BIOGRAPHICAL SKETCH

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NAME: Pacella, John J.

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

POSITION TITLE: Associate Professor of Medicine

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
Carnegie Mellon University, Pittsburgh, PA	B.S.	05/90	Mechanical Engineering
Lehigh University, Bethlehem, PA	M.S.	10/92	Mechanical Engineering
University of Pittsburgh, Pittsburgh, PA	M.D.	05/98	Doctor of Medicine
University of Pittsburgh, Pittsburgh, PA	Residency	06/00	Internal Medicine
University of Pittsburgh, Pittsburgh, PA	Clinical Fellow	07/05	Cardiovascular Disease
University of Pittsburgh, Pittsburgh, PA	Post Doctoral Fellow	07/05	Cardiology
University of Pittsburgh, Pittsburgh, PA	Interventional Fellow	06/06	Interventional Cardiology

A. Personal Statement

The overall aim of this proposal is to develop and characterize a new, targeted treatment approach for reperfusion injury in myocardial infarction. This is a collaborative proposal involving chemical synthesis and testing the resulting compounds in cell culture and animal models.

I am an academic interventional cardiologist, currently serving as PI on an NIH R01, and with multiple previous funding sources, including a previous NIH (K08) and multiple American Heart Association Beginning Grants in Aid. I am uniquely qualified to as a consultant to support the aims set forth in this proposal for the following reasons:

[1] I have extensive experience in numerous animal models of disease, spanning from rodent to large animal models.

[2] I have particular expertise in developing novel treatments for myocardial reperfusion injury. My expertise in mechanically disrupting distal microemboli resulting from PCI complements Josh's pharmacologic approach to minimizing reperfusion injury.

[3] I have been a practicing interventional cardiologist at UPMC for eleven years and can mentor Josh as he prepares for a career in academic cardiology.

B. Positions and Honors

1990 Teaching Assistantship, Lehigh University
1991 Teaching Assistantship, Lehigh University
1991 Research Assistantship, Lehigh University
1994 Young Investigator Fellowship Award, American Society for Artificial Internal Organs
2002 1st Prize, American Heart Association, Fellow's Day Research Competition
2002 Postdoctoral Fellowship Award, American Heart Association
2003 National Institute of Health Loan Repayment Award for Research
2004 Postdoctoral Fellowship Award, American Heart Association
2004 2nd Prize, University of Pittsburgh, Department of Surgery, Annual Research Day
2004 1st Prize, University of Pittsburgh, Department of Medicine, Annual Research Day
2004 1st Prize, American Heart Association, Fellow's Day Research Competition
2005 1st Prize, American Society of Echocardiography, Young Investigator Award
2005 Research Fellowship Award, American Society of Echocardiography
2006 Beginning Grand in Aid, American Heart Association
2006 National Institute of Health Loan Repayment Award for Research
2007 National Institute of Health, K08 Career Development Award
2009 National Institute of Health Loan Repayment Award for Research
2009 Beginning Grand in Aid, American Heart Association
2009 Claude R Joyner Award for Excellence in Research
2010 34th Annual Honors Convocation, University of Pittsburgh
2010 Pittsburgh Foundation Research Grant
2011 1st Prize, American Heart Association, Fellow's Research Day, Jonathan Leeman (Mentor)
2011 2nd Prize, American Heart Association, Fellow's Research Day, Judith Brands (Mentor)
2012 1st Prize, Martin Blomley Best Clinical Poster, 17th European Symposium on Ultrasound Contrast Imaging, Rotterdam, The Netherlands January 19-20, 2012
2014 1st Prize, University of Pittsburgh, Department of Medicine, Annual Research Day

