## BIOGRAPHICAL SKETCH

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NAME: Romain Harmancey

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

POSITION TITLE: Assistant 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 |
|---|---|---|---|
| Paul Sabatier University, Toulouse, France | B.S. | 06/2002 | Biology |
| Paul Sabatier University, Toulouse, France | Ph.D. | 09/2006 | Pharmacology |
| The University of Texas Medical School at Houston, TX | Post-doctoral | 12/2014 | Cardiac Physiology |

### A. Personal Statement

My research objective is to delineate the mechanisms by which an oversupply of glucose and the ensuing insulin resistance contribute to myocardial adaptation or maladaptation in the setting of obesity and diabetes. Specifically, my research goal is to identify novel molecular pathways involved in the regulation of myocardial metabolism and mitochondrial function. This area of research was initiated during my post-doctoral training in the laboratory of Dr. Heinrich Taegtmeyer at The University of Texas Medical School at Houston. There, under continuous support from the American Heart Association and the NHLBI, I acquired and perfected technical and intellectual skills to assess myocardial metabolism and function in rodent models of metabolic diseases. My current investigations as a junior investigator are in continuity with my initial findings that insulin resistance may contribute to poor prognosis after myocardial infarction by down-regulating mitochondrial uncoupling protein 3 (UCP3). The present grant proposal will build on very strong preliminary results to explore the mechanisms whereby a dietary intervention could be implemented to improve the recovery of type 2 diabetic patients following myocardial ischemia and reperfusion. To achieve these goals, I have assembled a very strong team of collaborators. I have the skills necessary to lead this project and have the support of a wide-range of senior investigators to ensure my success as an early stage investigator.

### B. Positions and Honors

**Positions and Employment**

2007-2014 Postdoctoral Fellow, Taegtmeyer Lab, Department of Internal Medicine, The University of Texas Medical School, Houston, TX

**2015- Assistant Professor, Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS.**

2015- Associate Director for Cardiac Metabolism Research, Mississippi Center for Heart Research, University of Mississippi Medical Center, Jackson, MS.

**Other Experience and Professional Memberships**

2011- Member, American Heart Association, Council on Basic Cardiovascular Sciences
2012- Editorial Board, ISRN Nutrition
2012- Reviewer, Endocrinology
2013- Member, The Endocrine Society
2013- Member, American Physiological Society, Cardiovascular Section
2013- Reviewer, Journal of Molecular and Cellular Cardiology

2013- Reviewer, British Journal of Pharmacology
2014- Reviewer, Nutrition & Metabolism
2014- Reviewer, American Journal of Physiology Heart and Circulatory Physiology
2014- Reviewer, International Journal of Cardiology
2015- Reviewer, Circulation Research
2015- Reviewer, PLOS ONE
2015- Reviewer, Nutrition Research
2015- Reviewer, Proteomics Clinical Applications
2015- Reviewer, Scientific Reports (NPG)
2015- Reviewer, Annals of Nutrition and Metabolism
2016 Reviewer, Comprehensive Physiology
2016 Reviewer, Physiological Genomics
2016 Reviewer, Cardiovascular Drugs and Therapy
2016 Reviewer, Cardiovascular Diabetology

**Awards and Honors**

2002 French Ministry of Education, Advanced Instruction and Research Predoctoral Fellowship
2002 French Ministry of Education Excellence Award
2003 France-Canada Youth Exchange Program Travel Award
2005 1st place Undergraduate Poster Award French Pharmacological Society Annual Meeting
2013 UTHealth Postdoctoral Association Travel Award
2015 UMMC Excellence in Research Bronze Award
2016 UMMC Excellence in Research Silver Award

**C. Contribution to Science**

**Mission Statement:** My laboratory is dedicated to advancing our scientific knowledge of the molecular mechanisms by which metabolic diseases such as obesity and diabetes increase the risk to develop and die from cardiovascular disease. This will be accomplished by generating and sharing new data, tools, and animal models with the scientific and medical communities.

**Research Focus:** My current research identifies myocardial transcriptional alterations induced by insulin resistance and hyperglycemia and their consequences on cardiac metabolism, structure, and function.

