SFF/RRG COVER SHEET

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Application Receipt Deadline: 4:00 p.m. Thursday, September 29, 2016

Type of application: ☐ SFF ☐ RRG ☒ Both

Review Panel: ☒ natural, physical and applied sciences ☐ humanities ☐ social sciences

Collaborative Application: ☒ No ☐ Yes

Descriptive Project Title (Limited to 120 character, including spaces)

Correlating wall shear stress to cellular proliferation in the setting of drugs used with current coronary artery stents

Name: John F. LaDisa, Jr., Ph.D.

Department: Biomedical Engineering

Phone: 414-288-6739 | **Email: john.ladisa@marquette.edu**

Academic Rank: ☐Assistant Professor ☒Associate Professor ☐Full Professor

MU Hire Date: January 2, 2007

This project involves (check all that apply):

☐Human Subjects ☐Vertebrate animals ☐Recombinant DNA ☐Radioactive Materials

Does this SFF/RRG application request graduate student support? ☒ Yes ☐ No

What other internal and external research support are you currently receiving (e.g., external grants, start-up funding, etc.)? Please provide a list of any **pending** applications and **current** awards.

Current:

Aurora Healthcare, Inc., Co-I (20% cost shared), Trivedi (PI) 1/1/16-12/31/16
Sullivan Cardiac Research Award for Residents and Fellows - "Evaluation of and prediction of complications after transcatheter aortic valve replacement using computational methods".

Marquette University Co-I (no direct support), S. Singer (PI) 7/1/16-6/30/17
Opus College of Engineering Legacy Initiative Research Seed Grant - "Modeling Chemical Deposition in the Human Airway from Electronic Cigarettes"

American Heart Association, PI (1 summer mo) 07/01/15-06/30/17
Grant-in-Aid Midwest Affiliate - "Mechanistic analysis of mechanical alterations to improve therapeutic interventions for aortic coarctation".

Marquette University PI (no direct support) 07/01/15-06/30/18
Innovation Fund - "Partnerships for Excellence through Advanced Visualization"

Marquette University Faculty Advisor (no direct support) - Student PI: A. Barrington 07/01/15-06/30/18
Innovation Fund - "ALIVE: the Assisted LIving Virtual Environment".

If awarded, describe your plans for submitting an external grant application.

This proposal will be used to obtain additional preliminary data in support of an NIH R01 A1 application that will be resubmitted at the conclusion of the funded SFF/RRG period.

Applicant signature and date

09/28/16

Chair/Unit Administrator signature and date

09/28/16

Please complete the following if this is a collaborative proposal

Collaborator Name:

Department:

Phone: | **Email:**

Academic Rank: ☐ Assistant Professor ☐ Associate Professor ☐ Full Professor

MU Hire Date:

Have you searched for external funding? ☐ Yes ☐ No

If yes, explain how you searched for external funding (even if your efforts were not successful)

What other support are you currently receiving?

Applicant signature and date

Chair/Unit Administrator signature and date

2) Abstract

Drug-eluting stents (**DES**) are used to restore blood flow to blocked coronary arteries of the heart. DES are coated with one of several drugs to prevent regrowth of the blockage (i.e. restenosis), but these drugs are ineffective for ~200,000 patients within the U.S. annually. Disruptions in wall shear stress (**WSS**; the frictional force/area on an artery from flowing blood) correlate with sites of restenosis for bare metal (i.e. non-drug eluting) stents, but it is unknown whether optimizing WSS can combats restenosis for DES. This proposal will quantify the ability of the drugs used with current DES to suppress surrogate markers of restenosis using the range of WSS induced by stenting. We hypothesize that the commercial dosing of drugs on current DES is inadequate to counteract the influence of pronounced WSS disruptions in some patients, which thereby limits the effectiveness of the DES. The proposal hypothesis will be tested by identify the mechanisms and range of WSS for which the drugs on current commercial DES are most effective using novel bench-top techniques. The preliminary data will be used to address reviewer comments from a prior NIH R01 submission. The proposal is innovative because it surveys mechanical stimuli (i.e. WSS) imparted by commercial DES with drugs on current DES to optimize and independently account for limitations in either component. The proposed research is significant because it will provide data related to a previously unstudied way of improving clinical outcomes for the estimated 200,000 Americans developing restenosis annually despite the use of DES.

3) Project Description

a) Significance and Innovation: Cardiovascular disease is the leading cause of death in the U.S. 84 million Americans (35% of adults) have cardiovascular disease and 49% of these patients suffer from coronary artery disease[1]. Minimally-invasive stent implantation has revolutionized treatment of coronary artery disease, but a coronary artery event still occurs every 34 seconds, and claims a life nearly every minute[1].

The success of current DES is primarily limited by restenosis. Restenosis is defined as ≥50% diameter reduction[2], and occurs primarily from excessive neointimal hyperplasia (**NH**; new tissue growth)[3]. NH is more pronounced for challenging lesions[4], and will certainly persist with future DES as their use extends to other arteries in the body without extensive experience[5].

