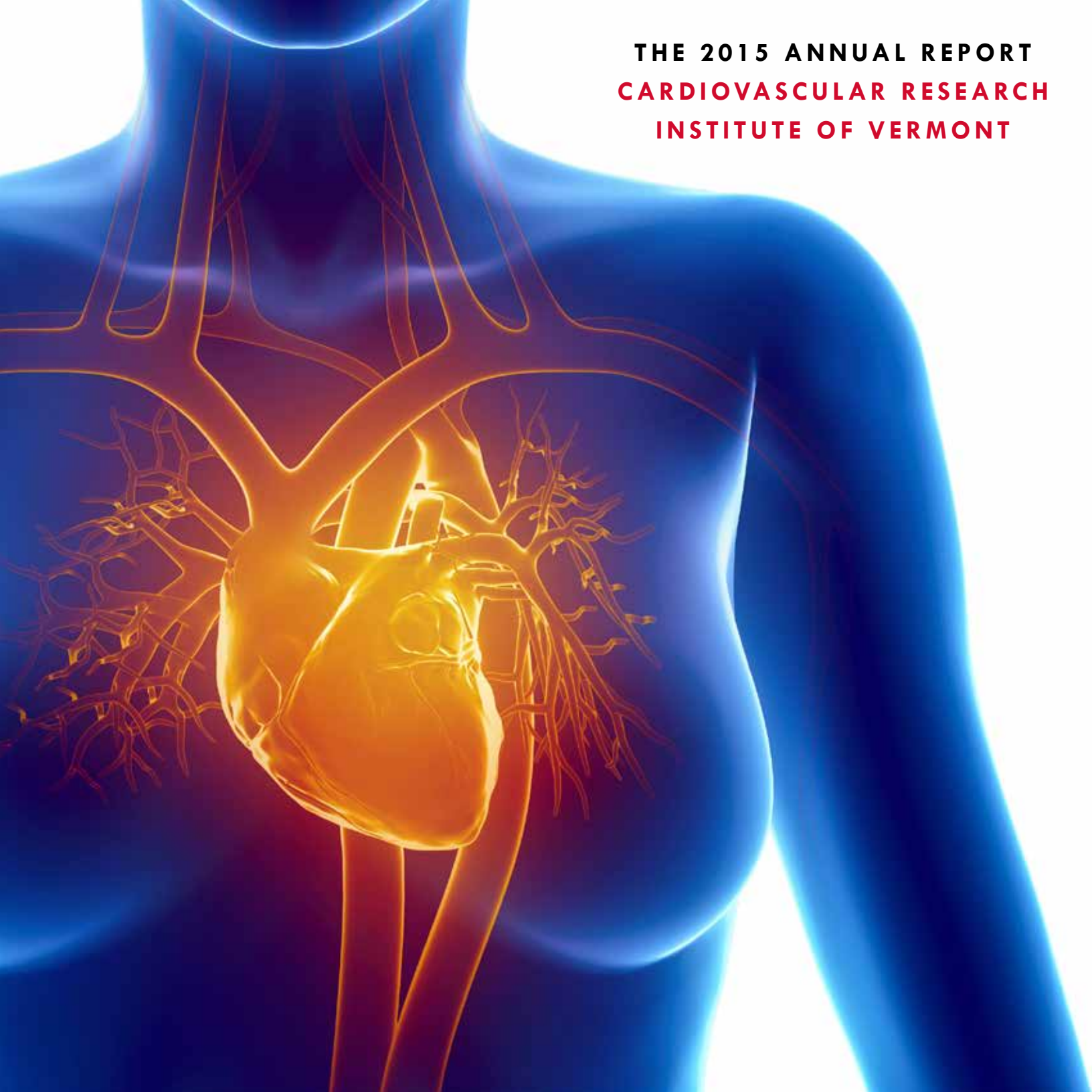
THE 2015 ANNUAL REPORT

CARDIOVASCULAR RESEARCH INSTITUTE OF VERMONT



THE CARDIOVASCULAR RESEARCH INSTITUTE OF VERMONT is dedicated to reducing the incidence, morbidity, and mortality of heart and vascular diseases through improving prevention, diagnosis, and treatment.

