project (RMIP)
2019 Reviewer for NHLBI Special Emphasis Panel ZHL1-CCT-R (C1)
2018 Reviewer for NHLBI lncRNA Special Emphasis Panel
2018 Reviewer for NHLBI Program Project Grant (P01)
2017 Reviewer for NHLBI Program Project Grant (P01)
2017 Reviewer for British Heart Foundation
2016 Reviewer for NHLBI Program Project Grant (P01)
2016 Reviewer for NIH Cardiac Contractility, Hypertrophy and Failure (CCHF) Study Section
2015 Reviewer for NHLBI Cardiovascular Development Consortium
2014 Reviewer for NHLBI Program Project Grant (P01)
2013 Reviewer for NHLBI Progenitor Cell Biology Consortium
2012 Reviewer for NIH Vascular Cell and Molecular Biology (VCMB) Study Section
2012 Reviewer for British Medical Research Council, England
2011 Reviewer for British Medical Research Council, England.
2011 Reviewer for American Heart Association CVD2 Study Section
2011-present Editorial Board Member, Journal of Clinical and Experimental Cardiology
2011-present American Heart Association Member
2009-present *Journal reviewer*: Circulation, Circulation Research, Journal of Clinical Investigation, Cell Reports, Advanced Drug Delivery, Biomaterials, Stem Cell Reports, Stem Cells, Cellular and Molecular Life Sciences, Circulation Heart Failure, Journal of Molecular and Cellular Cardiology, Plos One, Annals of Biomedical Engineering, Journal of Nuclear Medicine, Acta Biomaterialia, Differentiation, American Journal of Cardiology, Frontiers in Bioscience, Journal of Bioengineering and Biomedical Science.
2008-present Invited talks at national and international meetings including ISSCR, Keystone, Gordon, AHA, NAVBO, Cold Spring Harbor Stem Cell Biology, NHLBI Pulmonary RV research program, International Scientific & Professional Conference on William Syndrome
2008-present Invited talks at universities including Harvard U, Stanford U, Columbia U, Cornell U, Michigan U, Emory U, Mount Sinai, Albert Einstein, Temple U, New York Medical College, UT MD Anderson, Chinese Academy of Medical Sciences
2007-present The International Society for Stem Cell Research Member (ISSCR) Member

Honors and Awards

2020 Yale News in honor of Qyang laboratory cutting-edge stem cell vascular graft advancement https://news.yale.edu/2020/01/16/latest-tech-clinical-grafts-universal-blood-vessel
2016 WTNH TV interview in honor of Qyang laboratory stem cell research
2010-15 NIH Independent Scientist Award
2010-12 Scholar award from Yale Center for Clinical Investigation, Yale University.
2009-14 American Heart Association Scientist Development Award
2007 Best Abstract Award in the 2007 Retreat of Harvard Stem Cell Institute, Harvard Medical School (*1 of the 4 winners amongst over 100 competitors*).
2005-08 Ruth L. Kirschstein National Research Service Award (NRSA), Massachusetts General Hospital, Harvard Medical School.
2002 Presidents' Research Scholarship Awarded by the Presidents of UT M.D. Anderson Cancer Center and UT Health Science Center (*Only 4 awards given over 100 graduate students*).
2002 Alfred G. Knudson Best Dissertation Award by UT M.D. Anderson Cancer Center (*Only 2 awards given over 50 graduate students).*

C. Contribution to Science

1. **Novel role of the ubiquitous transcription factor USF in cellular proliferation and new findings of the p21-activated kinase, Shk1, in modulating microtubule dynamics.** My early publications as a graduate

student at The University of Texas M.D. Anderson Cancer Center were focused on studying the novel mechanism of the cell-type-dependent activity of the ubiquitous transcription factor USF in cellular proliferation and transcriptional activation. Through studying its protein expression, subcellular localization and DNA-binding activity, and performing mutational analysis and transcriptional domain swapping experiments, a highly conserved USF-specific region (USR) was proven to be responsible for the inactivity of USF in the osteosarcoma cell line (Saos-2). Furthermore, I investigated the cellular and molecular functions of the p21-activated kinase, Shk1, in the fission yeast. By showing malformed microtubules in *shk1* mutant cells, tight correlation between Shk1 kinase activity and microtubule polymerization and colocalization of Shk1 with microtubules, I established a novel role of this kinase as a microtubule regulator. The above research has contributed significantly to our understanding of transcriptional regulation of cellular proliferation and microtubule dynamics during cell cycle.

