A. Personal Statement

The general aim of our research program is to understand cellular and molecular mechanisms for in vivo cardiovascular phenomena. Our research encompasses experimental approaches at all levels – clinical, whole animal, organ, tissue, cell, and molecular. Our clinical study in human diabetics on intravascular ultrasound imaging of coronary atherosclerosis guides our studies in swine that superbly mimic human atherosclerosis. We primarily study ion transport adaptations in cardiac and vascular endothelial and smooth muscle cells after several in vivo manipulations: 1) dyslipidemia, 2) metabolic syndrome (“pre-diabetes”), and 3) diabetes. Each condition requires chronic treatment of intact animals and study of isolated tissues and single cells from these animals. Our in vivo (whole animal) studies involve hemodynamic and insulin sensitivity measures. We are the only research group in the world with a breeding colony of Ossabaw swine that express metabolic syndrome, progression to type 2 diabetes, and profound atherosclerosis. Organ level approaches utilize intravascular catheters, ultrasound, optical, and radiologic imaging, and localized gene targeting. Tissue level studies routinely involve culture of arterial segments and measurement of calcium and/or contraction. Typical cellular studies involve exposure of isolated cells to vasoactive agents in the metabolic syndrome and diabetic milieu (e.g. aldosterone), patch clamp electrophysiology, and fluorescence imaging. We have used multimodal nonlinear optical microscopy and vibrational photoacoustic imaging to characterize atherosclerotic lesions in our swine model. We are engineering catheters, drug delivery devices, diabetes monitoring devices, and new compounds for early detection and treatment of diabetes and diabetes-induced complications. One molecular approach we use is to localize molecules within tissues and cells using several modes of microscopic imaging. With molecular cloning we have identified a novel adenosine A₁ receptor, P2Y2 receptor, and TRPC channels that are regulated by several stressors and alter proliferation of coronary smooth muscle. We directly manipulate these potential molecular targets in vivo using drug-eluting stents and gene transfer via delivery catheters. A major goal is to prevent the progression of coronary smooth muscle Ca signaling from contractile to dedifferentiated proliferative and osteogenic phenotypes in coronary disease. Our proposed studies will rigorously compare coronary smooth muscle Ca signaling (review ref. 13) and coronary imaging in our unique swine model and humans.

B. Positions and Honors (selected; partial list)

Professional Positions and Employment

1980-1983 NIH Predoctoral Research Trainee, Exercise Science Program, University of Iowa
1982-1983 Assistant Laboratory Director and Instructor, Exercise Science Program, University of Iowa
1983-1986 NIH Predoctoral Research Trainee, Department of Pharmacology, University of Iowa
1986-1987 NIH Individual National Research Service Award Postdoctoral Fellow, Dept. Pharmacol. & Physiological Sciences, University of Chicago
1987 Research Associate, Department of Pediatrics, University of Chicago
1987-2000 Research Investigator, Dalton Cardiovascular Research Center, University of Missouri
1987-1993 Assistant Professor, Department of Physiology, School of Medicine, Univ. of Missouri
1993-1999 Associate Professor, Department of Physiology, School of Medicine, Univ. of Missouri
1999-2004 Professor, Dept. of Medical Pharmacology & Physiology, School of Medicine, Univ. of Missouri
2000-2004 Professor of Internal Medicine, School of Medicine, Univ. of Missouri
2002-2004 Associate Director of Basic Research, Center for Diabetes & Cardiovascular Health, U. Missouri
2010- Professor of Biomedical Engineering, Purdue University
2004- Professor and Chair, Dept. Cellular & Integrative Physiol., Indiana U. School of Medicine
C. Peer-Reviewed Publications or manuscripts in press (in chronological order)
Manuscripts relevant to proposal (15 selected; 52 in 2009-13 inclusive, 168 total; 294 abstract total)


D. Research Support

**STUREK, M.**

**COMPLETED (selected; partial list)**

<table>
<thead>
<tr>
<th>Project ID</th>
<th>PI</th>
<th>Start Date</th>
<th>End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>R01 HL020605</td>
<td>Bohlen</td>
<td>7/07-7/11</td>
<td></td>
</tr>
<tr>
<td>NIH/NHLBI</td>
<td>Microvascular regulation during intestinal absorption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major goals: Determine the mechanism, including localized endothelial intracellular Ca and Na, by which hypoxia causes release of nitric oxide in microcirculation and produces vasodilation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role: Co-I</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| R56 HL078715 | Park | 9/09-9/11 |
| NIH/NHLBI | Layer-by-layer assembly for making drug-eluting stents |
| Major goals: Design the most efficacious drug-eluting stent that optimizes inhibition of smooth muscle growth and stimulation of endothelial cell growth, which should minimize restenosis and in-stent thrombosis. |
| Role: Co-I (subcontract with Purdue University) |