The cause of restenosis with some DES is unknown, but >60% of NH occurs in the entrance region of the stent that experiences blood flow disruptions, thereby implicating WSS. WSS correlates with sites of NH in bare metal stents. In contrast to bare metal stents, the data relating WSS to NH for DES in prior studies yielded conflicting results[6-8]. *Some studies now suggest the mechanisms of action for the different types of drugs used with a given commercially-available DES may impact the relationship between NH and WSS previously observed with bare metal stents[9]. This hypothesis remains to be conclusively tested, especially with newer drugs.*

The critical barrier to reducing NH for DES is the cost of developing and obtaining regulatory approval for new stent geometries and drugs. The maturity of the coronary stent market together with the tremendous costs and number of patients required for clinical trials limits DES development to only the most established medical device companies. To remove this barrier, *our ultimate goal is to optimize WSS within the context of FDA-approved stent geometries, proven drugs used with current DES, and known mechanisms of action for WSS.* The direct benefits of this proposal will be results that quantify, for the first time, the contribution of stent-induced WSS to NH using a set of molecular mediators defined by the drugs used with commercial DES. The results will identify interactions between these players, which we ultimately plan to manipulate in a follow-up proposal by creating stents matching the geometric patterns of many commercial stents and coating them with different drugs at their commercial doses.

This proposal is innovative for two reasons. First, we will independently test the range of WSS values and drugs imposed by the most common commercial DES. As a result, we are not limited to the stimuli or drug that accompanies a single commercial DES, but can mix and match stimuli and drugs to account for limitations in either component. This is done within the attributes for FDA-approved DES to maintain clinical applicability and interest of key opinion leaders in the field of interventional cardiology and stent development companies of all sizes. Second, we will apply a rapid and efficient bench-top approach using flow chamber that resembles an intrastrut region (**Figure 1**) to apply a realistic range of WSS to single cell layers, thereby greatly reducing the number of experiments, limiting the cost of reagents and drugs, and also preserving information related to the spatial heterogeneity instructed by stent linkages (i.e. struts). These innovative approaches strive to make the offering of FDA-approved drugs and stent geometries using with current DES more effective, rather than unrealistically suggesting the pursuit of new stent designs.

b) Research Objectives: *Our objective is to quantify the activation of pathways modulated by WSS relative to the known molecular targets of drugs on current DES. The outcomes to be quantified are of functional relevance to NH.* Arteries contain two cell types that are impacted by stenting. NH is due to the proliferation of smooth muscle cells (**SMC**) while endothelial cells (**EC**) line arteries and sense WSS. Drugs used with first generation DES, sirolimus and paclitaxel, both inhibited SMC proliferation in a dose dependent manner, but sirolimus had no impact on EC migration regardless of dose. In contrast, paclitaxel dose-dependently inhibited EC migration[10]. These findings in static cells are consistent with the mechanisms of action for each drug, but may be altered in the presence of disrupted WSS and stenting. The orientation of WSS imparted directly on SMC due to EC removal common with stenting can lead to cell death and proliferation[11]. Of note, the extent of EC removal and subsequent orientation of WSS imposed on SMC are both dictated by stent geometry and the severity of injury to the artery during implantation. Cell studies further indicate there is a threshold value of WSS that promotes EC migration[12]. These prior findings suggest commercial doses of the drugs used with DES may not be sufficient when faced with pronounced stimuli for inducing proliferation or inhibiting EC migration in a coronary artery with pronounced WSS disruptions. This proposal will uncover the mechanisms by which the intended therapeutic effects of drugs used with newer DES (e.g. everolimus) may be altered in cells experiencing a range of WSS stimuli induced by stenting (see **Fig 1** for scope). This work will be performed by Dr. LaDisa, one of his current doctoral students, and an undergraduate student who previously worked in his lab over the past year.

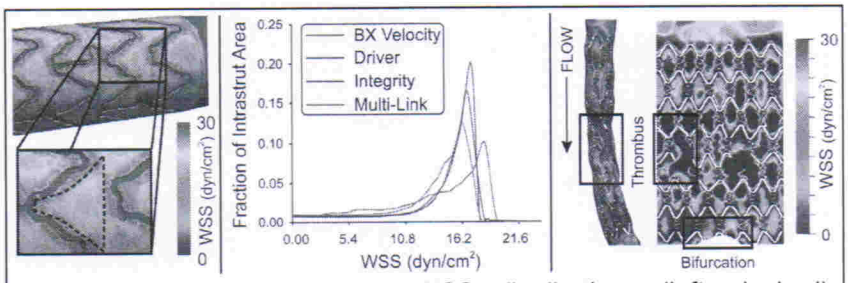

Fig 1. Example of intrastrut WSS distributions (left, dashed), histograms of intrastrut WSS for *idealized* commercial stents (middle), and *patient-specific* WSS distributions (right). This collective range of WSS values will be imposed with the Hele-Shaw flow chamber.