By fostering collaborations among departments at The University of Vermont and The University of Vermont Medical Center, the Cardiovascular Research Institute of Vermont encourages the critical thinking that challenges assumptions and promotes excellence in clinical practice.

CONTENTS

Cardiovascular Research Institute of Vermont

MESSAGE FROM THE DIRECTOR

During 2015, the Board of Directors of the Cardiovascular Research Institute of Vermont (CVRI) developed a five-year strategic plan. The Board used a retreat to review cardiovascular research at the University of Vermont and advance a strategy designed to further our mission of fostering cardiovascular research.

The Board noted that the University of Vermont is internationally recognized for research in vascular biology (including thrombosis) and cardiac muscle. A key element of the strategic plan is to enhance cross-disciplinary and cross-departmental research that encompasses the translation of basic and clinical research into improved care of patients. To that end, the Board established two sections – vascular biology and cardiac muscle. Co-leaders of each section were identified whose combined expertise would span the translation of basic and clinical research. For vascular biology, the section leaders are Marilyn Cipolla, Ph.D., and Ira Bernstein, M.D. For cardiac muscle, the section leaders are David Warshaw, Ph.D., and Peter VanBuren, M.D. Each section will develop focused strategic plans that include process metrics. Both the plans and the metrics of success will be reviewed annually by the Board of Directors.

As you will see from the pages that follow, the section leaders are working from a position of strength as they seek to enhance cardiovascular research at the University of Vermont. Our annual report highlights research accomplishments including publications and actively funded research projects during 2015. Because collaboration can yield synergistic advances, a key focus of the CVRI is to connect cardiovascular researchers both within the University of Vermont as well as in the broader scientific community.

David J. Schneider, M.D., F.A.C.C., F.A.H.A.

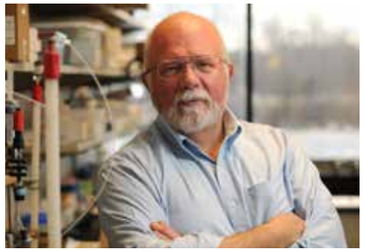
Director
Cardiovascular Research
Institute of Vermont

Professor of Medicine
University of Vermont College of Medicine

Director of Cardiovascular Services
University of Vermont Health Network

Cardiovascular Research News

TRACY RECEIVES AHA DISTINGUISHED SCIENTIST AWARD



CVRI Distinguished Investigator and Professor of Pathology and Laboratory Medicine **Russell Tracy, Ph.D.**, was awarded the Distinguished Scientist designation by the American Heart Association (AHA)/ American Stroke Association (ASA) during the AHA 2015 Scientific Sessions in November 2015 in recognition of his significant, original and sustained scientific contributions that have advanced the association's mission of "building healthier lives, free of cardiovascular diseases and stroke." Tracy is an AHA Fellow.

The director of the Laboratory for Clinical Biochemistry Research and a member of the UVM Medical Center Board of Trustees, Tracy served as senior associate dean for research and academic affairs at the College of Medicine from 2001 until 2009, and in that same position in an interim capacity from 2014 to 2015.

After completing a Ph.D. from Syracuse University and a postdoctoral fellowship at the Mayo Clinic, Tracy began work in cardiovascular clinical trials and, in the late 1980s, added epidemiological science, focusing on coagulation, inflammation and adaptive immune systems in cardiovascular disease (CVD), and other chronic diseases. His contributions include increasing understanding of inflammation in atherosclerosis and as a major cause of CVD and non-CVD morbidity and mortality in "well-controlled" HIV infected individuals. A leader on many major studies, including the Cardiovascular Health Study; the Multi-Ethnic Study of Atherosclerosis; and the National Heart, Lung and Blood Institute's Heart Failure Network, HIV-Cardiovascular Disease Consortium, and Exome Sequencing Program, he has been NIH-funded since 1984 and has more than 600 scientific publications. His numerous honors include the American Association of Clinical Chemistry Bernie Zak Award for Research.

