BIOGRAPHICAL SKETCH

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NAME: Steven R. Houser

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

POSITION TITLE: 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
Eastern College	BA	1973	Biology, Chemistry
Temple University School of Medicine	Ph.D.	1977	Physiology
Temple University School of Medicine	Post Doc	1979	Cardiovascular
University of California at San Francisco	Visiting Sci	1992	Sabbatical (Simpson)

A. Personal Statement

My laboratory has been active for more than 40 years. I am a cardiac physiologist with technical expertise in cardiac electrophysiology and Ca^{2+} imaging. My contributions to science will be presented in Section C. In this section I will discuss our current work. Much of the current focus is an exploration of causes and potential strategies for improving the structure and function of the failing heart. We have well established small (mouse) and large (pig and feline) models of heart failure with reduced ejection fraction (HFrEF; from ischemic injury) and heart failure with preserved ejection fraction (HFpEF; from slow progressive pressure overload).

Ongoing studies in HFrEF are being performed in mouse and pig myocardial infarction (MI) models. In this form of heart failure, the initiation of the adverse remodeling that leads to heart failure is an ischemic injury that results in the death of portions of the heart. These studies are exploring the idea that the injection of cells and/or their exosomes (that are derived from the bone stroma and then uniquely expanded and modified in-vitro) alter the post MI wound healing process. Some of the funding for these projects is listed below. Some publications resulting from the supported studies are listed below the list of grant applications. The major findings are that injection of these cortical bone stem cells or their exosomes modifies the wound healing process and reduces myocyte death. These cells and their exosomes have been shown to reduce infarct (scar) area and improve cardiac structure and function. The ongoing research is focused on how this therapy modifies post MI wound healing and in particular is defining how the paracrine factors from these cells modulate the immune response.

We also have active projects exploring the fundamental bases for the development of HFpEF. These are largely collaborative studies with the McKinsey laboratory at the University of Colorado (dual PI grant). This form of heart failure has many causative factors but, in general, myocyte death is not the initiating event. Instead, there is a development of LV filling defects that eventually lead to a heart failure phenotype, often with a severe pulmonary phenotype. These studies have already identified novel targets for therapy. The model system we use involves slow progressive pressure overload and the animals develop severe LV hypertrophy with elevations in filling pressures that cause pulmonary disturbances. We have recently shown that inhibition of HDACs can rescue much of the HFpEF phenotype.

A major strength of the laboratory is establishing and characterizing heart failure animal models that reflect the human condition. It is our view that these models will lead to identification of possible causes of human heart failure and allow for preclinical testing of novel heart failure therapies.

Grant support for this work:
R01 HL132391 Houser/Molkentin, Multi-P 07/15/16 -03/31/21
Paracrine hypothesis underlying cardiac stem cell therapy
NIH/NHLBI This project will examine the basic science mechanisms underlying how adult stem cell might function when injected into the human heart, to determine if this is truly protective, and if so, the ways in which such protective effects could be augmented.

P01 HL134608 Kishore (PPG) 09/01/17 – 08/31/22
Houser Project 3: Cortical bone stem cell-derived exosomes augment cardiac repair
NIH/NHLBI: The goal of this project is to investigate whether the beneficial effects of CBSCs on post MI remodeling results from their exosomes.

P01 HL134608 Kishore (PI) 09/01/17 – 08/30/22
Core C- Houser Co-Investigator: Small and large animal surgery, physiology and histology
NIH/NHLBI This core will develop reliable MI animal models, and the Houser group will be responsible for developing the large animal models to be used by all projects

R01 HL139660-01 Houser (PI) 06/01/18 –04/30/22
Cortical Bone Stem Cell Therapy for the Infarcted Heart
NIH/NHLBI: The goal of this research is to determine the best CBSC dose, route and time of delivery to induce more effective cardiac repair and determine if CBSCs improve post MI remodeling by cardioprotective, angiogenic, cardiogenic and/or immune modulatory effects.

R01 HL 147558 Houser/McKinsey (MPI) 04/04/19 –03/31/23
Deacetylase-Dependent Control of Diastolic Dysfunction and HFpEF
NIH/NHLBI The goal of this project will be to investigate the HCAC activity contributes to the pathogenesis of HFpEF by promoting diastolic dysfunction via deacyetylation of proteins that regulate myofibrilar relaxation, cardiac fibrosis and/or sarcoplasmic reticulum calcium uptake.