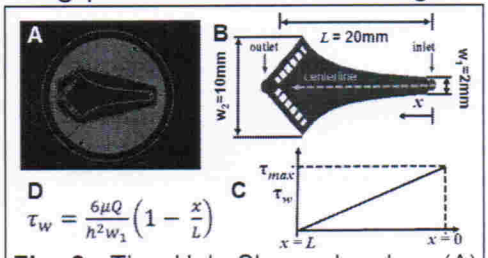

Fig 2. The Hele-Shaw chamber (A) resembles an intrastrut region (B) and imparts linear WSS down its centerline (C). A range of WSS magnitudes and spatial gradients can be studied by varying its flow rate and geometry (D).

c) Work Plan:

Methods to be employed. The flow profile for the Hele-Shaw chamber[13] in **Fig 2** resembles the diverging portion of intrastrut regions for the stents mentioned in **Fig 1**. The chamber induces a linear decrease in WSS magnitude along its center-line by designing its sidewalls to coincide with fluid streamlines and shaping its end to match theoretical velocity patterns of the flowing media[14]. The design facilitates the study of a wide range in WSS magnitudes within a single cell layer, greatly reducing the number of experiments, enabling studies with less cells and reagents, and preserving information related to the spatial heterogeneity imposed by stent linkages.

Vascular SMC and EC will be purchased and cultured on collagen-coated coverslips. The cells will be placed in the flow device and exposed to a range of WSS

spanning relevant physiological values[15-17]. Cells will be exposed for varying times (2, 4, 6, 12, and 24 hr, reflecting both short- and long-term responses) as needed to establish the optimal conditions for assessing the experimental outcomes. The relative importance of WSS magnitude vs. spatial WSS gradient will be assessed by changing the flow rate to modify the gradient **(Fig 2)**. Separate trials will be conducted for cells sheared in the absence and presence of paclitaxel and everolimus using doses reported in plasma for commercial DES (0.05, 0.5 and 1 ng/mL)[18-20]. The molecular targets and functional outcomes related to NH to be studied are shown in **Fig 3,** and the methods are summarized below:

1. Cell proliferation and death (Click-iT EdU/TUNEL Alexa Fluor, Molecular Probes)
2. Expression/distribution of rapamycin targets and regulators of cell cycle (immunofluorescence, Western blot): FK506 binding protein-12 (cytosolic receptor of rapamycin, complex binds to mTOR), mTOR (mammalian Target of Rapamycin), p70S6 kinase (target of WSS), $p27^{Kip1}$.
3. Microtubule structure/distribution (paclitaxel conjugate, Molecular Probes; α-tubulin)
4. Markers of phenotypic switch to synthetic SMC (immunofluorescence, Western blot, qPCR): platelet derived growth factor, vascular endothelial growth factor, matrix metalloproteinases 1, 2 and 9.
5. EC migration: cell distance (scratch assay)
6. EC junction integrity (immunofluorescence): PECAM & VE-cadherin expression
7. EC function and thrombotic balance (immunofluorescence, Western blot, qPCR): endothelial nitric oxide synthase, thrombomodulin, tissue factor pathway inhibitor, tissue-type plasminogen activator, plasminogen activator inhibitor 1, tissue factor

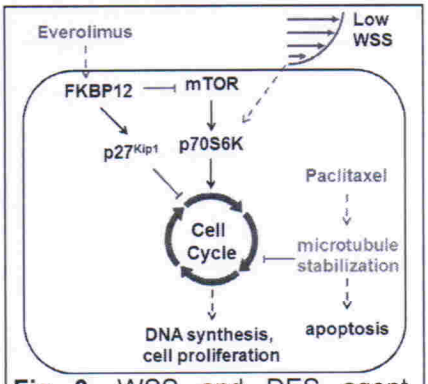

Fig 3. WSS and DES agent-mediated molecular targets and functional outcomes for NH

Mean fluorescence intensity per cell reflective of proliferation will be quantified using ImageJ from 4 fields at 100x magnification for each WSS magnitude on a slide (average 5 slides/experiment). Migration will be quantified by scraping the EC and SMC plates along the centerline to remove each cell type locally prior to shearing, and then quantifying migration distance across the range of WSS imparted. Data will be analyzed using GraphPad Prism. Multiple experimental groups will be analyzed by ANOVA and differences assessed with Dunnett's or Tukey's posttest as appropriate. Results will be interpreted relative to a WSS magnitude value of 12 dynes/cm^2 that is preferred in the coronary arteries. Comparisons will be considered significant for 2-tailed $P<0.05$.

Expected Outcomes, Potential Problems & Alternative Strategies. Based on an order of magnitude less paclitaxel concentration in plasma from the stented region relative to everolimus[19, 21] and case reports to date[25, 28], we expect proliferation will be elevated for cells from low, vs medium and high WSS regions, and everolimus to be more effective at reducing proliferation than paclitaxel at a given dose. Paclitaxel is expected to inhibit migration at all WSS levels, while everolimus is not expected to have an impact on this metric. Thus, we expect to find that WSS has a mitigating effect on the

ability of paclitaxel to inhibit proliferation. Moreover, we expect WSS and drug type as well as concentration to act in a concerted manner to impact EC migration.