CIPOLLA AND ADES NAMED 2015-16 UNIVERSITY SCHOLARS

Professor of Medicine **Philip Ades, M.D.**, and Professor of Neurological Sciences **Marilyn Cipolla, Ph.D.** were honored as University Scholars for 2015-16 by the University of Vermont Graduate College in recognition of their "sustained excellence in research, creative and scholarly activities."

Both professors have led extensive and internationally pioneering research in their fields – Ades in cardiac rehabilitation and Cipolla in brain blood vessel injury.

A cardiologist, Ades directs the UVM Cardiac Rehabilitation Program where he cares for patients and conducts research. With ongoing National Institutes of Health support, he began a series of studies in the late 1980s examining the benefits of exercise for patients who had had a heart attack or coronary bypass surgery. The research has focused on those at highest risk – older patients, women over 65, overweight patients and most recently, the low-income population. His latest work targets Medicaid patients with an aim to improve patient participation in a cardiac rehabilitation prescribed exercise and prevention regimen using incentives.

Cipolla, who has devoted much of her career to determining the causes of eclampsia – a life-threatening complication of pregnancy marked by seizures, coma and sometimes death – has examined neurotransmitter receptors that become more "excitatory" in the brain during pregnancy and the role of transporters through the blood-brain barrier in eclampsia. Her work on blood vessel malfunctions in the brain also informs her study of ischemic strokes. Ades is a CVRI Distinguished Investigator and Cipolla is a member of the CVRI Board of Directors.

Marilyn Cipolla, Ph.D. and Philip Ades, M.D.

Bruce Leavitt, M.D., with a patient during a surgical mission.

LEAVITT RECEIVES NEW ENGLAND SURGICAL SOCIETY NATHAN SMITH DISTINGUISHED SERVICE AWARD

University of Vermont Professor of Surgery and cardiothoracic surgeon **Bruce Leavitt, M.D.**, received the New England Surgical Society's 2015 Nathan Smith Distinguished Service Award in fall 2015.

The award is named in honor of Rehoboth, Mass. native and Upper Connecticut Valley surgeon Nathan Smith, who was born in 1762 and helped develop the specialty of surgery and was instrumental in the establishment of the country's first medical schools, including the UVM College of Medicine and Dartmouth Medical School. Smith also served as a surgeon and faculty member at the then-new Yale Medical School.

After earning his medical degree at UVM, Leavitt completed residencies in general surgery at Maine Medical Center and in cardiopulmonary surgery at SUNY Health Sciences Center in Syracuse, N.Y., and joined the UVM faculty in 1988. He has served as vice chairman of the UVM Medical Group Board, as president of the Vermont Chapter of the American College of Surgeons and as Vice President of the New England Surgical Society.

In addition to teaching in the College of Medicine's Foundations level and Surgery Clerkship and mentoring surgery majors and residents, Leavitt has been instrumental in translational multicenter studies involving all the major medical centers in the region and also engaged in several translational multidisciplinary UVM research projects. A member of the Northern New England Cardiovascular Research Consortium, he has been on eight surgical missions, including trips with Team Heart Cardiac Surgery to Rwanda, and with Doctors Without Borders to Sri Lanka and Nigeria.

