Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** Temple University of the Commonwealth System of Higher Education

2. **Reporting Period (start and end date of grant award period):** 01/01/2009 – 12/31/2012

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Germaine A Calicat

4. **Grant Contact Person's Telephone Number:** 215.204.7655

5. **Grant SAP Number:** 4100047651

6. **Project Number and Title of Research Project:** 26 - Improving Cell Therapy for the Damaged Heart

7. **Start and End Date of Research Project:** 07/01/2010 – 06/30/2011

8. **Name of Principal Investigator for the Research Project:** Steven R. Houser, Ph.D.

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 30,233

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost
Wang, Fang	Research Assistant	100%	$30,233

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project
Steven Houser	Professor	5%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No_____X____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No_____X____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert “not funded” in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds).

Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes____X_____ No_____

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

In the process of applying for an R01 to continue to expand this work

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____X___ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female		1		
Unknown				
Total		**1**		

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic		1		
Unknown				
Total		**1**		

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian		1		
Other				
Unknown				
Total		**1**		

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No_____x_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____ No____x_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes___x_____ No_____

If yes, please describe the collaborations:

We collaborate with Jeffery Molkentin's group at Cincinnati Children's Hospital to test cardiac function after myocardial infarction.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____x_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____x____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Improving Cell Therapy for the Damaged Heart - Loss of cardiomyocytes associated with either longstanding heart failure or acute myocardial infarction could be therapeutically addressed by a treatment that specifically replaces lost myocytes. Currently, a number of clinical trials to test the efficacy of injecting different types of stem cells into the damaged heart are ongoing. Our research is basic in nature and explores the idea that there are already cells within the heart that have the capacity to repair it if it is damaged. The purpose of our research is to modify adult stem cells so that they will repair the damage of the heart after a myocardial infarction. Our goal in these studies was to identify a stem cell that could be easily isolated, readily expanded in-vitro, and when injected back into the damaged heart had the capacity to regenerate new cardiac myocytes.

Duration of Project

09/01/2010 – 08/31/2011

Project Overview

We will test the idea that cardiac repair will be enhanced if we use cardiogenic stem cells with a greater potential to survive in the hostile environment of the injured heart and a greater ability to make electrical contact with myocytes in this heart. The first step in the research is to generate genetically modified cardiac stem cells. We have already shown that the cardiac stem cells have the potential to differentiate into a cardiac myocyte when cultured on a feeder layer of neonatal ventricular myocytes. We will use this system to test the idea that we have made new stem cells with an enhanced ability to differentiate into cardiac myocytes and survive hostile environments.

Stem cells will be infected with viruses containing normal and modified gap junction proteins. Gap junctions are proteins that electrically connect cells to one another. Our hypothesis is that if we can induce gap junctional contacts between our injected stem cells and the myocytes that survive an ischemic event, we can induce these stem cells to become new cardiac myocytes. We have these reagents in hand. Stem cells will be expanded in vitro, infected with gap junctional viruses and then plated on neonatal myocytes. We will then measure the percent of these cells that differentiate into cardiac myocytes and over what time course. We have 5 different gap junctional modifications to test. We will determine which of these modifications makes the stem cells best suited for cardiac regeneration. Once these studies are completed we will move on to studies in animal models of cardiac injury.

Cardiac stem cells with documented ability to improve cardiac function will be injected into damaged hearts. These cells will be labeled with molecules that allow us to track these cells. We will determine the ability of these cells to improve cardiac pump function. Noninvasive imaging techniques will be used to quantify cardiac function changes 3, 7 and 28 days after cell injection. At sacrifice we will fix hearts and determine the fate of the injected cells.

These studies have the potential to determine if cardiac stem cells with enhanced engraftment capabilities can increase cardiac regeneration and improve cardiac function.