Plasma concentrations of DES agents reported in literature do not necessarily represent the arterial concentration[22]. Nonetheless, values to be used represent relative doses for each agent. Doses at two additional orders of magnitude will be tested to account for a range of arterial concentrations. For studies in which cell intensity alone will not yield adequate data, cells will be exposed to select WSS values in a cone-and-plate-based flow chamber to acquire sufficient cells for further quantification using other approaches (e.g. Western blotting or qPCR).

Table 1. Timeline for the Proposed Research

	Month		
	1-2	3-4	5-6
Training, obtaining & culturing cells	XX		
Control proliferation & migration studies	XX	XX	
Paclitaxel proliferation & migration studies		XX	X
Everolimus proliferation & migration studies			XXX

d) Relation to Research Goals: The current proposal describes steps to obtain the preliminary data that is needed to translate 15 years of the PI's research dedicated to blood flow through stents. The resulting preliminary data is also imperative for the revised version of an NIH R01 proposal to be competitive. Through a series of studies the PI was able to show a correlation between altered blood flow patterns and the localization of NH after stenting. Additional studies by the PI[17, 23, 24] and others[25-27] further demonstrated that geometric properties of a stent may contribute to adverse (i.e. low) WSS associated with NH. The PI revealed the number, width and thickness of stent linkages, as well as the local scaffolding (i.e. uniformity), and degree of curvature created by a stent can introduce adverse flow disturbances leading to NH[9, 17, 24, 28, 29]. These findings are supported by controlled preclinical and clinical studies[30-32]. Together with his collaborators and lab members, work in the PI's lab has improved scientific knowledge in this area, and has led the lab to being recognized as one of its foremost groups pertaining to fluid dynamics through stents. This proposal adds recent advancements in the lab to also consider DES. Preliminary data using a proliferation maker with the Hele-Shaw flow chamber revealed differences in expression (i.e. intensity) at high vs low WSS ranges for control and paclitaxel-treated EC, but not everolimus-treated cells, pointing to a potential WSS-mediated mechanism to be tested further. The proposal team is now poised to complete this work of optimizing local flow patterns, together with drugs on current DES, to suggest a combination that achieves the best possible outcome after DES implantation.

The proposal continues the PI's long-standing desire to conduct internationally-recognized research, while training the next generation of engineers and scientists in the methods applied for this purpose. The quality of this work is supported by >40 peer-reviewed publications made possible by the current participation of 4 undergraduate, 3 MS, 2 PhD students, and a postdoctoral scholar, as well as 10 prior graduate students (7 MS, 3 PhD), and a postdoctoral fellow, who have all gone on to prominent academic or industry positions. The PI is very proud of the work these trainees have accomplished, and the detailed, personalized, plans implemented with each individual to foster his or her success. Personalized training plans will also be developed for the graduate and undergraduate students included in the current proposal.

4) Bibliography

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SFF/RRG PROJECT BUDGET

Name(s): John F. LaDisa, Jr., Ph.D.

Department(s): Biomedical Engineering

Project Title: Correlating wall shear stress to cellular proliferation in the setting of drugs used with current coronary artery stents

SFF/RRG BUDGET TABLE

Double click on the table, and then add your budget figures:

Type of Application (Y/N)	Item	Funds Requested from the Committee on Research	Funds Requested from Other Sources	Source of Other Funds
	SFF ($0, $5500, $11000 (joint app))	**$5,500.00**		
	RRG			
	Please itemize RRG amount below			
	Personnel			
	Graduate Research Assistant(s)	**$3,000.00**		
	Undergraduate Research Assistant(s)	**$1,500.00**		
	Other Personnel, please list.			
	Equipment			
	Supplies	**$1,500.00**		
	Travel			
	Consultants/Professional Services, please list.			
	Other, please list.			
	TOTAL RRG REQUEST, if applicable	**$6,000.00**	**$0.00**	
	TOTAL COR REQUEST (SFF + RRG):	**$11,500.00**		

RRG PROJECT BUDGET JUSTIFICATION

On a separate sheet under the heading "RRG Project Budget Justification," describe **each item you listed in the RRG portion of the budget table**. The description should enable reviewers to understand a) how the cost of each item was computed, and b) how the budget items relate to your project objectives.

NOTE: Awardees will be notified before winter break. RRG funds may be spent in an 11-month period. Awardees must provide spending plans for two fiscal periods:
1)-Start Date of February 1 – 6/30 (current fiscal year), and 2) 7/1 – 12/31 (next fiscal year). RRG funds are bound by fiscal year budgeting restraints. Awardees will be required to provide carefully crafted and accurate spending plans for these two periods. Funds budgeted in any fiscal period must be spent in that fiscal year or they will no longer be available. Awardees will work with ORSP staff to administer their awards.

6) RRG Project Budget Justification

Personnel

John LaDisa Ph.D. (PI, funded through SFF) - Dr. LaDisa will facilitate and conduct cell experiments together with the students included below. Specifically, the graduate and undergraduate students will culture and maintain cells, expose them to shear stress and obtain images of fluorescent intensity. Dr. LaDisa will participate in these activities, but will also be responsible for quantification and analysis of resulting data, as well as directing next steps such as determining additional drug doses and refinement of methods to achieve the proposed objectives.