a. **Qyang, Y.,** X. Luo, T. Lu, P.M. Ismail, D. Krylov, C. Vinson, M. Sawadogo. (1999). Cell-type-dependent activity of the ubiquitous transcription factor USF in cellular proliferation and transcriptional activation. ***Mol. Cell. Biol.*** 19, 1508-17. PMCID:PMC116079
b. *Kim, H., *Yang, P., ***Qyang, Y.**, H. Lai, H. Du, J.S. Henkel, K. Kumar, S. Bao, S. Marcus. Genetic and molecular characterization of Skb15, a highly conserved inhibitor of the Fission Yeast PAK, Shk1. (2001). ***Mol. Cell* 7**, 1095-1101. (*contributed equally.) PMID:11389855.
c. *Bao, S., ***Qyang, Y**., *Yang, P., H. Kim, H. Du, G. Bartholomeusz, R. Pimental, F. Verde, S. Marcus**.** (2001). The highly conserved protein methyltransferase, Skb1, is a mediator of hyperosmotic stress response in the fission yeast, *Schizosacchromyces pombe.* ***J. Biol. Chem.*** 276, 14549-14552. (*contributed equally.) PMID:11278267.
d. **Qyang, Y.,** P. Yang, H. Kim, H. Du, H. Lai, S. Marcus. (2002). The p21-Activated Kinase, Shk1, is required for proper regulation of microtubule dynamics in the fission yeast, *Schizosaccharomyces pombe*. ***Mol. Microbiol.*** 44, 325-334. PMID:11972773.

2. **First demonstration that Wnt/β-catenin signaling pathway plays a key role during pre-specification, self-renewal and cardiac differentiation of *Isl1*$^{+}$ cardiovascular progenitor cells (ISL1-CPCs), as well as showing for the first time robust myocardial regeneration potential of human ISL1-CPCs using a rapid 3D methylcellulose approach.** I performed my postdoctoral research in Dr. Kenneth Chien's laboratory at The Harvard Stem Cell Institute and Harvard Medical School. I isolated a novel population of cardiovascular progenitor cells (CPC) marked by ISL1—a LIM-Homeo domain transcription factor, from rodent and human tissues as well as from murine ES cells. Using a high-throughput small molecule screen, coupled with murine embryonic heart developmental and ES cell-based assays, I discovered that the Wnt/β-catenin pathway promotes the renewal of these CPC, while negating the pre-specification of mesodermal precursors into CPC and differentiation of these CPC into cardiomyocytes. In my independent group at Yale University, we discovered a cardiomyogenic role for Bmp4 directly on a pure population of Isl1-CPCs, which could lead to enhancement of cardiac differentiation and engraftment, holding a therapeutic value for cardiac repair. Moreover, we have established highly efficient approaches to derive ISL1-CPCs from human pluripotent stem cells and to enhance the cellular engraftment after implantation into injured hearts, and uncovered novel function of ISL1-CPCs during cardiac repair and regeneration.