Expected Research Outcomes and Benefits

In this study we expect to develop methods to modify adult cardiac stem cell survival and engraftment. Recent studies have shown that when stem cells are injected into the damaged heart, most if not all of these cells die and there is little improvement in cardiac function. Our research will explore novel methods to improve the survival of stem cells and to enhance their coupling to cardiac myocytes in the parent myocardium. Our basic research has shown that in order for a stem cell to differentiate into a cardiac myocyte it must make physical contact with the myocyte. Unfortunately, in the environment of the damaged heart, myocytes uncouple from their neighbors. Our approach will improve stem cell - myocyte interactions that we believe will increase cardiac regeneration. If we are successful we will rapidly translate these techniques to a small scale clinical trial. Our long term plan is to develop more effective therapies for individuals with poor cardiac function secondary to myocardial infarction. We hope to eventually develop a novel cell therapy product that can be used to treat patients with ischemic cardiomyopathies.

Summary of Research Completed

We have made substantial progress in this research project this year. We have been working in three areas; 1: animal model development and characterization; 2: characterization of modified cardiac precursor (stem) cell lines, and; 3: development of novel reagents to modify stem cell survival and engraftment.

1: Cardiac injury models: We have now fully established small (mouse and rats) and large (pigs) animal models of cardiac ischemic injury that models the clinical scenario of myocardial infarction, and therapy in humans. Small animal models were developed so that we can develop proof of concept for our ideas. As an example, we are testing the idea that modifying the ability of stem cells to make electrical connections to myocytes on the infarct border zone is essential for cardiac regeneration. We have developed mouse genetic strains that have stem cells with modified gap junctions. These cells will be critical in the early testing that we are about to perform. In addition, we can rapidly test the therapeutic efficacy of multiple cell types in mouse models. These approaches are now fairly high throughput and will give us the ability to define those approaches that might translate into novel therapies. We have performed more than 40 studies in MI mice and have defined the fundamental changes in function during 6 weeks following an ischemic event. We have characterized this mouse injury model and have documented the natural course of structural and functional remodeling. These data are essential for comparison as we now begin to test novel therapies. The therapeutic cells that have the most promising effects in mouse MI models will then be tested in a porcine model that we developed this year. Experiments will be performed in adult swine with MI induced by percutaneous balloon catheter placement in the coronary arteries, to induce 60 minutes of ischemia followed by reperfusion. We have shown this year that 80% of the animals survive this procedure, with significant (>25%) decreases in cardiac performance.

We have also developed techniques to electrically map the MI and have shown that we can inject therapeutic agents into specific regions of the MI border zone, the place where we believe cells must engraft to regenerate new cardiac tissue. We are now ready to test novel cells for their ability to improve cardiac function after this injury in this large animal model. If we can show a

benefit of these cells in post MI remodeling with improved cardiac function we will begin the process of developing a clinical trial in patients with ischemic heart disease.

2: We have developed techniques to isolate and expand cardiovascular precursor cells from both the bone marrow and the heart. We digest heart tissue and isolate cKit+ cardiac progenitor cells. These cells are then plated in defined media and expanded over the next month. We have developed techniques to infect these cells with lentivirus' containing molecular that can track cell in-vivo (green fluorescent protein). We have performed a series of preliminary studies to show the feasibility of the proposed studies and are about to perform a detailed investigation of the utility of these cells as mediators of enhanced post MI remodeling.

3: We have developed a number of novel reagents that we believe will enhance the survival and engraftment of cardiac and bone marrow derived stem cells in the ischemic heart. We have mutated connexin 43 so that it is resistant to acidosis and ischemia. The theory is that this will allow stem cells expressing this mutant protein to make electrical contacts with myocytes in the infarct border zone, thereby enhancing their survival and engraftment, leading to new cardiac tissue and improved cardiac function.

Publications completed during period of research project, but which did not cite PA Department of Health as a funding source:

Gao, H., Wang, F., Wang, W. Makarewich, C., Zhang, H. Kubo, H. Berretta, R. Barr, L, Molkentin, J., Houser, SR, Ca2+ influx through l-type Ca2+ channels and transient receptor, Journal of Molecular and Cellular Cardiology 53 (2012) 657-667.

Wang, F. Gao, H. Kubo, H. Fan, X, Zhang, H. Berretta, R. Chen, X. Sharp, T. Starosta, T., Makarewich. Li, Y. Molkentin, J., Houser, SR., T-Type Ca2+ channels regulate the exit of cardiac myocytes from the cell cycle after birth, Journal of Molecular and Cellular Cardiology 62 (2013) 122-130.