Graduate Research Assistant $3,000 - These funds are being requested to provide summer support for a doctoral student in the PI's lab from the Department of Biomedical Engineering. The student's stipend does not cover the summer months, which are essential for advancing research objectives. The current project will serve as the primary responsibility for the doctoral student and s/he will play an integral role in the day-to-day experimental methods proposed.

Undergraduate Research Assistant $1,500 - An undergraduate student in good academic standing (≥3.3 GPA), an interest in the proposed work, and the scientific background to appreciate the proposal objectives will be invited to participate in the proposed cell studies next summer. Historically, undergraduate students participating in similar research experiences within the PI's lab have attended associated lab meetings for at least one semester before starting a project, and projects selected by the student are aligned with his/her career goals. Of note, a portion of the preliminary data shown in this application was obtained by an undergraduate researcher.

Supplies

Consumables $1,500 - These funds are respectfully requested to defray the cost of consumable supplies including purchasing of arterial cells from a commercial vendor, media to keep these cells viable, immunofluorescence stains for labeling proliferation, pharmacological agents including paclitaxel and everolimus, and related reagents. These costs were determined based on those incurred previously while conducting similar research.

7) Results of Prior SFF/RRG Awards

a) Accomplishments from a prior SFF/RRG award: Dr. LaDisa used SFF/RRG funding in 2008 to continue his research on coarctation of the aorta (CoA), which is a different line of research than the current proposal. Children with CoA are prone to developing hypertension, coronary artery disease, aneurysms and stroke in addition to a reduced life expectancy. Hypertension is particularly common and persists despite surgical repair. Prior studies showed that repetitive forearm isometric exercise (IE) can reduce hypertension in adults through beneficial arterial changes. The objective of the prior SFF/RRG was to assess the safety and efficacy of IE in children previously treated for CoA to chronically alleviate hypertension. The study was arranged in 2 phases. Initially, the hypothesis that altered hemodynamics (forces associated with moving blood) are present after CoA was to be verified using an animal model of CoA and computational fluid dynamics (CFD) techniques. CFD is a simulation tool that uses noninvasive data of artery geometry, blood flow and pressure to create realistic computer models and quantify associated engineering parameters (e.g. strain and shear stress). Secondly, the hypothesis that IE is safe and can lower blood pressure in CoA was to be tested. Phase 1 of the proposal revealed several adverse changes in arteries resulting directly from CoA, and indicated these changes may be permanent. Dr. LaDisa and his colleagues have since focused on identifying root causes of these adverse changes before moving to phase 2 as proposed in the prior SFF/RRG. This has resulted in a number of accomplishments and submissions to characterize the mediators of arterial remodeling and dysfunction resulting from CoA, and to develop strategies to mitigate their adverse changes.

b) Publications from prior SFF/RRG support (students indicated in boldface):

1. J.F. LaDisa, Jr., S. Bozdag, **J. Olson**, R. Ramchandran, J.R. Kersten, T.J. Eddinger. Gene expression in experimental aortic coarctation and repair: candidate genes for therapeutic intervention? PLoS One. 2015 Jul 24;10(7):e0133356.
2. **A. Menon**, **D.C. Wendell**, **H. Wang**, T.J. Eddinger, J.M. Toth, **R.J. Dholakia**, **P.M. Larsen**, E.S. Jensen, J.F. LaDisa, Jr. A novel coupled experimental and computational approach to quantify deleterious hemodynamics, vascular alterations, and mechanisms of long-term morbidity in response to aortic coarctation. J Pharm Tox Meth. 2012 Jan;65(1):18-28.
3. **A. Menon**, T.J. Eddinger**, H. Wang**, **D.C. Wendell**, J.M. Toth, J.F. LaDisa, Jr. Altered hemodynamics, endothelial function and protein expression occur with aortic coarctation and persist following repair. AJP-Heart 2012;303(11):H1304-18.

c) Proposals for extramural funding to support work related to prior SFF/RRG awards:

1. American Heart Assoc., "Mechanistic analysis of mechanical alterations to improve therapeutic interventions for aortic coarctation". Grant-in-Aid Midwest Affiliate. 7/1/15-6/30/17 Role: PI. $142,816
2. NIH, "Mechanisms of morbidity after correcting aortic coarctations of varying severity". R01 4/1/15-3/31/20 Role: PI. (Scores: Impact=48, %=43; payline=21)
3. NIH, "Impact of native and treated CoA on vessel structure and function". R15 - AREA *resubmission*. 7/1/13-6/30/16 Role: PI. Unfunded (score=22; payline=20)
4. NIH, "Impact of native and treated CoA on vessel structure and function". R15-AREA. 12/1/12-11/30/15 Role: PI Unfunded (score=26, payline=20)

8) Curriculum Vitae for John F. LaDisa, Jr., Ph.D.

