BIOGRAPHICAL SKETCH

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NAME: Ngan Fong Huang, PhD

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POSITION TITLE: Assistant Professor of Cardiothoracic Surgery (Stanford University); and Biomedical Engineer (Veterans Affairs Palo Alto Health Care System)

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
Massachusetts Institute of Technology, Cambridge, MA	BS	06/2002	Chemical Engineering
University of California Berkeley & University of California San Francisco, Berkeley, CA	MS	12/2005	Bioengineering
University of California Berkeley & University of California San Francisco, Berkeley, CA	PhD	12/2006	Bioengineering
Stanford University, Stanford, CA	Postdoctoral	01/2007-07/2010	Cardiovascular Medicine

A. Personal Statement

My laboratory aims to understand the biochemical and mechanical interactions between extracellular matrix (ECM) proteins and stem cells that regulate cardiovascular and skeletal muscle function, and survival, with the goal of translating these basic insights towards treatment of disease. I have the necessary expertise, leadership, motivation, and scientific knowledge to successfully carry out the proposed project. I have extensive training in bioengineering, stem cell biology, and cardiovascular medicine. This multidisciplinary background uniquely positions my research team to develop new technologies to address medical challenges and biological questions. I have academic degrees in both bioengineering and chemical engineering to study the interaction of biomaterials on stem cells. I have developed strong leadership and organizational skills through my active awards from NIH-funded research grant awards (two active R01s), as well as other funding from the Department of Veteran Affairs, California Institute for Regenerative Medicine and National Science Foundation to engage other collaborators in a productive and frequent manner with feasible timelines and milestones. I am highly motivated, as evidenced by publication track record and funded grants. In summary, my expertise and qualifications make me well-suited to serve as the principal investigator in this grant proposal.

a. Huang NF, Patel S, Thakar RG, Wu J, Hsiao BS, Chu B, Lee RJ, Li S. Skeletal Muscle Morphogenesis on Micropatterned and Nanopatterned Biopolymers. **Nano Lett** 6:537-542, 2006
b. Nakayama KH, Hong G, Lee JC, Patel J, Edwards B, Zaitseva TS, Paukshto MV, Dai H, Cooke JP, Woo YJ, Huang NF. Aligned-Braided Nanofibrillar Scaffold with Endothelial Cells Enhances Arteriogenesis. **ACS Nano**, 9*:* 6900–6908, 2015. PMCID: PMC4757475.
c. Zaitseva T, Alcazar C, Zamani M, Hou L, Sawamura S, Yakubov E, Hopkins M, Woo YJ, Paukshto M, Huang NF. Aligned Nanofibrillar Scaffolds for Controlled Delivery of Modified mRNA. **Tissue Eng Part A.** 2018 May 2. doi: 10.1089/ten.TEA.2017.0494 (epub). PMCID: in progress.
d. Nakayama KH, Alcazar C, Yang G, Quarta M, Paine P, Doan L, Davis A, Rando TA, Huang NF. Rehabilitative Exercise and Spatially Patterned Nanofibrillar Scaffolds Enhance Vascularization and

Innervation Following Volumetric Muscle Loss. **npj Regen Med**, 2018. doi: 10.1038/s41536-018-0054-3. PMCID: in progress.

B. Research and/or Professional Experience

Positions and Employment

2002 - 2006	Doctoral candidate, University of California Berkeley & University of California San Francisco, Joint Graduate Program in Bioengineering, Berkeley, CA; Dr. Song Li, PhD (mentor, Associate Professor of Bioengineering, University of California Berkeley);
2007 - 2010	Postdoctoral Research Fellow, Stanford University, Division of Cardiovascular Medicine Dr. John Cooke, MD, PhD (mentor, Professor of Medicine)
2010 - 2012	Instructor, School of Medicine, Division of Cardiovascular Medicine, Stanford University
2012 - Present	Biomedical Engineer, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA
2013 - Present	Assistant Professor, Department of Cardiothoracic Surgery, Stanford University