UNEXPECTED HEALTH DISCOVERY LEADS TO STROKE RESEARCH GIFT

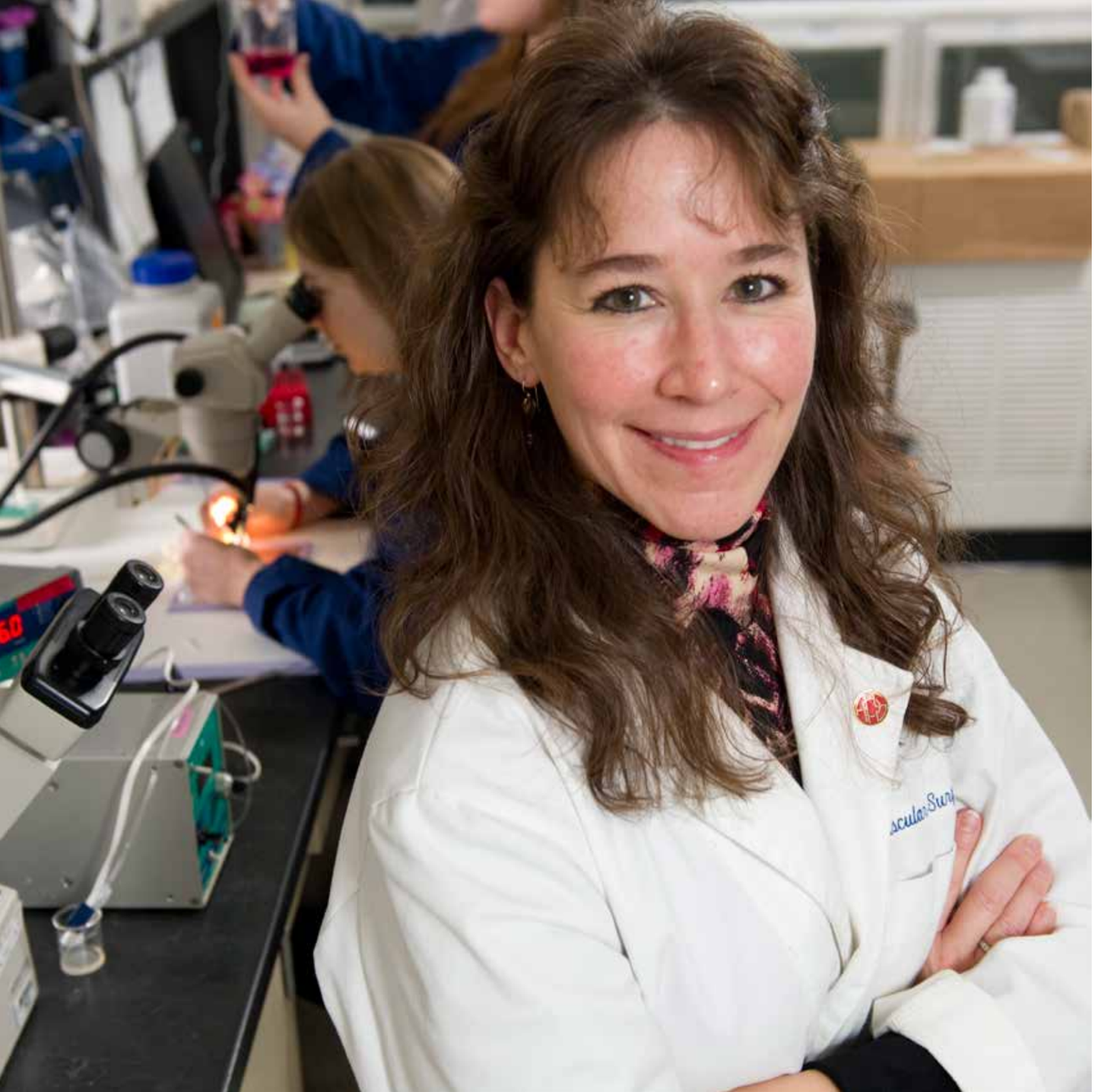
A chance occurrence involving philanthropy workshop presenter Joe Golding, CEO of Advancement Resources, Yael Friedman, a major gift officer for Academic Health Sciences at UVM, and **Mary Cushman, M.D., M.Sc.**, director of the UVM Thrombosis and Hemostasis Program and CVRI Board of Directors member, led to a $25,000 gift for research.