Duran, J..Makarewich, C. Sharp, T. Starosta, T. Zhu, F. Hoffman, N. Chiba, Y. Madesh, M. Berretta, R, Kubo, H., Houser, SR., Bone-Derived Stem Cells Repair the Heart after Myocardial Infarction through Transdifferentiation and Paracrine Signaling Mechanisms, Circulation Research (2013) 113: 539-552.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__x___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___x__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__x___ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed

acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1.				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes___X___ No_____

If yes, please describe your plans:

We have performed experiments with stem cells that were modified to express connexin 43 gap junctional proteins. Preliminary studies suggest that these cells enhance cardiac repair after injury. We are in the process of finishing a final series of studies and then we will prepare this work for publication.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The impact of our work is difficult to predict at present. We believe we are on the way to developing a novel cell therapy for ischemic heart disease. We need to complete a series of studies in our mouse model. If we find improvement in cardiac function we will then test these novel cells in a large animal model. If we are successful we will then move toward a phase 1 clinical trial.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable."

Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

Our major findings are that bone and cardiac derived stem cells can be effective in the treatment of post MI remodeling. We are testing the idea that genetically modifying these cells to enhance their engraftment will enhance their ability to repair the damaged heart.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No_____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

BIOGRAPHICAL SKETCH

NAME:
Houser, Steven, R.

eRA COMMONS USER NAME
SRHOUSER

POSITION TITLE
Professor of Physiology and Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Eastern College	BA	1973	Biology,
Temple University School of Medicine	Ph.D.	1977	Chemistry
Temple University School of Medicine	Post Doc	1979	Physiology
University CA at San Fran.	Visiting Sci.	1992	Cardiovascular
			Sabbatical

A. Positions and Honors.

1979 – 85 Assistant Professor of Physiology, Temple University School of Medicine, Department of Physiology, Philadelphia, PA
1985 – 91 Associate Professor of Physiology, Temple University School of Medicine, Department of Physiology, Philadelphia, PA
1991- Professor of Physiology, Temple University School of Medicine, Department of Physiology, Philadelphia, PA
1973 Magna Cum Laude, Eastern College
1977 Summa Cum Laude, Temple University School of Medicine (Ph.D.)
1983 A.N. Richards Research Prize Award Winner
1984 RFA Reviewer (NIH) "Molecular Mechanisms of Cardiac Hypertrophy"
1988-92 Member, Cardiovascular (A) Study Section
1998-2003 Co-Director, Cardiovascular Research Group, Temple University School of Medicine
2002-03 Member, Cardiovascular (A) Study Section
2003-present Director, Cardiovascular Research Center
2003-2006 Chair, Cardiac Contractility, Hypertrophy and Failure Study section
2006 Chair, Department of Physiology, Temple University School of Medicine

B. Selected peer-reviewed publications or manuscripts in press.

Harris DM, Mills GD, Chen X, Kubo H, Berretta RM, Votaw VS, Santana LF, Houser SR Alterations in early action potential repolarization causes localized failure of sarcoplasmic reticulum Ca^{2+} release.Circ Res.
2005 Mar 18;96(5):543-50

Rodrigue-Way A, Burkhoff D, Geesaman BJ, Golden S, Xu J, Pollman MJ, Donoghue M, Jeyaseelan R,Houser S, Breitbart RE, Marks A, Acton S. Sarcomeric genes involved in reverse remodeling of the heart during left ventricular assist device support. J Heart Lung Transplant. 2005 Jan;24(1):73-80.

Harris DM, Mills GD, Chen X, Kubo H, Berretta RM, Votaw VS, Santana LF, Houser SR. Alterations in early action potential repolarization causes localized failure of sarcoplasmic reticulum Ca2+ release.Circ Res. 2005 Mar 18;96(5):543-50.

Houser, SR. Can novel therapies for arrhythmias caused by spontaneous sarcoplasmic reticulum Ca2+ release be developed using mouse models?Circ Res. 2005 May

27;96(10):1031-2.