Honors

2004 - 2006	National Science Foundation Graduate Research Fellowship
2008 - 2009	American Heart Association Postdoctoral Research Fellowship
2009 - 2010	Ruth L. Kirschstein National Research Service Award (NRSA) Postdoctoral Fellowship
2010	NIH/NHLBI K99/R00 Pathway To Independence Career Award
2011	Society for Vascular Medicine Jay D. Coffman Young Investigator Award, 1st Place
2012	American Heart Association Council on Peripheral Vascular Disease, Robert W Hobson II MD Early Career Investigator Award
2014	Stanford CHEM-H (Chemistry, Engineering & Medicine for Human Health) Fellow
2015	McCormick and Gabilan Fellow, Stanford University
2016	Fellow of the American Heart Association (FAHA), Council of Peripheral Vascular Disease
2017	Rising Star Award, Cellular and Molecular Bioengineering Annual Conference
2017	Young Innovator Award, journal of *Cellular and Molecular Bioengineering*
2017	Young Investigator Award, Tissue Engineering and Regenerative Medicine-Americas
2017	American Heart Association Council on Peripheral Vascular Disease, Jay D. Coffman Young Investigator Award, 2nd Place Winner

Grant Reviewer

2014-2016	Review Committee Member, American Heart Association National Innovative Research Grant (Summer)
2017	Review Committee Member, NIH CVRS IRG - Myocardial Ischemia and Metabolism Study Section [MIM]
2017	Austrian Science Fund FWF grant reviewer
2017-Present	Stanford Child Health Research Institute seed grant reviewer
2017-Present	Swiss National Science Foundation grant reviewer

National Service

01/2014-Present	American Heart Association, Council on Peripheral Vascular Disease, Early Career and Fellows in Training Committee member
10/2016-Present	International Committee Member, Biomedical Engineering Society
01/2017-Present	New Organ Alliance Roadmap, Cardiovascular Committee Member
05/2017-Present	Tissue Engineering Special Interest Group, Society for Biomaterials, web representative
06/2017-Present	Diversity Committee, Subcommittee on Education and Community Outreach, American Heart Association, Council on Arteriosclerosis Thrombosis and Vascular Biology
12/2017-Present	Vice Chair, Cardiac & Vascular Regeneration and Remodeling Thematic Working Interest Group, Tissue Engineering and Regenerative Medicine-Americas (TERMIS-Am)
01/2018-Present	Editorial Board (*Communications Biology*; *Sci Rep*; *Frontiers in Cardiovascular Science*)
05/2018-Present	Membership Chair, Int'l Society for Applied Cardiovascular Biology (ISACB)

C. Contribution to Science

1. Muscle Tissue Engineering and Morphogenesis: By employing spatially patterned and/or three-dimensional biomaterials, we have built prototypes of engineered muscle tissue constructs. Some of these constructs employ nanoscale or microscale cues derived from the extracellular matrix to induce spatial patterning, resulting in engineered tissues with physiologically relevant morphology. The engineered muscles include skeletal muscle, vascular smooth muscle, and cardiac muscle. Our published works demonstrate the ability of these tissue constructs to mimic physiological structure and/or function. These tissue constructs are primed for *in vivo* translational applications.

a. Thakar RG, Ho F, Huang NF, Liepmann D, Li S. Regulation of Vascular Smooth Muscle Cells by Micropatterning. **Biochem Biophys Res Com** 307:883-890, 2003
b. Huang NF, Patel S, Thakar RG, Wu J, Hsiao BS, Chu B, Lee RJ, Li S. Skeletal Muscle Morphogenesis on Micropatterned and Nanopatterned Biopolymers. **Nano Lett** 6:537-542, 2006
c. Huang NF, Lee RJ, Li S. Engineering of Aligned Skeletal Muscle by Micropatterning. **Am J Transl Res**, 2:43-55, 2010. PMCID: PMC 2826821
d. Wanjare M, Hou L, Nakayama KH, Kim JJ, Mezak NP, Abilez OJ, Tzatzalos E, Wu JC, Huang NF. Anisotropic microfibrous scaffolds enhance the organization and function of cardiomyocytes derived from induced pluripotent stem cells. **Biomat Sci.** 5: 1567–1578, 2017. PMCID: PMC5348721