Manuscripts from this work (selected):
Duran JM, Makarewich CA, Sharp TE, Starosta T, Zhu F, Hoffman NE, Chiba Y, Madesh M, Berretta RM, Kubo H, Houser SR. Bone-derived stem cells repair the heart after myocardial infarction through transdifferentiation and paracrine signaling mechanisms. Circ Res. 2013 Aug 16;113(5):539-52. doi: 10.1161/CIRCRESAHA.113.301202. Epub 2013 Jun 25. PubMed PMID: 23801066; PubMed Central PMCID: PMC3822430.

Wallner M, Duran JM, Mohsin S, Troupes CD, Vanhoutte D, Borghetti G, Vagnozzi RJ, Gross P, Yu D, Trappanese DM, Kubo H, Toib A, Sharp TE, Harper SC, Volkert MA, Starosta T, Feldsott EA, Berretta RM, Wang T, Barbe MF, Molkentin JD, Houser SR. Acute Catecholamine Exposure Causes Reversible Myocyte Injury Without Cardiac Regeneration. Circ Res. 2016 Jul 26. pii: CIRCRESAHA.116.308687. [Epub ahead of print] PubMed PMID: 27461939.

Hobby ARH, Sharp TE 3rd, Berretta RM, Borghetti G, Feldsott E, Mohsin S, Houser SR. Cortical bone-derived stem cell therapy reduces apoptosis after myocardial infarction. Am J Physiol Heart Circ Physiol. 2019 Oct 1;317(4):H820-H829. doi: 10.1152/ajpheart.00144.2019. Epub 2019 Aug 23. PubMed PMID: 31441690; PubMed Central PMCID: PMC6843016.

Wallner M, Eaton DM, Berretta RM, Liesinger L, Schittmayer M, Gindlhuber J, Wu J, Jeong MY, Lin YH, Borghetti G, Baker ST, Zhao H, Pfleger J, Blass S, Rainer PP, von Lewinski D, Bugger H, Mohsin S, Graier WF, Zirlik A, McKinsey TA, Birner-Gruenberger R, Wolfson MR, Houser SR. HDAC inhibition improves cardiopulmonary function in a feline model of diastolic dysfunction. Sci Transl Med. 2020 Jan 8;12(525). pii: eaay7205. doi: 10.1126/scitranslmed.aay7205. PubMed
PMID: 31915304

B. Positions, Scientific Appointments, and Honors

2016-2017	President, American Heart Association
2015-2016	President-Elect, American Heart Association
2013-2015	Chair, Research Committee, American Heart Association
2015 - 2019	Member NHLBI T32 review committee
2012 - 2013	NIH Study Section Members conflict SEPs
2009 - 2013	Chair, NHLBI K08 study section
2006 - present	Chair, Department of Physiology, Temple University School of Medicine
2003 - 2006	Chair, Cardiac Contractility, Hypertrophy and Failure Study section
2003 - present	Director, Cardiovascular Research Center
1998 - 2003	Co-Director, Cardiovascular Research Group, Temple University School of Medicine
1991 -	Professor of Physiology, Temple University School of Medicine, Department of Physiology, Philadelphia, PA
1988 - 92	Member, Cardiovascular (A) Study Section
1985 - 91	Associate Professor of Physiology, Temple University School of Medicine, Department of Physiology, Philadelphia, PA
1979 - 85	Assistant Professor of Physiology, Temple University School of Medicine, Department of Physiology, Philadelphia, PA
1977	Summa Cum Laude, Temple University School of Medicine (Ph.D.)
1973	Magna Cum Laude, Eastern College

Honors

2021	AHA Gold Heart Award
1983	A.N. Richards Research Prize Award Winner

C. Contributions to Science

My group has contributed to many areas of cardiac biology and pathophysiology over the past few decades. 4 areas where we have made impactful observations are discussed below.

1. **Characterization of cardiac Ca^{2+} handling and its role in the normal physiology of the heart**. When I started my laboratory, it was not clear how Ca^{2+} entered cardiac myocytes and how it initiated contraction. My group was among the first to show that Ca^{2+} entry through the L-type calcium channel is the major, and in reality, the exclusive, trigger for induction of calcium release from the sarcoplasmic reticulum. We were at the forefront of the fundamental biology of cardiac myocyte calcium handling and excitation contraction coupling. Initially, there were at least three competing theories of Ca^{2+} induced Ca^{2+} release and my group documented that other modes of EC coupling including voltage dependent Ca^{2+} release and “slip mode conductance” (Ca^{2+} entry through Na channels) were not involved in cardiac EC coupling. These studies established calcium entry through the voltage regulated LTCC as the trigger for cardiac EC coupling.