1. Role of glucose as a metabolic signal in the regulation of cardiac inflammatory response:
During the past 3 years since my transition as an independent investigator at UMMC, I have succeeded in developing a research program focusing on the transcriptional regulatory effects of glucose and insulin in the heart, and on the consequences of their dysregulation on cardiac metabolic and functional remodeling (a). Our most recent study identified several transcription factors acting as potential cardiac glucose sensors and exposed the heart as a significant source of proinflammatory mediators released in response to stress (b). **These findings have opened new avenues in the study of the modulation of the cardiac inflammatory response by metabolic signals and on their impact on cardiac remodeling post myocardial infarction (c).**

a. Bakrania B, Granger JP, **Harmancey R**. Methods for the determination of rates of glucose and fatty acid oxidation in the isolated working rat heart. *J Vis Exp*. 2016;(115).doi:10.3791/54497; PMC5092065
b. Bux AS, Lindsey ML, Vasquez HG, Taegtmeyer H, **Harmancey R**. Glucose regulates the intrinsic inflammatory response of the heart to surgically induced hypothermic ischemic arrest and reperfusion. *Physiol Genomics.* 2016; doi: 10.1152/physiolgenomics.00102.2016; PMID 27940566
c. Lindsey ML, Hall ME, **Harmancey R**, Ma Y. Adapting extracellular matrix proteomics for clinical studies on cardiac remodeling post-myocardial infarction. *Clin Proteomics.* 2016;13:19. PMC5024439.

2. Role of insulin resistance in cardiac adaptation and maladaptation in obesity and diabetes:
While hyperglycemia and insulin resistance are well-known risk factors for cardiovascular diseases, the molecular alterations caused by both factors in the heart are far less well investigated than in other insulin sensitive organs. My initial goal was to investigate whether myocardial insulin resistance may be a physiological response for the stressed heart in diabetes, rather than a primary cause for heart failure (a). My findings have exposed the two faces of insulin resistance for the heart. While we observed better adaptation to an acute increase in workload, we found that the insulin resistant heart is more sensitive to ischemia-reperfusion injury (b, c). In the mouse heart, we further demonstrated that chronic hyperinsulinemia induces a state of selective insulin resistance that is directly responsible for the down-regulation of UCP3 through activation and binding of the lipogenic transcription factor SREBP-1 to the *Ucp3* locus (d). **Our ongoing study funded by the NIH is now investigating whether this decrease in UCP3 levels is directly responsible for poor functional recovery of the type 2 diabetic heart following myocardial infarction and reperfusion.**

a. Taegtmeyer H, Beauloye C, **Harmancey R**, Hue L. Insulin resistance protects the heart from fuel overload in dysregulated metabolic states. *Am J Physiol Heart Circ Physiol. 2013;*305(12):H1693-7. PMC3882545
b. **Harmancey R**, Lam TN, Lubrano GM, Guthrie PH, Vela D, Taegtmeyer H. Insulin resistance improves metabolic and contractile efficiency in stressed rat heart. *FASEB J*. 2012; 26(8):3118-26; PMC3405268
c. **Harmancey R**, Vasquez H, Guthrie P, Taegtmeyer H. Decreased long-chain fatty acid oxidation impairs post-ischemic recovery of the insulin-resistant rat heart. *FASEB J*. 2013; 27(10):3966-78; PMC4046182
d. **Harmancey R**, Haight DL, Watts KA, Taegtmeyer H. Chronic hyperinsulinemia causes selective insulin resistance and down-regulates Uncoupling Protein 3 (UCP3) through the activation of Sterol Regulatory Element-Binding Protein (SREBP)-1 transcription factor in the mouse heart. *J Biol Chem*. 2015;290(52):30947-61. PMC4692222