2. Determinants of Endothelial Differentiation: My laboratory has a long-standing focus in understanding the role of soluble chemical factors, extracellular matrix (ECM) signaling, and genetic modification in regulating endothelial differentiation from pluripotent stem cells. In particular, we interrogated the signaling pathways known to maintain or modulate endothelial function (ie. nitric oxide, Notch, and vascular endothelial growth factor signaling pathways) to determine their role in inducing the formation of CD31+ endothelial cells derived from pluripotent stem cells. Since CD31+ cells represent a heterogeneous mixture of arterial, venous, and lymphatic subtypes, we further tune these signaling pathways to induce subtype specification into arterial, venous, or lymphatic subtypes. We believe that subtype specification is critical to the function of the pluripotent stem cell-derived endothelial cells, since physiologically each subtype is associated with distinct functional differences. However, current translational research mainly focuses on delivery of the heterogeneous CD31+ cells, and so we believe our work in modulating subtype specification is critical for translational purposes. Given the physiological interactions that occur between cells and their surrounding ECM, we also interrogate the role of ECM ligand combinations that modulate stem cell differentiation, particularly focusing on combinatorial ECM microenvironments. We also apply these concepts towards direct transdifferentiation of somatic cell (ie, fibroblasts) into endothelial cells by employing transient genetic modification in the presence of endothelial inducing chemical factors.

a. Huang NF, Fleissner F, Sun J, Cooke JP. Role of nitric oxide signaling in endothelial differentiation of embryonic stem cells **Stem Cells Dev** 19:1617-1625, 2010. PMCID: PMC3121801.
b. Li J, Huang NF*, Zou J, Laurent TJ, Lee JC, Okogbaa J, Cooke JP, Ding S. Conversion of Human Fibroblasts to Functional Endothelial Cells by Defined Factors. **Arterioscler Thromb Vasc Biol**, 33:1366-75, 2013 (*co-first author) PMCID: PMC3898631.
c. Jalil RA, Huang NF*, Kim J, Herold J, Volz KS, Park TS, Lee JC, Zambidis ET, Reijo-Pera R, Cooke, JP. Human Induced Pluripotent Stem Cell-Derived Endothelial Cells Exhibit Functional Heterogeneity **Am J Transl Res** 5:21-35, 2013 (*co-first author) PMCID: PMC3560482.
d. Hou L, Kim JJ, Wanjare M, Patlolla B, Coller J, Natu V, Hastie TJ, Huang NF. Combinatorial Extracellular Matrix Microenvironments for Probing Endothelial Differentiation of Human Pluripotent Stem Cells. **Sci Rep** 7, 6551, 2017. PMCID: PMC5529516

3. Stem Cell Therapy for Treatment of Ischemic Cardiovascular Disease: Towards identifying stem cell candidate as the cell source for tissue engineering and regenerative medicine applications, we have made substantial process in evaluating the efficacy of adult and pluripotent stem cells for cardiovascular remodeling and for restoring blood perfusion in the ischemic limb. These cells include embryonic stem cells, induced pluripotent stem cells, and bone marrow-derived mesenchymal stem cells. Efficacy of these cells was evaluated for treatment of experimentally induced myocardial infarction or peripheral arterial disease. These studies demonstrate the ability of these cells to incorporate into native tissue structures (ie blood vessels) as well as release angiogenic paracrine factors. These studies show the translational relevance of stem cells for repair of ischemic tissues.

a. Huang NF, Lam A, Fang Qizhi, Sievers RE, Li S, Lee RJ. Bone Marrow-Derived Mesenchymal Stem Cells in Fibrin Augments Angiogenesis in the Chronically Infarcted Myocardium. **Regen Med** 4:527-538, 2009. PMCID: PMC2778008.
b. Huang NF, Niiyama H, Peter C, De A, Natkunam Y, Fleissner F, Li Z, Rollins MD, Wu JC, Gambhir SS, Cooke JP. Embryonic Stem Cell-Derived Endothelial Cells Engraft into the Ischemic Hindlimb and Restore Perfusion. **Arterioscler Thromb Vasc Biol** 30:984-91, 2010. PMCID: PMC2874560.
c. Abdul Jalil R, Huang NF*, Jame S, Lee J, Nguyen HN, Byers B, De A, Okogbaa J, Rollins MD, Reijo-Pera R, Gambhir SS, Cooke JP. Endothelial Cells Derived From Human iPSCs Increase Capillary Density and Improve Perfusion in a Mouse Model of Peripheral Arterial Disease. **Arterioscler Thromb Vasc Biol**, 31:e72-79, 2011 (*co-first author). PMCID: PMC3210551.
d. Nakayama KH, Hong G, Lee JC, Patel J, Edwards B, Zaitseva TS, Paukshto MV, Dai H, Cooke JP, Woo YJ, Huang NF. Aligned-Braided Nanofibrillar Scaffold with Endothelial Cells Enhances Arteriogenesis. **ACS Nano**, *9:* 6900–6908, 2015. PMCID: PMC4757475.