Following his presentation to UVM faculty and health providers, Friedman noticed Golding suffering leg pain. Worried it could be a blood clot, and knowing that Cushman would be at Golding's next presentation, she had Cushman examine Golding's leg when she arrived.

"His leg looked terrible," said Cushman, who arranged for an ultrasound that afternoon, which found no blood clot. The scan showed a mass in Golding's chest, which was later diagnosed as lymphoma upon his return home to Iowa. He credits his survival from lymphoma to Friedman and Cushman's efforts, and calls it "a life-changing experience."

As thanks, he and his wife donated $25,000 to a stroke research project under Cushman's watch being conducted by Kara Landry, M.D.'15, then a fourth-year UVM medical student and currently a UVM neurology resident and CVRI Early Career Advisory Committee member. Golding, whose grandfather had had a severe stroke, said "I truly believe that philanthropy is all about engagement. And Mary was willing to listen and never shut me down as we talked, which takes the engagement beyond care."

From left: Kara Landry, M.D., Cindy Golding, Joe Golding, and Mary Cushman, M.D., M.Sc.



Vascular Biology and Thrombosis

The circulatory system of the human body is the setting for many disease conditions that can benefit from research into the vessels themselves, and the clotting that can occur within them.

IDENTIFYING THE IMPACT OF STROKE-INDUCED BLOOD SUBSTANCES

Most strokes – about 87 percent of all cases – are caused by a blocked blood vessel, which not only injures the brain, but also triggers inflammation and the release of stress-related substances into the blood. **Marilyn Cipolla, Ph.D.**, professor of neurological sciences, along with Isabella Canavero, M.D., a neurology resident from Pavia, Italy, and Helene Sherburne, a Dartmouth College student, investigated how those substances might affect the blood vessels in the brain that were not directly impacted by the stroke and elsewhere in the body. The results of their research, published in January 2016 in the journal *Translational Stroke Research*, found that healthy blood vessels became more constricted when filled with serum from the blood of ischemic stroke patients.

"It is a very simple idea of asking these very simple questions about circulating factors in post-stroke patients," says Cipolla, yet "nobody's done this before."

The researchers used serum obtained from three subtypes of ischemic stroke patients: those with large vessel disease; those with large vessel disease with high blood pressure; and those with cardioembolic stroke – a type of ischemic stroke in which the clot originates in the heart and migrates to the cerebral vessels – as well as high blood pressure. Serum that was taken at 24 hours post-stroke was perfused into healthy rat blood vessels. The effect of serum from these different stroke patients was compared between blood vessels from the brain (cerebral) and gut (mesenteric).

Serum from all three types of stroke patients – compared against a control of a normal saline solution – caused the cerebral arteries to constrict or increase in tone, which could potentially reduce blood flow. Brain vessel tone increased the most with the serum from the patients with cardioembolic stroke. To a lesser degree, tone increased in the gut vessels with serum from the patients with cardioembolic stroke and large vessel disease without hypertension.

The significance of the vasoactive effect of stroke serum in non-ischemic vessels is unknown. Cipolla believes further research should explore the characteristics of the serum that cause the increase in tone and whether it negatively impacts outcome. Scientists also could look at the significance of this change, how these circulating factors affect blood flow in the other regions of the brain unaffected by the stroke, and perhaps uncover ways to minimize that effect.

"So, if a vasoconstricting agent is being produced," Cipolla says, "we could probably inhibit it with therapies." Whether these factors are detrimental due to reducing blood flow in normal tissues, or beneficial due to helping in the repair process is not known, but may be important to understand for future therapies.

Left: Marilyn Cipolla, Ph.D.