EDUCATION AND TRAINING

Postdoctoral Scholar, Pediatric Cardiology, Stanford University, CA, 2004-2006
Ph.D., Biomedical Engineering, Marquette University, Milwaukee, WI, 2004
M.S., Biomedical Engineering, Marquette University, Milwaukee, WI, 2001
B.S., Biomechanical Engineering, Marquette University, Milwaukee, WI, 2000

POSITIONS, EMPLOYMENT, RESEARCH AND PROFESSIONAL EXPERIENCE:

Aug. 2015 - present	Associate Professor of Medicine & Physiology, Medical College of Wisconsin
Aug. 2013 - present	Associate Professor with Tenure, Department of Biomedical Engineering, Marquette University
Jan. 2013 - present	Director - MARquette Visualization Laboratory (MARVL; www.eng.mu.edu/vizlab/)
Dec. 2007 - Aug. 2015	Assistant Professor, Department of Cardiovascular Medicine, Medical College of Wisconsin
Jan. 2007 - present	Director - Laboratory for Translational, Experimental and Computational Cardiovascular Research (CV T.E.C. Lab; www.eng.mu.edu/cvtec/)
Jan. 2007 - July 2013	Assistant Professor, Department of Biomedical Engineering, Marquette University
Sept. 2004-Dec. 2006	Postdoctoral Scholar, Department of Pediatrics - Division of Pediatric Cardiology, Stanford University
Aug. 2001-May 2004	Doctoral Candidate, Department of Biomedical Engineering, Marquette University
Aug. 1998-Aug. 2004	Research Technician, Department of Anesthesiology, Medical College of Wisconsin

AWARDS AND HONORS (Received during faculty position at Marquette University)

Feb 2015	40 Under 40 - Milwaukee Business Journal
July 2014	MS student Josh Hughey awarded 2nd place in the Biofluids category of the World Congress of Biomechanics poster competition - Boston
January 2013	e-learning Faculty Fellowship - Marquette University Center for Teaching & Learning.
Dec. 2012	2012 Editor's Choice paper - Journal of Biomechanical Engineering
Feb. 2012	Young Engineer of the Year - STEM Forward (F/K/A Engineers & Scientists of Milwaukee)
April 2010	2010 Rising Star Award - Sigma Xi Scientific Research Society
January 2009	The Next Generation: New leaders under 40 - Milwaukee Magazine
April 2008	Best Technology Business Plan Award Winner - 6th Kohler Center for Entrepreneurship Business Plan Competition, Marquette University

RESEARCH MENTORSHIP, THESIS AND DISSERTATION COMMITTEES

(Mentees since becoming faculty at Marquette University):

Undergraduate Research Mentor:

- William Wang (B.S. in Biomedical Engineering 2013 - Marquette University)
- Mia Helfrich (B.S. in Biomedical Engineering 2013 - Brown University)

- Michael Kamykowski (B.S. in Biomedical Engineering 2014 - Marquette University)
- Daphne Gutierrez (B.S. in Biomedical Engineering 2015 - Marquette University)
- Keelia Doyle (B.S. in Biomedical Engineering 2015 - Marquette University)
- Elise Hahn (B.S. in Biomedical Engineering 2018 - Marquette University)
- Sophia Shanahan (B.S. in Biomedical Engineering 2018 - Marquette University)
- Kathryn Repp (B.S. in Biology 2018 - Wake Forest University)

Master's Thesis Chair and Primary Advisor (see website for current student positions):

- Andrew Williams M.S. (B.S. Biomedical Engineering - Marquette University), Dec. 2008
- Ronak Dholakia M.S. (B.S. Biomedical Engineering - Univ. of Mumbai), Dec. 2009
- Sara Nomeland M.S. (B.S. Biomedical Engineering - Michigan Tech), August 2010
- Timothy Gundert M.S. (B.S. Biomedical Engineering - Marquette University), Dec. 2011
- DJ Quam M.S. (B.S. Biomedical Engineering - Marquette University), May 2012
- Sung Kwon (B.S. Biomedical Engineering - Univ. of Minnesota), Dec. 2013
- Joshua Hughey (B.S. Biomedical Engineering - Univ. of Missouri), May 2014
- Ali Aleiou (B.S. Biomedical Engineering - Univ. of Minnesota), 2012 - present
- Daniel Greenheck (B.S. Biomedical Engineering - UW Madison), Aug. - Dec. 2013
- Brandon Wegter (B.S. Materials Science - UW Milwaukee), 2014 - present
- John Venn (B.S. Biomedical Engineering - Michigan State), 2016 - present

Doctoral Dissertation Primary Advisor (see website for current student positions):

- Dave Wendell (B.S. Electrical Engineering - Purdue University), Dec. 2011
- Arjun Menon (B.S. Biomedical Engineering - Univ. of Minnesota), May 2012
- Hongfeng 'Nick' Wang (Doctor of Veterinary Medicine and M.S. in Embryonic Engineering, Northwest A&F University, China, M.S. in Genetics, Mississippi State University), May 2013
- Thomas Dienhart (B.S. Biomedical Engineering - Michigan Tech), 2012-13
- Scott Loberg (B.S. Biology - Winona State University), August - Dec. 2013
- Benjamin Dickerhoff (B.S./M.S. Biomedical Engineering - Univ. of Iowa), Dec. 2013 - present
- Atefeh Razavi (B.S./M.S. Mechanical Engineering, Yazd University, Iran; M.S. Biomedical Engineering, University of Arkansas), Aug. 2015 - present
- Jesse Garringer (B.S. Bioengineering, Univ. of Illinois - Chicago), Aug. 2016 - present