C. Contribution to Science

1) I have maintained a long standing interest in microvascular research and developing techniques to optimize microvascular perfusion. I began my study of the microcirculation by investigating the effects of drag reducing polymers on coronary blood flow. In a canine model of severe flow limiting coronary stenosis, I was the first to demonstrate that intravenous drag reducing polymers restored coronary perfusion to normal, as measured by radiolabeled microspheres and myocardial contrast echocardiography. Due to the potential therapeutic applications for patients with acute coronary syndromes, or any ischemic pathology, this led me to delve more deeply into the microvascular mechanisms of drag reducing polymers. This formed the basis for my NIH K08 award and my AHA Beginning Grant in Aid. During my K08 funding, I independently mastered several complex microvascular techniques, such as measurement of the cell free layer using dual fluorescence methodology, measurement of RBC microvascular flux and velocity, and assessment of white blood cell endothelial cell interactions. I also mastered the intricate servonull method for direct measurement of microvascular pressure. Using this technique, I uncovered a long held purported microvascular mechanism of drag reducing polymers; that is, drag reducing polymers reduce pressure loss from the aorta to the arteriolar compartment. I also demonstrated that drag reducing polymers reduce the width of the microvascular cell free layer. Both of these seminal findings have advanced this field, and further elucidated their microvascular mechanisms. I published multiple manuscripts detailing this work in high impact cardiovascular journals listed below:

a) **Pacella JJ**, Villanueva FS. Effect of coronary stenosis on adjacent bed flow reserve: assessment of microvascular mechanisms using myocardial contrast echocardiography. *Circulation* 2006;114:1940-1947.
b) **Pacella JJ**, Kameneva MV, Lu E, Fischer D, Csikari M, Villanueva FS. A novel hydrodynamic approach for the treatment of coronary artery disease. *Eur Heart J* 2006;27:2362-2369 (with Editorial Comment).
c) (FRONT COVER) **Pacella JJ**, Kameneva MV, Villanueva FS. Drag Reducing Polymers Improve Coronary Flow Reserve through Modulation of Capillary Resistance. *Biorheology* 2009; 46(5):365-378.
d) **Pacella JJ**, Kameneva MV, Brands J, Lipowsky HH, Vink H, Lavery LL, Villanueva FS. Modulation of pre-capillary arteriolar pressure with drag reducing polymers: a novel method for enhancing microvascular perfusion. *Microcirculation* 2012;19:580-585.

2) As an interventional cardiologist, I recognized the clinical significance of microvascular obstruction **(MVO)** following primary coronary stenting for acute myocardial infarction due in large part to distal embolization of atherothrombotic debris -- which affects up to 60% of patients, and leads to adverse cardiac events, including increased mortality. I started a research program to develop a new therapeutic strategy for this highly prevalent condition, for which there is currently no good treatment. Using my unique combination of engineering skills in fluid mechanics, my clinical knowledge in interventional cardiology, my understanding of therapeutic potential of ultrasound and microbubble therapy, and my portfolio of microvascular analytic techniques, I was the first to use ultrasound and

microbubble therapy to restore coronary microvascular perfusion in the setting of MVO (*Ultrasound Med Biol.* 2015;41:456-64), opening up exciting new possibilities for mitigating this complication of coronary stenting and improving outcome in patients with myocardial infarction.