UVM researchers (from left to right) Thomas Moon, Ph.D., former UVM postdoctoral fellow; Jessica Sheehe, Cellular, Molecular and Biomedical Sciences graduate student; Wolfgang Dostmann, Ph.D., professor of pharmacology; Nathan Tykocki, Ph.D., assistant professor of pharmacology; and Joseph Brayden, Ph.D., professor of pharmacology.

PATENTED MOLECULE COULD LEAD TO NEW HYPERTENSION THERAPY

Sometimes serendipity can play a role in research. That was the case with UVM Professor of Pharmacology **Wolfgang Dostmann, Ph.D.**, and colleagues, in a process that led to a patent award for the discovery of a molecule that rescues damaged blood vessels, yet preserves healthy vessels. The work, which was published in *Chemistry & Biology* in December 2015 could serve as a springboard for a new pharmaceutical therapy for hypertension with fewer side effects.

The research team, including Professor of Pharmacology **Joseph Brayden, Ph.D.**; former postdoctoral fellows **Brent Osborne, Ph.D.**, and **Thomas Moon, Ph.D.**; Assistant Professor of Pharmacology **Nathan Tykocki, Ph.D.**; and graduate student **Jessica Sheehe**, were studying the atomic structure of the major target for the enzyme cGMP when they learned how protein kinase 1alpha (PKG 1α) could be regulated not only by its natural activator – cGMP – but also by a series of carefully designed short synthetic peptides – called "S-tides." These S-tides demonstrate a range of efficacy and are highly specific for the PKG 1α subtype critical for arterial relaxation and blood pressure regulation. The researchers determined that when applied directly to arteries harvested from animal models, S-tides activated critical biological signaling components related to PKG 1α activation, which in turn led to a prevention of the pressure-induced constriction of the vessels that causes high blood pressure.

Dostmann explains that drugs like nitroglycerine and Viagra – the latter was originally developed to treat blood pressure – all act on this signaling pathway and are designed to keep intracellular cGMP molecules at an elevated level. In contrast, he adds, S-tides do not change the endogenous levels of cGMP. The group's development of first-in-class PKG-targeted therapies could lead to treatments for more diseases than just high blood pressure, because the type 1α cGMP-dependent PKG has been shown to be relevant in cancer, obesity, chronic obstructive pulmonary disorder (COPD) and all forms of cardiovascular disease, and the signaling pathway involved in this mechanism has historically been a target for drug development.

An additional surprise the group uncovered: only small arterial vessels were affected by these molecules if the tissue lining the blood side was damaged – what is known as arterial dysfunction. Atherosclerosis, a condition marked by plaque buildup in the arteries, is a more common example of arterial dysfunction.

"The peptides rescue the damaged vessels, but they have no effect on the healthy vessels," says Dostmann. The team is currently generating peptide libraries for further study and intends to collaborate with medicinal and computational chemists to screen compound libraries to gain leads on how to develop more potent activators.

"This therapeutic pathway has huge potential for the average person, since about 30 percent of people develop hypertension or cardiovascular disease in their lifetime," Dostmann says.

UNCOVERING INTERVENTION OPPORTUNITIES FOR NEUROLOGICAL DISEASE

In fall 2013, Marie-Germaine Bousser, M.D., the renowned neurology chief at Hospital Lariboisière in Paris, approached UVM's **Mark Nelson, Ph.D.**, at a conference with a concern. Dr. Brousser, who identified the gene responsible for a rare small vessel disease in the brain -- called CADASIL, an anagram for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy -- expressed her frustration that, two decades after the identification of CADASIL, she had little new information to offer her patients about the mechanisms and progression of the disease, which can cause heightened risk of recurring strokes. CADASIL is rare, affecting about 1 in 50,000 people. But research into it could more widely inform the study of stroke and dementia.

In the years since that discussion with Bousser, Nelson, who is Chair and University Distinguished Professor of Pharmacology at UVM has, as part of an international research team, studied CADASIL and other small artery diseases in depth, focusing on uncovering what occurs in the brains of people born with the genetic mutation of a protein known as Notch3.