Doctoral Dissertation and Master's Thesis Committee Member:

- John A. Wheeldon BSEE MSEE, November 2008 (PhD)
- Jason J. Hallman, December 2010 (PhD)
- Zhuohui Gan, December 2011 (PhD)
- Daniel Stassi BS, July 2014 (MS)
- Sally Lin BS, May 2015 (MS, anticipated)

Postdoctoral Scholar(s):

- Laura Ellwein, Ph.D. (B.S. in Chemical Engineering from UW - Madison; Ph.D. in Interdisciplinary Physiology of Applied Math at North Carolina State University; Thesis advisor: Mette S. Olufsen, Ph.D.), 2009-2012
- Harkamaljot 'Rocky' S. Kandail, Ph.D. (Ph.D. in Chemical Engineering from Imperial College London, UK; Thesis advisor: Xiao Yun Xu Ph.D.) 2016 - present

GRANTS AND CONTRACTS

Received: 22 grants received to date. Total direct costs (DC): $1,688,308; with indirect costs (wIDC): $1,913,832

Current:

Marquette University Opus College of Engineering, "Modeling Chemical Deposition in the Human Airway from Electronic Cigarettes"
Legacy Initiative Research Seed Grant
DC: $75,000 wIDC $75,000 7/1/16-6/30/17 Role: Co-I, S. Singer (PI)

Medical College of Wisconsin Center of Imaging Research Intramural Pilot Award, "Magnetic Resonance Imaging for an experimental model of aortic coarctation"
DC: $5,000 4/27/16-4/26/16 Role: PI

Marquette University College of Engineering Summer Undergraduate Research Program, "2016 Summer Virtual Reality aiding in the Research of Stroke Rehabilitation"
DC: $4,820 5/27/13-8/9/13 Role: co-PI (with S. Schindler-Ivens)

Aurora Healthcare, Inc., "Evaluation of and prediction of complications after transcatheter aortic valve replacement using computational methods".
Sullivan Cardiac Research Award for Residents and Fellows
DC: $29,952 1/1/16-12/31/16 Role: Co-I (20% cost shared), Trivedi (PI)

American Heart Assoc., "Mechanistic analysis of mechanical alterations to improve therapeutic interventions for aortic coarctation". Grant-in-Aid Midwest Affiliate
DC: $129,832 wIDC: $142,816 7/1/15-6/30/17 Role: PI (1 summer mo)

Kobe University School of Medicine, "Optical coherence and computed tomography for evaluation of wall shear stress and thrombus potential in coronary arteries after stenting". Educational Research Agreement Supplement
DC: $37,000 01/01/15-5/31/16 Role: PI (as needed)

NSF University of Wisconsin-Milwaukee I-Corps Site, "Immersive Fitness by MARVL". Summer 2015 I-Corps Program
DC: $2,400 4/1/15-7/31/16 Role: project PI, Avdeev (site PI)

Marquette University College of Engineering (CoE), "Proposal for the purchase of an ILUMIEN optical coherence tomography (OCT) and pressure measurement system" CoE RFP for Research Equipment - revised
DC: $95,500 Role: PI

Marquette University, "Partnerships for Excellence through Advanced Visualization".
Innovation Fund
DC: $164,250 7/1/15-6/30/18 Role: PI

Marquette University, "ALIVE: the Assisted LIving Virtual Environment".
Innovation Fund
DC: $79,858 7/1/15-6/30/18
Role: faculty advisor (Student PIs: A. Barrington, M. Barrowclift, T. Pawlicki)

Pending:

NONE

Unfunded: 44 unfunded grants were authored since becoming faculty at Marquette University

PATENTS AND DISCLOSURES

- Progressive expansion diameter stent, disclosed to Stanford University April 2005
- Apparatus and method for minimizing flow disturbances in a stented region of a lumen - #US20080140179, published June 12, 2008 (abandoned)
- Gesture-based visualization system for biomedical imaging and scientific datasets - disclosed April 30, 2014. Patent pending.
- Ultra-High-Resolution Content for Immersive Fitness and Wellness - disclosed Oct. 20, 2015. Content licensed to Surround Fit & Wellness, LLC

PRESENTATIONS (from 30 offered since becoming faculty at Marquette University):

National:

"An efficient approach to playback of stereoscopic videos using a wide field-of-view." IS&T International Symposium on Electronic Imaging 2016 - Stereoscopic Displays & Applications Conference. Invited presentation. San Francisco. Feb. 17, 2016. *Awarded best use of stereoscopic content in a presentation*

"Optimizing mechanical stimuli around stents to reduce restenosis and thrombosis: MIT/Harvard Collaboration Discussion." Edelman lab meeting - Massachusetts Institute of Technology. Boston. July 9, 2014.