I used my microvascular analytic skills coupled with my expertise in contrast ultrasound to develop 3 new *in vitro* and *in vivo* models. These models included: (1) A new *in vitro* model of MVO, in which I devised an experimental setup and protocol that uniquely simulates that microvasculature and creates microthrombi used to create MVO for testing various therapeutic ultrasound/microbubble platforms. I published a manuscript detailing this model and that ultrasound and microbubble therapy can be used to successfully resolve MVO and restore perfusion (*Ultrasound Med Biol.* 2012;38:1589-1598). I was awarded a research prize for this work at the international Contrast Ultrasound Symposium in Rotterdam, in 2012. (2) To strive toward more clinical relevance, I developed a new rodent hind limb model of MVO. In this model of intact skeletal muscle microcirculation, I demonstrated, for the first time, that ultrasound and microbubble therapy can be used to specifically treat MVO and restore perfusion (*Ultrasound Med Biol.* 2015;41:456-64). (3) These promising findings in rodents motivated further efforts towards clinical translation. I developed a highly clinically relevant porcine model of acute MI and MVO in collaboration with the Reed Research Group (University of Wisconsin) to utilize the atherosclerotic Rapacz pig, the most clinically relevant model of human atherosclerosis known. To recapitulate clinical MVO, I designed this model to precisely mimic the events (embolization of atherothrombotic debris) that lead to MVO during treatment of acute myocardial infarction in patients with coronary stenting in the catheterization laboratory. In this model, I obtained donor atherosclerotic plaque and performed specialized processing techniques to generate microatherothrombi to create MVO. We mimicked acute myocardial infarction in the left anterior descending (LAD) coronary artery of the Rapacz pig using percutaneous balloon inflation and formed MVO, in the setting of a patent epicardial coronary artery. Combining this new model with my interventional skills, I was the first to successfully simulate “no reflow” in contemporary acute myocardial infarction -- microvascular occlusion by atherothrombotic material in the presence of a revascularized (patent) epicardial coronary artery. This model will be crucial for testing ultrasound and microbubble therapy to restore microvascular perfusion. These models, in general, were considered major strengths of my NIH R01 application, for which I received a 5th percentile score, with funding commencing July 2015.

a) Leeman JE, Kim JS, Yu F, Chen X, Kim K, Wang J, Chen X, Villanueva FS, **Pacella JJ**. Effect of acoustic conditions on microbubble-mediated microvascular sonothrombolysis. *Ultrasound Med Biol.* 2012;38:1589-1598.
b) Kim JS, Leeman JE, Kagemann L, Yu FT, Chen X, **Pacella JJ**, Schuman JS, Villanueva FS, Kim K. Volumetric quantification of in vitro sonothrombolysis with microbubbles using high resolution optical coherence tomography. *J Biomed Opt* 2012;17:070502.
c) Chen X, Leeman JL, Wang J, **Pacella JJ**, Villanueva FS. New insights into mechanisms of sonothrombolysis using ultra-high-speed imaging. *Ultrasound Med Biol.* 2014: 40(1):258-62.
d) **Pacella JJ**, Brands J, Schnatz FG, Chen X, Villanueva FS. Treatment of microvascular micro-embolization using microbubbles and long tone-burst-ultrasound: an *in vivo* study *Ultrasound Med Biol* 2015;41:456-64.

3) I have also maintained a longstanding interest in cardiovascular device design. As a bioengineer, I designed, fabricated and tested a left ventricular assist device. I initially worked as a project engineer but was then promoted to project manager and led the project through large animal preclinical testing in over 40 studies and presented the findings to the FDA for 510 k approval. The device was later modified for use as a percutaneous system and I was part of the team the implanted the first 3 devices in patients with cardiogenic shock at the University of Pittsburgh. I has received 5 patents pertaining to the device design enumerated below:

a) **Pacella JJ**, Goldstein AH, Trumble DR, Clark RE, and Moeller FW. Blood Pump Device and Method of Pumping Blood. Patent 5,711,753. January 27, 1998.
b) Goldstein AH, **Pacella JJ**, Trumble DR, Clark RE, Moeller FW, and Magovern, Sr, GJ. Blood Pump Device Having a Journal**.** Patent 6,162,167. December 19, 2000.
c) **Pacella JJ** and Clark RE. Occluder Device and Method of Making. Patent 6,045,496. April 4, 2000.
d) **Pacella JJ** and Clark RE. Occluder Device and Method of Making. Patent 6,186,149. February 13, 2001.
e) **Pacella JJ**, Goldstein AH, Trumble DR, Clark RE, Moeller FE, and Magovern Sr., GJ. Blood Pump Device and Method of Producing. Patent 6,808,482. October 26, 2004.