Weisser-Thomas J, Kubo H, Hefner CA, Gaughan JP, McGowan BS, Ross R, Meyer M, Dillmann W, Houser SR. The Na+/Ca2+ exchanger/SR Ca2+ ATPase transport capacity regulates the contractility of normal and hypertrophied feline ventricular myocytes. J Card Fail. 2005 Jun;11(5):380-7.

MacDonnell SM, Kubo H, Crabbe DL, Renna BF, Reger PO, Mohara J, Smithwick LA, Koch WJ, Houser SR, Libonati JR. Improved myocardial beta-adrenergic responsiveness and signaling with exercise training in hypertension Circulation. 2005 Jun 28;111(25):3420-8.

Libonati JR, Kendrick ZV, Houser SR. Sprint training improves postischemic, left ventricular diastolic performance. J Appl Physiol. 2005 Dec;99(6):2121-7.

Chen X, Zhang X, Kubo H, Harris DM, Mills GD, Moyer J, Berretta R, Potts ST, Marsh JD, Houser SR. Ca2+ influx-induced sarcoplasmic reticulum Ca2+ overload causes mitochondrial-dependent apoptosis in ventricular myocytes Circ Res. 2005 Nov 11;97(10):1009-17.

Reger PO, Barbe MF, Amin M, Renna BF, Hewston LA, MacDonnell SM, Houser SR, Libonati JR. Myocardial hypoperfusion/reperfusion tolerance with exercise training in hypertension. J Appl Physiol. 2006 Feb;100(2):541-7..

Jung AS, Kubo H, Wilson R, Houser SR, Margulies KB. Modulation of contractility by myocyte-derived arginase in normal and hypertrophied feline myocardium. Am J Physiol Heart Circ Physiol. 2006 May;290(5):H1756-62..

Petre RE, Quaile MP, Wendt K, Houser SR, Wald J, Goldman BI, Margulies KB. Regionally heterogeneous tissue mechanics in cardiac amyloidosis. Amyloid. 2005 Dec;12(4):246-50.

Rota M, Boni A, Urbanek K, Padin-Iruegas ME, Kajstura TJ, Fiore G, Kubo H, Sonnenblick EH, Musso E, Houser SR, Leri A, Sussman MA, Anversa P. Nuclear targeting of Akt enhances ventricular function and myocyte contractility. Circ Res. 2005 Dec 9;97(12):1332-41.

Litvin J, Blagg A, Mu A, Matiwala S, Montgomery M, Berretta R, Houser S, Margulies K. Periostin and periostin-like factor in the human heart: possible therapeutic targets. Cardiovasc Pathol. 2006 J:24-32.

Altamirano J, Li Y, Desantiago J, Piacentino 3rd V, Houser SR, Bers DM. The inotropic effect of cardioactive glycosides in ventricular myocytes requires Na+/Ca2+ exchanger function. J Physiol. 2006

Mills GD, Kubo H, Harris DM, Berretta RM, Piacentino V 3rd, Houser SR. Phosphorylation of phospholamban at threonine-17 reduces cardiac adrenergic contractile responsiveness in chronic pressure overload-induced hypertrophy. Am J Physiol Heart Circ Physiol. 2006 Jul;291(1):H61-70..

Mills GD, Kubo H, Harris DM, Berretta RM, Piacentino V 3rd, Houser SR..Intracellular Sodium Determines Frequency-Dependent Alterations in Contractility in Hypertrophied Feline Ventricular Myocytes. In Press.

Jung AS, Kubo H, Wilson R, Houser SR, Margulies KB. Modulation of contractility by myocyte-derived arginase in normal and hypertrophied feline myocardium. Am J Physiol Heart Circ Physiol. 2006 May;290(5):H1756-62.

Renna BF, Kubo H, MacDonnell SM, Crabbe DL, Reger PO, Houser SR, Libonati JR. Enhanced acidotic myocardial Ca2+ responsiveness with training in hypertension. Med Sci Sports Exerc. 2006 May;38(5):847-55.

Reger PO, Barbe MF, Amin M, Renna BF, Hewston LA, MacDonnell SM, Houser SR, Libonati JR. Myocardial hypoperfusion/reperfusion tolerance with exercise training in hypertension. J Appl Physiol. 2006 Feb;100(2):541-7.