4. Biomaterials that Induce Angiogenesis and/or Cell Function: In recognition that conventional stem cells therapy by injection in saline suffers from poor cell survival and a lack of cell-ECM adhesion, we are developing strategies to co-deliver cells with biomaterials that can enhance cell function and/or promote survival in ischemic tissues *in vivo*. The biomaterials of interest include naturally derived ECMs such as collagen as well as synthetic hydrogels. We have explored the influence of parallel-aligned (anisotropic) nanofibrillar scaffolds for promoting cell survival, and reorganizing cell morphology and motility through nanoscale signaling cues. Most recently we have applied a rational basis to engineer shear-thinning synthetic hydrogels that inhibit injection shear-induced cell death. Our publications highlight the importance of co-delivery of cells within a therapeutic scaffold for enhancing cell function or survival. By applying these biomaterials for treatment preclinical testing in small and large animals, one translational application is the development of acellular scaffolds for inducing lymphatic angiogenesis, which is now in testing in a Phase I clinical trial at Stanford University.

a. Huang NF, Lai E, Fuller GG, Ribeiro AS, Pan S, Pruitt B, Fuller GG, Cooke JP. Spatial patterning of endothelium modulates cell morphology, adhesiveness and transcriptional signature. **Biomaterials** 34: 2928-2937, 2013. PCMID: PMC3581686.
b. Mulyasasmita W, Cai L, Dewi RE, Jha A, Ullmann SD, Luong RH, Huang NF, Heilshorn SC. Avidity-controlled hydrogels for injectable co-delivery of induced pluripotent stem cell-derived endothelial cells and growth factors. **J Control Release** 191:71-81, 2014. PMCID: PMCID: PMC4518026.
c. Nakayama KH, Surya VN, Gole M, Walker TW, Yang W, Lai ES, Ostrowski MA, Fuller GG, Dunn AR, Huang NF. Nanoscale Patterning of Extracellular Matrix Alters Endothelial Function under Shear Stress. **Nano Lett,** 16:410-9, 2016. PMCID: PMC4758680.
d. Hadamitzky C, Zaitseva TS, Bazalova-Carter M, Paukshto MV, Hou L, Strassberg Z, Ferguson J, Matsuura Y, Dash R, Yang PC, Kretchetov S, Vogt PM, Rockson SG, Cooke JP, Huang NF. Aligned nanofibrillar collagen scaffolds - Guiding lymphangiogenesis for treatment of acquired lymphedema. **Biomaterials** 102:259-67, 2016. PMCID: PMC5157930.

5. Imaging and Devices Technology: In order to study the function of cells and/or engineered constructs *in vivo*, we have engineered devices or platforms to overcome existing technological limitations. We are engineering microscale high-throughput arrayed platforms for studying combinatorial extracellular matrix proteins on stem cell fate in a facile manner. To study the role of hemodynamic shear stress gradients on cell behavior, we developed a novel fluid flow device that recapitulates shear stress gradients and disturbed flow. In another example, we have tested the utility of near infrared fluorophores in the second window (~1400nm emission) as angiographic contrast dyes to visualize blood flow, blood perfusion, and microvasculature at high architectural resolution in mice. These technological developments together enable us to study cell biology and pathophysiology of limb ischemia in unprecedented ways.