Relevant publications pertaining to the device are enumerated below as well:

a) Goldstein AH, **Pacella JJ**, Trumble DR, and Clark RE. Development of an Implantable Centrifugal Blood Pump. *American Society for Artificial Internal Organs,* 1992;38:M362-M365.

b) Goldstein AH, **Pacella JJ**, and Clark RE. Predictable Reduction of Stroke Work and Ventricular Oxygen Utilization with an Implantable Centrifugal Blood Pump. *Annals of Thoracic Surgery*, 1994;58:1018-1024.
c) **Pacella JJ**, Goldstein AH, Magovern GJ, and Clark RE. Modified Fabrication Techniques Lead to Improved Centrifugal Blood Pump Performance. *American Society for Artificial Internal Organs*, 1994;40:M767-M772.
d) Reddy RC, Goldstein AH, **Pacella JJ**, Cattivera GR, Clark RE, Magovern GJ. End Organ Function with Prolonged Non-Pulsatile Circulatory Support. *American Society for Artificial Internal Organs*, 1995;41:M547-M551.

4) As an extension of my clinical work in the catheterization laboratory and his interest in hemodynamics, I sought to determine whether simple handheld ultrasound could be used to measure a patient's intravascular volume status; i.e. predict central venous pressure, a critical clinical metric for guiding diuretic therapy in patients with heart failure. I found that a normal increase in internal jugular vein cross sectional area during Valsalva could be used to rule out elevated right atrial pressure with 97% negative predictive value (*Am Heart J* 2010;159:421-7). I recently determined that this technique can predict 30 day hospital readmission for patients admitted with acute decompensated heart failure, a finding which could have a major impact on efforts to avoid readmission of patients with congestive heart failure (oral presentation, Scientific Sessions of the American Heart Association 2014, manuscript under preparation).

a) Simon MA, Girod JP, Kliner DE, Moguilansky D, Villanueva FS and **Pacella JJ**. Detection of elevated right atrial pressure using a simple bedside ultrasound measure. *Am Heart J* 2010;159:421-7.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/john.pacella.1/bibliography/41152454/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1R01HL125777-01A1 (5th percentile score) Pacella (PI) 07/1/15-06/30/19
National Institute of Health
Microbubble-Mediated Ultrasonic Therapy for Coronary Microvascular Obstruction

Completed Research Support

NIH K08 (1 K08 HL086730-01) Pacella (PI) 2007 – 2012
National Institutes of Health
Title: Myocardial Flow Enhancement with Drag Reducing Polymers: Microvascular Mechanisms
The goal of this project is to determine the mechanism of action of drag reducing polymers in the microcirculation.

Pittsburgh Foundation Pacella (PI) 2010-2012
Title: Development of an Accelerated Swine Model of Human-Like Atherosclerosis
The goal of this study is to develop an accelerated swine model of atherosclerosis using the technique of endoluminal paving with biodegradable hydrogels.

University of Pittsburgh Chen/Pacella (Co-PI) 2011-2012
Clinical and Translational Science Institute (CTSI)
Title: Development of nonlinear intravascular ultrasound system for the diagnosis of coronary atherosclerosis
The aim of this study is to validate a novel contrast based intravascular ultrasound imaging technique of the detection of coronary atherosclerosis, in a rabbit model of coronary atherosclerosis.

Postdoctoral Fellowship Award
American Heart Association Pacella (Sponsor) Brands (PI) 2012-2014
Title: The endothelial glycocalyx: a new therapeutic target for vascular health?
The goal is to study the time course of glycocalyx replenishment during exogenous administration of its components and to determine whether myocardial contrast echocardiography can be used to measure glycocalyx volume noninvasively.

1RO1 HL093230 Kim (PI) 2010-2015
National Institutes of Health
Title: Ultrasound-induced Thermal Strain Imaging for Arterial Plaque Characterization
The goal of this project is to develop an ultrasound based platform of thermal strain imaging to measure the lipid content of an atherosclerotic plaque.

University of Pittsburgh, Bridge Funding Pacella (PI) 07/01/14-06/30/15
Title: Microvascular Sonothrombolysis: A mechanistic and therapeutic investigation