Piacentino V 3rd, Dipla K, Gaughan JP, Houser SR. Voltage-dependent Ca^{2+} release from the SR of feline ventricular myocytes is explained by Ca^{2+}-induced Ca^{2+} release. J Physiol. 2000 Mar 15;523 Pt 3:533-48. PubMed PMID: 10718736; PubMed Central PMCID: PMC2269826.

Piacentino V 3rd, Gaughan JP, Houser SR. L-type Ca(2+) currents overlapping threshold Na(+) currents: could they be responsible for the "slip-mode" phenomenon in cardiac myocytes? Circ Res. 2002 Mar 8;90(4):435-42. PubMed PMID: 11884373.

Nuss HB, Houser SR. T-type Ca^{2+} current is expressed in hypertrophied adult feline left ventricular myocytes. Circ Res. 1993 Oct;73(4):777-82. PubMed PMID: 8396509.

Bailey BA, Houser SR. Calcium transients in feline left ventricular myocytes with hypertrophy induced by slow progressive pressure overload. J Mol CellCardiol. 1992 Apr;24(4):365-73. PubMed PMID: 1535666.

2. **Ca^{2+} handling in heart failure:** My laboratory was one of the first (maybe the first) to study the idea that Ca^{2+} influx through the L-type calcium channel is abnormal in cardiac disease and is centrally involved in the disrupted Ca^{2+} regulation that causes reduced contractility reserve in heart failure. We also were one of the first groups to show that calcium also enters diseased myocytes through another class of channels (T-type calcium channels). These studies documented the nature of disrupted Ca^{2+} regulation in human heart failure. My conclusion of these studies was that there is substantial demand for enhanced contraction in heart failure and the disrupted Ca^{2+} handling is largely the consequence of the heart failure syndrome rather than its cause.

Dipla K, Mattiello JA, Margulies KB, Jeevanandam V, Houser SR. The sarcoplasmic reticulum and the Na+/Ca2+ exchanger both contribute to the Ca2+ transient of failing human ventricular myocytes. Circ Res. 1999 Mar 5;84(4):435-44. PubMed PMID: 10066678.

Piacentino V 3rd, Weber CR, Chen X, Weisser-Thomas J, Margulies KB, Bers DM, Houser SR. Cellular basis of abnormal calcium transients of failing human ventricular myocytes. Circ Res. 2003 Apr 4;92(6):651-8. Epub 2003 Feb 20. PubMed
PMID: 12600875.

Chen X, Piacentino V 3rd, Furukawa S, Goldman B, Margulies KB, Houser SR. L-type Ca2+ channel density and regulation are altered in failing human ventricular myocytes and recover after support with mechanical assist devices. Circ Res. 2002 Sep 20;91(6):517-24. PubMed PMID: 12242270.

Zhang H, Chen X, Gao E, MacDonnell SM, Wang W, Kolpakov M, Nakayama H, Zhang X, Jaleel N, Harris DM, Li Y, Tang M, Berretta R, Leri A, Kajstura J, Sabri A, Koch WJ, Molkentin JD, Houser SR. Increasing cardiac contractility after myocardial infarction exacerbates cardiac injury and pump dysfunction. Circ Res. 2010 Sep 17;107(6):800-9. doi: 10.1161/CIRCRESAHA.110.219220. Epub 2010 Jul 29. PubMed PMID: 20671241; PubMed Central PMCID: PMC3021375.

3. **Ca^{2+} stress in cardiac disease can cause hypertrophy and cell death**: Our studies on Ca^{2+} regulation in disease led us to studies to test the idea that persistent Ca^{2+} stress, as is seen in human disease, can cause pathological cardiac hypertrophy, myocyte death and lethal cardiac arrhythmias. We are still exploring these topics and are looking for strategies that reduce the Ca^{2+} that promotes hypertrophy and death signaling without reducing myocyte contractility. Most recently we have identified a role for a specific region of juntophilin in the trafficking of LTCC to EC coupling domains.

Smith SC, Zhang X, Zhang X, Gross P, Starosta T, Mohsin S, Franti M, Gupta P, Hayes D, Myzithras M, Kahn J, Tanner J, Weldon SM, Khalil A, Guo X, Sabri A, Chen X, MacDonnell S, Houser SR. GDF11 Does Not Rescue Aging-Related Pathological Hypertrophy. Circ Res. 2015 Nov 6;117(11):926-32. doi: 10.1161/CIRCRESAHA.115.307527. Epub 2015 Sep 17. PubMed PMID: 26383970; PubMed Central PMCID: PMC4636963.