a. Hong G, Lee JC, Robinson JT, Raaz U, Xie L, Huang NF[#], Cooke JP, Dai H. Multi-Functional In Vivo Vascular Imaging Using Near-Infrared II Fluorescence. **Nat Med**, 18:1841-6, 2012 ([#]co-corresponding author). PMCID: PMC3595196
b. Hou L, Kim JJ, Wanjare M, Patlolla B, Coller J, Natu V, Hastie TJ, Huang NF. Combinatorial Extracellular Matrix Microenvironments for Probing Endothelial Differentiation of Human Pluripotent Stem Cells. **Sci Rep** 7, 6551, 2017. PMCID: PMC5529516

c. Nakayama KH, Surya VN, Gole M, Walker TW, Yang W, Lai ES, Ostrowski MA, Fuller GG, Dunn AR, Huang NF. Nanoscale Patterning of Extracellular Matrix Alters Endothelial Function under Shear Stress. **Nano Lett,** 16:410-9, 2016. PMCID: PMC4758680.
d. Ma Z, Zhang M, Yue J, Alcazar C, Zhong Y, Doyle TC, Dai H, Huang NF. Near-Infrared IIb Fluorescence Imaging of Vascular Regeneration with Dynamic Tissue Perfusion Measurement and High Spatial Resolution. **Adv Funct Mater**, 2018 (in press). https://doi.org/10.1002/adfm.201803417. PMCID: In process.

Online List of Published Work:
https://www.ncbi.nlm.nih.gov/pubmed/?term=huang+nf

D. Research Support

Ongoing Research Support

Merit Review 1I01BX002310 (Huang) 10/1/14 – 9/30/18
Department of Veterans Affairs
Vascularized Cardiac Patch with Physiological Orientation for Myocardial Repair
The aims are to engineer a vascularized and aligned iPSC-derived cardiac patch for treatment of myocardial infarction and to elucidate the basic signaling mechanisms

R01 HL127113-01A1 (Huang) 2/1/16-1/31/21
NIH / NHLBI
Aligned Nanofibrillar Scaffolds Enhance Angiogenesis and Viability in Ischemia
The aims are to evaluate the efficacy of parallel-aligned nanofibrillar scaffolds to enhance iPSC-EC survival and angiogenesis under ischemic conditions in vitro. We will then assess arteriogenesis, blood perfusion recovery, and cell survival upon implantation of the iPSC-EC seeded scaffold into murine ischemic limb.

P2CHD086843, Subaward of Univ. of Pittsburgh (Huang) 7/1/16 – 6/28/19 (NCE)
Alliance for Regenerative Rehabilitation & Research Training
Nano-aligned Scaffold Conjugated with Insulin-Like Growth Factor-1 mRNA for Treatment of Volumetric Muscle Loss
The goal is to assess the regenerative capacity of a nanofibrillar collagen scaffold that delivers insulin-like growth factor-1 mRNA for treatment of volumetric muscle loss in a murine animal model.

DISC1 Research Grant #10603 (Huang) 4/1/2018-3/31/2019
California Institute for Regenerative Medicine
iPSC-Derived Smooth Muscle Progenitors for Treatment of Abdominal Aortic Aneurysm
We propose to deliver human induced pluripotent stem cell-derived smooth muscle progenitors to the site of abdominal aortic aneurysm will replenish smooth muscle cells, enhance elastin production, and abrogate wall dilatation in a murine model.

R01HL142718 (Huang/Heilshorn MPI) 7/1/18-6/30/22
NIH / NHLBI
Engineered Matrix Microarrays to Enhance the Regenerative Potential of iPSC-Derived Endothelial Cells
We propose to develop a combinatorial family of engineered ECMs (eECMs) with independently tunable biochemical and biomechanical cues, including stiffness and stress relaxation rate for high-throughput, matrix array studies of induced pluripotent stem cell-derived endothelial cell (iPSC-EC) survival and angiogenic potential. The optimally designed eECMs will then be coinjected with iPSC-EC for treatment of peripheral arterial disease in a mouse model of hindlimb ischemia.

1829534 (Huang) 10/1/18-9/30/21
National Science Foundation/Center for the Advancement of Science in Space
Tissue Engineered Muscle in Microgravity as a Novel Platform to Study Sarcopenia
The goal of this study is to test the efficacy of engineered skeletal muscle in microgravity to resemble salient characteristics of muscle with sarcopenia, and to apply this platform for testing drugs for treatment of sarcopenia.