Renna BF, MacDonnell SM, Reger PO, Crabbe DL, Houser SR, Libonati R. Relative systolic dysfunction in female spontaneously hypertensive rat myocardium. J Appl Physiol. 2007 Jul;103(1):353-8. Epub 2007 Apr 12. PMID: 17431084 [PubMed - indexed for MEDLINE]

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C. Current Research Support:

Title: "Ca2+ Regulation in Newly Formed Ventricular Myocytes"
Agency: National Heart Lung and Blood Institute, HL033921 **Dates**: 06/01/85 – 06/30/09
Principal Investigator: Steven R. Houser, Ph.D. 2.76 calendar
Objectives: The long standing goals of this research program are to determine the cellular and molecular
bases of the myocytes electromechanical abnormalities induced by pathological hemodynamic stress
(pressure overload) that lead to sudden death and heart failure.

Title: "Calcium as a Molecular Signal in the Heart"
Agency: National Heart Lung and Blood Institute, HL089312 **Dates**: 08/15/07 – 06/30/12
Principal Investigator: Steven R. Houser, Ph.D. 1.92 Calendar
Objectives: The major goals of this study is to determine if enhanced TTCC activity in the heart can increase ventricular myocyte numbers, cell cycle activity, and myocardial recovery after injury and
To determine if reduced TTCC activity reduces ventricular myocyte numbers in the heart, cell cycle activity, and impairs myocardial regeneration after injury.

Title: "Ca^{2+}-influx Regulated Cardiac Hypertrophy, Arrhythmia, and Myocyte Apoptosis"
Agency: National Heart Lung and Blood Institute, HL61495 **Dates**: 07/01/07 – 06/30/12
Principal Investigator: Xiongwen Chen, Ph.D.
Co- Investigator: Steven R. Houser, Ph.D. .96 calendar
Objectives: The major goals of this study are to elucidate the cellular and molecular signaling pathways that link moderate to marked increases in Ca2+ influx through the L-type Ca2+ channel to cardiac myocyte
hypertrophy and arrhythmias.

Title: "Ca2+ Influx Mediated Damage and Regeneration of Adult Myocardium"

Agency: National Heart Lung and Blood Institute, HL090979 **Dates**: 04/01/08 – 03/31/12
Principal Investigator: Walter Koch, Ph.D.
Principal Investigator at Temple: Steven R. Houser, Ph.D. 1.92 calendar
Objectives: The major goal of this study is to identify many novel targets for CHF therapy and would change the thinking from current approaches that seek to increase myocyte force generation to those that seek to reduce myocyte death and promote myocyte regeneration.

Title: Beta Adrenergic Receptors and Focal Adhesion Cross
Agency:DHHS 1 R01 HL088626-01A2 **Dates**: 07/14/08-06/30/12
Co-Investigator : Steven R. Houser, Ph.D. .96 calendar
Objectives: The proposed study will integrate the novel role of focal adhesion signaling in beta-adrenergic receptor-induced myocyte contractile dysfunction and myocyte apoptosis that may lead to heart failure. Understanding how these approaches achieve their effects will provide a greatest impetus for developing ovel therapies for human heart failure.

Title: Inflammatory Proteases, Ubiquitin Proteasome System, and Myocyte Death
Agency: 2R01HL076799-05 **Dates**: 09/15/04-05/30/13
Co-Investigator : Steven R. Houser, Ph.D. .96 calendar
Objectives: The research proposed in this application will delineate the role of ubiquitin ligases in focal adhesion signaling alterations caused by inflammatory proteases and will determine if serine proteases and the ubiquitin ligase Cbl could be novel targets for therapies that diminish myocyte death and dysfunctional remodeling after myocardial IR injury.

Title: Integrative Cardiovascular Pathophysiology
Agency: DHHS 1 T32 HL091804-01A01 **Dates**: 09/01/08-08/31/2009
Co-Investigator : Steven R. Houser, Ph.D. 1.2 calendar
Objectives: The purpose of our program is to provide a broad based multidisciplinary training experience for predoctoral fellows and summer medical students in the area of integrative cardiovascular pathophysiology