3. Regulation of glucose and fatty acid metabolism in cardiac and cancer biology:
Other than transcriptional changes, the mechanisms by which dietary composition induces myocardial remodeling during the development of obesity was the basis of the first years of my post-doctoral fellowship. The consumption of both fat and carbohydrates in excess (Western diet) impairs cardiac contractile function in the rat through the reprogramming of liver metabolism and a change in myocardial fatty acid composition (a, b). The tools and techniques I learned during that time to study metabolism were also successfully applied to collaborative projects, which identified the inhibition of fatty acid oxidation as a way to sensitize leukemia cells to chemotherapeutic agents (c), and glucose 6-phosphate as an activator of ChREBP-mediated gene transcription (d). **These studies identified general metabolic processes as a target for the treatment of obesity-associated cardiac diseases and certain types of cancers, particularly leukemia.**

a. **Harmancey R**, Wilson CR, Wright NR, Taegtmeyer H. Western diet changes cardiac acyl-CoA composition in obese rats: A potential role for hepatic lipogenesis. *J Lipid Res*. 2010; 51(6):1380-93; PMC3035501
b. Ballal K, Wilson CR, **Harmancey R**, Taegtmeyer H. Obesogenic high fat western diet induces oxidative stress and apoptosis in rat heart. *Mol Cell Biochem*. 2010; 344(1-2):221-230; PMC3656656
c. Samudio I, **Harmancey R**, Fiegl M, Kantarjian H, Konopleva M, Korchin B, Kaluarachchi K, Bornmann W, Duvvuri S, Taegtmeyer H, Andreeff M. Pharmacologic inhibition of fatty acid oxidation sensitizes human leukemia cells to apoptosis induction. *J Clin Invest*. 2010;120(1):142-156; PMC2799198
d. Li MV, Chen W, **Harmancey R**, Nuotio-Antar AM, Imamura M, Saha P, Taegtmeyer H, Chan L. Glucose-6-phosphate mediates activation of the carbohydrate responsive binding protein (ChREBP). *Biochem Biophys Res Commun*. 2010; 395(3):395-400; PMC2874883

4. Functional characterization of two novel secreted factors up-regulated with obesity:
One potential mechanism explaining the effects of obesity on the heart is the secretion of endocrine factors, or adipokines, by adipose tissue. My main doctoral research project focused on the characterization of the

vasodilator peptide adrenomedullin as an adipokine. I showed that adrenomedullin inhibits β-adrenergic-stimulated lipolysis by a mechanism involving NO-dependent oxidation of the β-adrenergic agonists (a). Adrenomedullin is an anti-adipogenic factor whose expression is inhibited by insulin at the transcriptional level (b). During my graduate years, I also contributed to the cloning and characterization of a novel apolipoprotein up-regulated in the human heart during obesity and diabetes. This novel apolipoprotein is also found in cardiac mitochondria where it regulates fatty acid oxidation and ATP generation (c, d). **These studies contributed to expand our knowledge on the molecular mechanisms controlling fat metabolism and their dysregulation with obesity.**

a. **Harmancey R**, Senard JM, Pathak A, Desmoulin F, Claparols C, Rouet P, Smih F. The vasoactive peptide adrenomedullin is secreted by adipocytes and inhibits lipolysis through no-mediated beta-adrenergic agonist oxidation. *FASEB J*. 2005;19:1045-1047; PMID 15788445
b. **Harmancey R**, Senard JM, Rouet P, Pathak A, Smih F. Adrenomedullin inhibits adipogenesis under transcriptional control of insulin. *Diabetes*. 2007;56:553-563; PMID 17327422
c. Lamant M, Smih F, **Harmancey R**, Philip-Couderc P, Pathak A, Roncalli J, Galinier M, Collet X, Massabuau P, Senard JM, Rouet P. Apoo, a novel apolipoprotein, is an original glycoprotein up-regulated by diabetes in human heart. *J Biol Chem*. 2006;281:36289-36302; PMID 16956892
d. Turkieh A, Caubère C, Barutaut M, Desmoulin F, **Harmancey R**, Galinier M, Berry M, Dambrin C, Polidori C, Casteilla L, Koukoui F, Rouet P, Smih F. Apolipoprotein O is mitochondrial and promotes lipotoxicity in heart. *J Clin Invest.* 2014;124(5):2277-86. PMC4001558