"It's a cascade of things that happen afterward," says Nelson.

The 10-person team's research is supported by a Transatlantic Networks of Excellence grant worth about $6 million from Fondation Leducq, an organization based in Paris that supports efforts to combat cardiovascular and neurovascular disease. Nelson oversees the work in North America, and his longtime collaborator at the University of Paris, Anne Joutel, M.D., Ph.D., directs their activities in France and Germany.

Joutel and colleagues developed a new mouse model with the human mutation for CADASIL, which exhibits the pre-clinical CADASIL pathology. Since they received the five-year Leducq grant in October 2012, the team of investigators has focused on the disease progression starting early in life, and thereby has gained crucial information about its effects on blood flow and role in brain function.

The researchers found that they can restore some normal blood flow within the tiniest arteries within the brain by correcting the early deficits caused by CADASIL. And if they can control function, Nelson says, that suggests the possibility of controlling and diminishing the consequences of the disease at an early stage and throughout a patient's life. Their findings were published in the journal *PNAS* in 2015.

That's "the holy grail of this area," Nelson says. "It puts us in the position of now having targets for intervention."

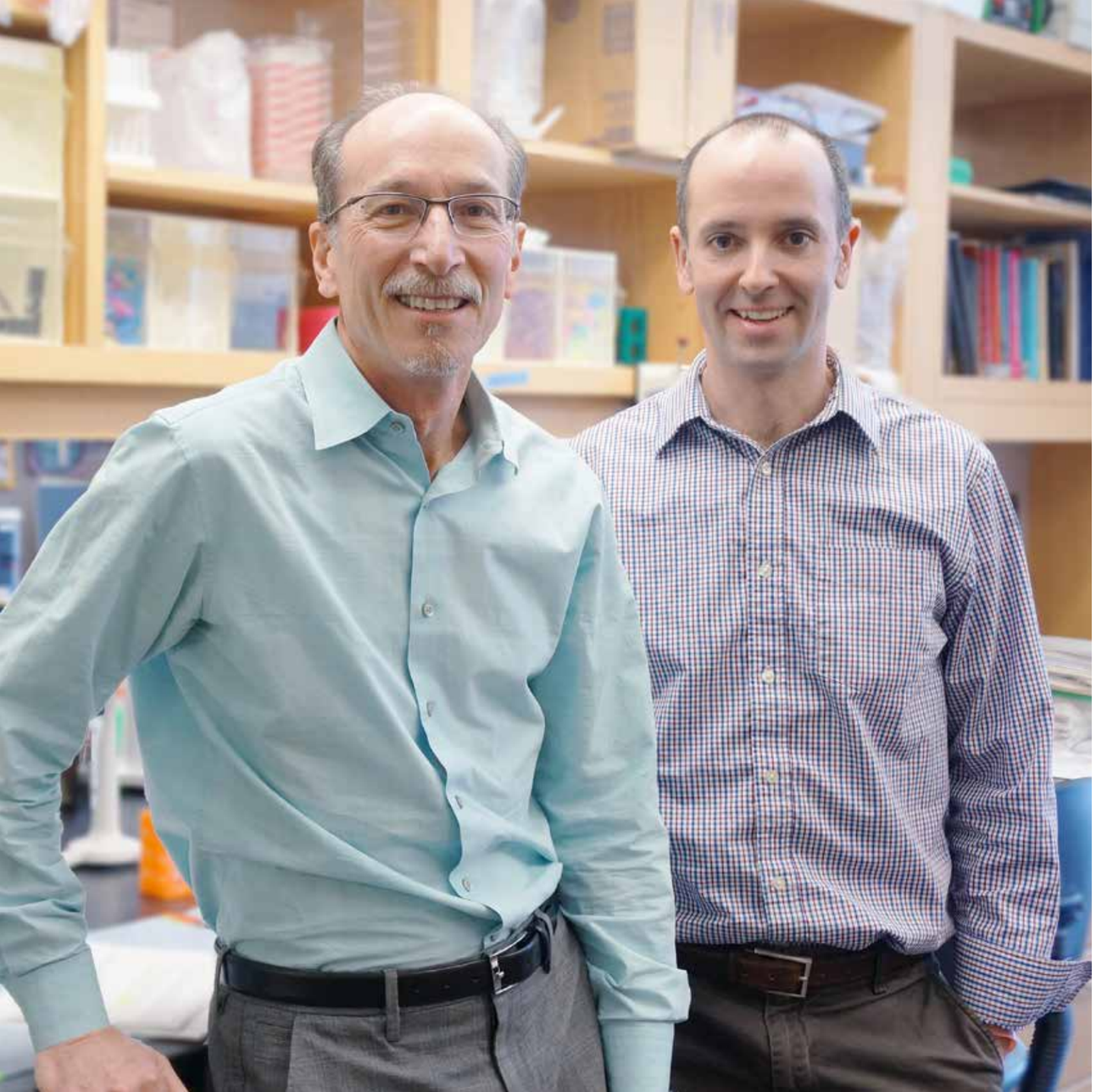
One function researchers managed to restore is functional hyperemia, the process by which the brain rapidly and precisely supplies extra blood to regions needed for motor control and cognition, such as the ability to recognize someone's face.