| R01 HL092048 | Kassab | 7/09-7/13 |
| NIH/NHLBI | CT-based diagnosis of diffuse coronary artery disease |
| Major goals: Compare computed tomography assessment to intravascular ultrasound measures of diffuse coronary artery disease in Ossabaw miniature swine with metabolic syndrome and human patients. |
| Role: Co-I |

| R01 HL092245 | Tune | 7/09-7/13 |
| NIH/NHLBI | Mechanisms of coronary microvascular dysfunction in metabolic syndrome |
| Major goals: Determine K channel mechanisms of microvascular dysfunction in metabolic syndrome. |
| Role: Co-I |

| (Alloosh, PI) | Merck Sharp & Dohme Corp. | 3/12-12/13 |
| NIH/NHLBI | Pathogenesis of hypertension in metabolic syndrome Ossabaw swine |
| Major goals: Determine blood pressure and electrocardiographic changes in metabolic syndrome Ossabaw swine and assess the model with standard of care anti-hypertensive drugs spironolactone and nifedipine. |
| Role: Co-I |

**ACTIVE**

| T32 HL079995 | March | 7/10-7/15 |
| NIH/NHLBI | Training in vascular biology and medicine |
| Major goals: Provide postdoctoral vascular biology training to PhD, MD, or DVM fellows from an interdisciplinary perspective, emphasizing translation of basic research into clinical research and practice. |
| Role: Associate Director and mentor |

| UL1 RR025761 | Shekhar | 10/13-10/18 |
| NIH/NCRR | Indiana Clinical and Translational Sciences Institute |
| Major goals: Establish a statewide Institute for enhancing clinical and translational research in Indiana, proposed by Indiana University in partnership with Purdue University and several key community organizations. |
| Role: Co-I |
Mechanisms of glycemic improvement following gastrointestinal surgery
Major goals: Determine in obese Ossabaw miniature swine with metabolic syndrome whether “upper” vs. “lower intestinal hypotheses” may explain the improvement of glycemic status independent of changes in food intake or body weight after Roux-en-Y bariatric surgery.
Role: Co-I (subcontract with University of Washington)

Role: PI

Purdue-Indiana University Comparative Medicine Program
Ossabaw Swine Facility
Major goals: Selectively breed and produce Ossabaw miniature swine predisposed to metabolic syndrome (pre-diabetes) and type 2 diabetes. Swine are phenotyped by metabolic using metabolic, endocrine, and cardiovascular criteria. Revenue generated supplements extramurally funded research.
Role: PI

R01 HL062552 (Sturek, PI) 4/10-4/15
NIH/NHLBI
Exercise, diabetes, and coronary smooth muscle Ca2+
Major goals: Determine adenosine A1 and P2Y2 receptor regulation and Ca signaling mechanisms and the role of aldosterone underlying the coronary smooth muscle adaptations in metabolic syndrome pigs after atherosclerosis, coronary stenting, and exercise training.
Role: PI

R01 HL106792 (Panitch, PI) 4/11-4/15
NIH/NHLBI
Improved therapeutics for drug eluting stents
Major goals: A peptidoglycan will be delivered via a porous balloon catheter to inhibit coronary thrombosis and restenosis.
Role: Co-I (subcontract with Purdue University)

R21 RR032384 (Cheng, PI) 7/11-7/14
NIH/NHLBI
Vibrational photoacoustic microscopy for bond-selective tissue analysis
Major goals: Develop an intravascular catheter for vibrational photoacoustic imaging of atherosclerosis in a swine model of metabolic syndrome.
Role: Co-I (subcontract with Purdue University)

R01 HL115140 (Obukhov, PI) 4/12-4/17
NIH/NHLBI
TRPC channels in the metabolic syndrome
Major goals: Determine TRPC channel signaling mechanisms underlying coronary artery vasospasm
Role: Co-I

R01 HL112883 (Seye, PI) 4/12-4/17
NIH/NHLBI
Purinergic signaling in atherosclerosis
Major goals: Determine the role of P2Y2 nucleotide receptors in vascular smooth muscle, endothelial, and blood cells in atherosclerosis.
Role: Co-I

Sturek, PI) 9/13-9/14
Cardiometabolic Disease Research Foundation
Epicardial fat and coronary artery disease 2
Major goals: Determine the role of epicardial fat in coronary atherosclerosis.
Role: PI