5. Identification of the myocardial transcriptional signatures induced by obesity and hypertension:
Since my undergraduate and graduate training, I have contributed to the determination of obesity and hypertension effects on transcriptional remodeling in the heart. Using high-fat fed dogs and custom microarrays, we first showed that up-regulation of the transforming growth factor (TGF)β pathway in the heart strongly associated with the development of obesity-related hypertension (a). By combining microarray and NMR spectroscopy analyses on hearts from Spontaneously Hypertensive Heart Failure (SHHF) lean and obese rats, we demonstrated that obesity alone or in combination with hypertension induces very distinct effects on the cardiac transcriptome (b). We confirmed this in humans by showing that the Wnt signaling pathway is down-regulated in obese normotensive patients, whereas the same pathway is up-regulated with obesity-associated hypertension (c). **These studies revealed that obesity and hypertension exert complex, non-additive effects on the cardiac transcriptome.**

a. Philip-Couderc P, Smih F, Hall JE, Pathak A, Roncalli J, **Harmancey R**, Massabuau P, Galinier M, Verwaerde P, Senard JM, Rouet P. Kinetic analysis of cardiac transcriptome regulation during chronic high-fat diet in dogs. *Physiol Genomics*. 2004;19:32-40; PMID 15226482
b. Roncalli J, Smih F, Desmoulin F, Dumonteil N, **Harmancey R**, Hennig S, Perez L, Pathak A, Galinier M, Massabuau P, Malet-Martino M, Senard JM, Rouet P. Nmr and cdna array analysis prior to heart failure reveals an increase of unsaturated lipids, a glutamine/glutamate ratio decrease and a specific transcriptome adaptation in obese rat heart. *J Mol Cell Cardiol*. 2007;42:526-539; PMID 17222424
c. Philip-Couderc P, Pathak A, Smih F, Dambrin C, **Harmancey R**, Buys S, Galinier M, Massabuau P, Roncalli J, Senard JM, Rouet P. Uncomplicated human obesity is associated with a specific cardiac transcriptome: Involvement of the wnt pathway. *FASEB J*. 2004;18:1539-1540; PMID 15289443

**Complete List of Published Work in MyBibliography:**
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/49034245/?sort=date&direction=descending

**D. Research Support**

**Ongoing Research Support**
P20GM104357 Pilot Grants Program-Center of Biomedical Research Excellence (COBRE) “Obesity, Cardiorenal and Metabolic Disease Center”
Harmancey (PI) 04/01/2017-03/31/2018
Molecular Basis of Postischemic Maladaptation in the Insulin Resistant Heart

This project will generate the preliminary data to submit a R01 application aiming to identify the mechanisms by which insulin resistance contributes to poor prognosis of type 2 diabetic individuals following myocardial infarction and reperfusion.
Role: PI

R00 HL112952 Harmancey (PI) 02/01/2015-01/31/2018
Unexpected Consequences of Insulin Resistance for the Heart
This project investigates the role of myocardial insulin resistance as an adaptive mechanism with which the heart protects itself from the hyperglycemic milieu of diabetes mellitus. Specific Aim 1 investigates the role of glucose and hyperglycemia as regulators of gene expression in the heart. Specific Aim 2 defines the effect of myocardial insulin resistance on energy metabolism and contractile function of the heart subjected to chronic pressure overload. Specific Aim 3 tests the hypothesis that the uncoupling protein 3 (UCP3) decreases efficiency of the heart subjected to a high workload by inhibiting glucose oxidation.
Role: PI

**Completed Research Support**

K99 HL112952 Harmancey (PI) 07/22/2013-01/31/2015
Unexpected Consequences of Insulin Resistance for the Heart
Role: PI

R01 HL061483 Taegtmeyer (PI) 05/01/2011-04/30/2016
Self-renewal of the Cardiomyocyte
The goal of this project was to identify metabolic signals as regulators of myocardial protein turnover in the normal and failing heart. The key findings of this research that I directly supervised were that myocardial insulin resistance protects the heart from a detrimental accumulation of glycolytic and fatty acid intermediates under substrates oversupply conditions, which results in a better adaptation to an acute increase in workload; 40 publications resulted from this funding.
Role: Co-Investigator