a. Moretti, A., Caron, L., Nakano, A., Lam, J.T., Bernshausen, A., Chen, Y., **Qyang, Y.,** Bu, L., Sasaki, M., Martin-Puig, S., Sun, Y., Evans, S.M., Laugwitz, K.L., Chien, K.R. (2006) Multipotent embryonic isl1+ progenitor cells lead to cardiac, smooth muscle, and endothelial cell diversification. ***Cell*** 127, 1151-1165. PMID:17123592.
b. **Yibing Qyang**, Silvia Martin-Puig, Murali Chiravuri, Susanna Chen, Huansheng Xu, Lei Bu, Xin Jiang, Lizhu Lin, Anne Granger, Alessandra Moretti, Leslie Caron, Xu Wu, Jonathan Clarke, Makoto M. Taketo, Karl-Ludwig Laugwitz, Randall T. Moon, Peter Gruber, Sylvia M. Evans, Sheng Ding, Kenneth R. Chien (2007). The Renewal and Differentiation of *Isl1*$^{+}$ Cardiovascular Progenitors Are Controlled by a Wnt/β-Catenin Pathway. ***Cell Stem Cell*** 1, 165-179. PMID: 18371348.
c. Esra Cagavi, Oscar Bartulos, Carol Y. Suh, Baonan Sun, Zhichao Yue, Zhengxin Jiang, Lixia Yue, **Yibing Qyang** (2014). Functional cardiomyocytes derived from Isl1 cardiac progenitors via Bmp4 stimulation. ***PLOS ONE*** 9(12):e110752. PMID:25522363. PMCID: PMC4270687
d. Oscar Bartulos, PhD, Zhen Wu Zhuang, MD, Yan Huang, PhD, Nicole Mikush, BS, Carol Suh, MS, Alda Bregasi, MD, Lin Wang, MS, William Chang, MD, PhD, Diane S. Krause, MD, PhD, Lawrence H. Young, MD Jordan S. Pober, MD, PhD, **Yibing Qyang**, PhD (2016). ISL1 Cardiovascular Progenitor Cells for Cardiac Repair after Myocardial Infarction. ***JCI Insight*** 2016;1:e80920. PMCID: PMC4982472