"Recent progress in the use of experimental and computational tools to optimize flow patterns around stents and reduce coronary artery restenosis" Department of Mechanical Engineering and Materials Science, Univ. of Pittsburgh, Oct. 15, 2013

"The Success of Aortic Arch Surgery: An Engineer's Perspective" American Heart Association Scientific Sessions 2011: Cardiovascular Seminar entitled Biomedical Engineering Insights into Congenital Heart Disease, Orlando, Nov. 15, 2011

"Coupling experimental and computational tools to quantify hemodynamic alterations introduced by stents" CardioVascular Innovation Seminar (CVIS) series, Medtronic CardioVascular, Santa Rosa, CA, Jan. 19, 2011

"Aortic coarctation: recent developments in experimental and computational methods to assess treatments for this *simple* condition." 1st International Conference on Computational Simulation in Congenital Heart Disease, San Diego, Feb. 27, 2010

"Coupling clinical and computational resources to quantify hemodynamic alterations as indices of morbidity and engineer novel treatment strategies for carotid artery disease", Penner Biomechanics Seminar, Department of Mechanical Engineering, University of California - San Diego, May 20, 2009

International:

"Analysis of hemodynamic stimuli, persistent vascular changes and gene expression in a rabbit model of human aortic coarctation and repair." 4th International Frontiers Conference on Pediatrics and Congenital Heart Diseases. Sponsored by Stanford University and INRIA. Paris, France. May 21-22, 2014.

"Reducing restenosis in challenging coronary lesions: optimization-based treatment planning and follow-up using immersive visualization." 9th International Symposium on Biomechanics in Vascular Biology and Cardiovascular Disease. Montreal, Canada, April 28-29, 2014.

"Combined use of imaging and computational techniques to investigate fluid dynamics in normal and stented coronary artery bifurcations" IMAGING & PHYSIOLOGY

Summit 2008, sponsored by the CardioVascular Research Foundation (CVRF), Seoul, Korea, November 22, 2008

Local:

"Choices & Freedom: Finding Balance in Academic Life" Marquette University Faber Center - Freedom and Choices in Academic Life Series, September 24, 2014

"Computational cardiology: using optimization and advanced visualization to reduce restenosis in challenging coronary lesions" MCW REU Friday Morning Lecture Series, June 27, 2014

"Reducing restenosis in challenging coronary lesions: optimization-based treatment planning and follow-up using advanced visualization techniques" First Look Forum 2014, May 29, 2014

"Your simulation ran...now what? Extracting simulation details using immersive visualization" High-Performance Computing seminar, Marquette University, April 2014

"Leveraging current imaging techniques for next-generation medical diagnosis, monitoring and treatment" Cultivating Innovation Symposium, GE Healthcare, Milwaukee, December 12, 2008

PEER-REVIEWED JOURNAL ARTICLES (from 44 since 2002; students & postdocs in bold)

Most relevant to the current application

1. Chiastra C, Wu W, **Dickerhoff B**, **Aleiou A**, Otake H, Migliavacca F, LaDisa Jr JF. Computational replication of the patient-specific stenting procedure for coronary artery bifurcations: from OCT and CT imaging to structural and hemodynamics analyses. J Biomech. 2016;49(11):2102-11. Special Issue CFD in Medicine & Biology II
2. **Gundert TJ**, Marsden AL, Yang W, Marks DS, LaDisa Jr JF. Identification of hemodynamically optimal coronary stent designs based on vessel diameter. IEEE Trans Biomed Eng 2012; 59(7):1992-2002. PMID: 22547450
3. **Gundert TJ**, Marsden AL, Yang W, LaDisa Jr JF. Optimization of cardiovascular stent design using computational fluid dynamics. *J Biomech Eng* 2012, Jan;134(1):011002 doi:10.1115/1.4005542. *1 of 9 papers selected to the 2012 Editor's Choice list*. PMID: 22482657
4. **Ellwein LM**, Otake H, **Gundert TJ**, Koo BK, Shinke T, Honda Y, Shite J, LaDisa Jr JF. Optical coherence tomography for patient-specific 3D artery reconstruction and evaluation of wall shear stress in a left circumflex coronary artery. *Cardiovasc Eng Tech*. 2011, 2(3):212-7.
5. **Gundert TJ**, Shadden SC, **Williams AR**, Koo BK, Feinstein JA, LaDisa Jr. JF. A rapid and computationally inexpensive method for assessing patient-specific hemodynamic alterations introduced by commercially available and next-generation stents. *Ann Biomed Eng* 2011; 39(5):1423-37. PMID: 21203844
6. LaDisa Jr JF, Olson LE, Molthen RC, Hettrick DA, Hardel MD, Pratt PF, Kersten JR, Warltier DC, Pagel PS. Alterations in wall shear stress predict sites of neointimal hyperplasia after stent implantation in rabbit iliac arteries. *Am J Physiol Heart Circ Physiol* 2005; 288(5):H2465-75. PMID: 15653759