Makarewich CA, Zhang H, Davis J, Correll RN, Trappanese DM, Hoffman NE,
Troupes CD, Berretta RM, Kubo H, Madesh M, Chen X, Gao E, Molkentin JD, Houser SR. Transient receptor potential channels contribute to pathological structural and functional remodeling after myocardial infarction. Circ Res. 2014 Aug 29;115(6):567-80. doi: 10.1161/CIRCRESAHA.115.303831. Epub 2014 Jul 21. PubMed PMID: 25047165; PubMed Central PMCID: PMC4149870.

Wallner M, Eaton DM, Berretta RM, Liesinger L, Schittmayer M, Gindlhuber J, Wu J, Jeong MY, Lin YH, Borghetti G, Baker ST, Zhao H, Pfleger J, Blass S, Rainer PP, von Lewinski D, Bugger H, Mohsin S, Graier WF, Zirlik A, McKinsey TA, Birner-Gruenberger R, Wolfson MR, Houser SR. HDAC inhibition improves cardiopulmonary function in a feline model of diastolic dysfunction. Sci Transl Med. 2020 Jan 8;12(525). pii: eaay7205. doi: 10.1126/scitranslmed.aay7205. PubMed
PMID: 31915304

Interaction of the Joining Region in Junctophilin-2 With the L-Type Ca^{2+} Channel Is Pivotal for Cardiac Dyad Assembly and Intracellular Ca^{2+} Dynamics. Gross P, Johnson J, Romero CM, Eaton DM, Poulet C, Sanchez-Alonso J, Lucarelli C, Ross J, Gibb AA, Garbincius JF, Lambert J, Varol E, Yang Y, Wallner M, Feldsott EA, Kubo H, Berretta RM, Yu D, Rizzo V, Elrod J, Sabri A, Gorelik J, Chen X, Houser SR. Circ Res. 2021 Jan 8;128(1):92-114. doi: 10.1161/CIRCRESAHA.119.315715. Epub 2020 Oct 23.PMID: 33092464

4. **Cardiac repair after injury**: Our studies with Ca^{2+} stress led us to the hypothesis that Heart Failure (HF) induction and progression results from cell death, often after an ischemic insult. Studies related to this topic are a major focus of ongoing studies in the laboratory. There are many aspects of this work and all cannot be reviewed here. The goals and strategies are closely linked to the studies outlined in topic 3 above. We are testing a variety of strategies to explore novel mechanisms of injury-induced dysfunction and to test novel strategies to repair the injured hearts. Gene therapy studies are testing the effects of novel microdomain Ca^{2+} channel antagonists. Cell therapy studies are exploring how a novel cell type, cortical bone stem cells, are able to repair the heart after injury. The major goal of the laboratory during its existence has been to develop new understanding of the heart in health and disease. In particular, we are currently focused on developing novel strategies to more effectively repairing the heart after ischemic insult or chronic pressure overload stress that cause HFrEF and HFpEF.

Harper SC, Brack A, MacDonnell S, Franti M, Olwin BB, Bailey BA, Rudnicki MA, Houser SR. Is Growth Differentiation Factor 11 a Realistic Therapeutic for Aging-Dependent Muscle Defects? Circ Res. 2016 Apr 1;118(7):1143-50; discussion 1150. doi: 10.1161/CIRCRESAHA.116.307962. PubMed PMID: 27034276; PubMed Central PMCID: PMC4829942.

Duran JM, Makarewich CA, Sharp TE, Starosta T, Zhu F, Hoffman NE, Chiba Y, Madesh M, Berretta RM, Kubo H, Houser SR. Bone-derived stem cells repair the heart after myocardial infarction through transdifferentiation and paracrine signaling mechanisms. Circ Res. 2013 Aug 16;113(5):539-52. doi: 10.1161/CIRCRESAHA.113.301202. Epub 2013 Jun 25. PubMed PMID: 23801066; PubMed Central PMCID: PMC3822430.

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Wallner M, Eaton DM, Berretta RM, Liesinger L, Schittmayer M, Gindlhuber J, Wu J, Jeong MY, Lin YH, Borghetti G, Baker ST, Zhao H, Pfleger J, Blass S, Rainer PP, von Lewinski D, Bugger H, Mohsin S, Graier WF, Zirlik A, McKinsey TA, Birner-Gruenberger R, Wolfson MR, Houser SR. HDAC inhibition improves cardiopulmonary function in a feline model of diastolic dysfunction. Sci Transl Med. 2020 Jan 8;12(525). pii: eaay7205. doi: 10.1126/scitranslmed.aay7205. PubMed
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