3. **First report of investigating Supravalvular aortic stenosis (SVAS) using patient-specific induced pluripotent stem cells (iPSCs) and first development of functional 3D tissue rings and tissue-engineered blood vessels using human iPSC-derived vascular smooth muscle cells (VSMCs).** Having patient-specific VSMCs available may facilitate the study of disease mechanisms and development of novel therapeutic interventions. We were the first to describe the development of a hiPSC line from a patient with SVAS. SVAS iPSC-VSMCs recapitulate key pathological features of patients with SVAS and may provide a promising strategy to study disease mechanisms and to develop novel therapies. Furthermore, the availability of unlimited supply of ESC- or iPSC-derived VSMCs has allowed us for the first time to generate 3D tissue rings for disease mechanism studies in a physiologically more relevant model, as well as to develop tissue-engineered blood vessels for vascular disease treatment.
    a. X. Ge, Y. Ren, Z. Yue, K. Kim, M. Lee, W. Li, P. Amos, E. Bozkulak, W. Zheng, H. Zhao, K. Martin, D. Kotton, G. Tellides, I. Park, L. Yue, **Y. Qyang** (2012). Modeling Supravalvular Aortic Stenosis Syndrome Using Human Induced Pluripotent Stem Cells. ***Circulation*** 126 (14):1695-1704. PMC3586776
    b. Liqiong Gui, Biraja C. Dash, Jiesi Luo, Lingfeng Qin, Liping Zhao, Kota Yamamoto, Takuya Hashimoto, Hongwei Wu, Alan Dardik, George Tellides, Laura E. Niklason, **Yibing Qyang** (2016). Implantable Tissue-Engineered Blood Vessels from Human Induced Pluripotent Stem Cells. ***Biomaterials*** 102:120-129 (Available online 14 June 2016). PMCID: PMC4939127
    c. Jiesi Luo, Lingfeng Qin, Liping Zhao, Liqiong Gui, Matthew W. Ellis, Yan Huang, Mehmet H Kural, J. Alexander Clark, Shun Ono, Juan Wang, Yifan Yuan, Shang-Min Zhang, Xiaoqiang Cong, Guangxin Li, Muhammad Riaz, Colleen Lopez, Akitsu Hotta, Stuart Campbell, George Tellides, Alan Dardik, Laura E Niklason, **Yibing Qyang** (2020). Tissue-Engineered Vascular Grafts with Advanced Mechanical Strength from Human iPSCs. ***Cell Stem Cell*** 26:251-261. PMID:31956039. PMC7021512
    d. Jiesi Luo, Lingfeng Qin, Jinkyu Park, Mehmet H Kural, Yan Huang, Xiangyu Shi, Muhammad Riaz, Juan Wang, Matthew W. Ellis, Christopher W. Anderson, Yifan Yuan, Yongming Ren, Mervin C Yoder, George Tellides, Laura E Niklason, **Yibing Qyang** (2022). Readily Available Tissue-Engineered Vascular Grafts Derived from Human iPSCs. ***Circulation Research*** 130:925-927. PMC9113663
4. **Novel application of small molecule Wnt inhibitor in promoting cardiomyocyte differentiation of ESC and iPSCs, cardiac tissue engineering, and cardiac disease modeling.** Human iPSCs potentially provide a unique resource for generating patient-specific cardiomyocytes to study cardiac disease mechanisms and treatments. We were the first group to report that small molecule Wnt inhibitors IWP1 or IWP4, instead of costly growth factors, lead to highly efficient production of cardiomyocytes from ESCs or iPSCs with typical electrophysiological function and pharmacologic responsiveness, thereby offering highly affordable platforms for studying cardiac disease mechanisms. Human iPSC-derived cardiomyocytes have been successfully used to develop tissue-engineered pulsatile conduits that produce appreciable luminal pressure. We have also employed these human cardiomyocytes for robust cardiac disease modeling.
    a. Ren Y, Lee MY, Schliffke S, Paavola J, Amos PJ, Ge X, Ye M, Zhu S, Senyei G, Lum L, Ehrlich BE, **Qyang Y** (2011). Small molecule Wnt inhibitors enhance the efficiency of BMP-4-directed cardiac differentiation of human pluripotent stem cells. ***J Mol Cell Cardiol*** 51(3): 280-7. PMC3334336
    b. Min Young Lee, Baonan Sun, Simon Schliffke, Zhichao Yue, Mingyu Ye, Jere Paavola, Esra Cagavi Bozkulak, Peter J. Amos, Yongming Ren, Rong Ju, Yong Woo Jung, Xin Ge, Lixia Yue, Barbara E. Ehrlich, **Yibing Qyang** (2012). Derivation of functional ventricular cardiomyocytes using endogenous promoter sequence from murine embryonic stem cells. ***Stem Cell Research*** 8(1):49-57. PMC3222859
    c. Park J, Anderson CW, Sewanan LR, Kural MH, Huang Y, Luo J, Gui L, Riaz M, Lopez CA, Ng R, Das SK, Wang J, Niklason L, Campbell SG, **Qyang Y** (2020). Modular Design of a Tissue Engineered Pulsatile Conduit using Human Induced Pluripotent Stem Cell-derived Cardiomyocytes. ***Acta Biomater.*** 102:220-230. PMID: 31634626. PMC7227659
    d. Muhammad Riaz, Jinkyu Park, Lorenzo R. Sewanan, Yongming Ren, Jonas Schwan, Subhash K. Das, Pawel T. Pomianowski, Yan Huang, Matthew W. Ellis, Jiesi Luo, Juli Liu, Loujin Song, I-Ping Chen, Caihong Qiu, Masayuki Yazawa, George Tellides, John Hwa, Lawrence H. Young, Lei Yang, Charles C. Marboe, Daniel L. Jacoby, Stuart G. Campbell, and **Yibing Qyang** (2022). Muscle LIM Protein Force-Sensing Mediates Sarcomeric Biomechanical Signaling in Human Familial Hypertrophic Cardiomyopathy. ***Circulation*** 145(16):1238-1253. PMC9109819

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