"The parts of the brain that are working need blood immediately," Nelson says.

Nelson and his colleagues recently received a Horizon 2020 grant from the European Union, which provides funding to translate research and innovation from the lab to the marketplace and – in this case – to patients.

"This is a window into the more common, sporadic small vessel disease that affects millions of people," Nelson says. "We're now making very significant inroads."

Mark Nelson, Ph.D.



From left: David Warshaw, Ph.D., and Michael Previs, Ph.D.

Cardiac Muscle

The distinct qualities of cardiac muscle are the focus of several researchers at the CVRI. They probe the make-up of this muscle type, the conditions that cause it to mutate or fail, and ways to repair its damage.

A POTENTIAL TREATMENT TARGET FOR A DEADLY CARDIAC MUTATION

New research by Chair of Molecular Physiology and Biophysics **David Warshaw, Ph.D.**, and Assistant Professor **Michael Previs, Ph.D.**, moves a step closer to a possible new treatment to address the underlying root cause of familial hypertrophic cardiomyopathy, an inherited disease that causes the heart muscle to thicken and struggle to pump blood. Their study, published recently in the *Proceedings of the National Academy of Sciences*, provides insight into what happens structurally in the heart when there is a mutation in a protein critical to the heart's pumping process.

Warshaw and Previs examined the function of cardiac myosin-binding protein C (cMyBP-C), one of the key controls of the heart's contraction and relaxation functions, and found that phosphorylation – or the addition of phosphate at a key link in the cMyBP-C protein chain – alters the protein's structure and ensures that it effectively facilitates heart-pumping.

In cases of hypertrophic cardiomyopathy (HCM), a frequent cause of sudden death in young athletes, cMyBP-C lacks phosphorylation, though it is not clear why this is the case. Without phosphorylation, cMyBP-C becomes overactive; it allows the heart muscle to contract too vigorously, such that it then cannot relax and fill with blood – a condition known as diastolic dysfunction.

Using a car engine analogy, the researchers describe cMyBP-C as the driver's foot, regulating the speed by stepping on the gas pedal to rev up the mechanism that makes the heart contract. Specifically, it enhances the presence of calcium inside the trillions of microscopic cells that make up the heart muscle.

In each of those cells, calcium allows one protein – myosin, the heart's molecular motor – to move another protein – actin – to make the heart contract. As soon as the calcium level is high enough to trigger contraction, cMyBP-C switches its role to put on the brakes, forcing myosin to release the actin, which slows down the heart's engine so that it can refill with blood.

Warshaw and Previs's new research shows structurally what happens: Phosphorylation changes the shape of cMyBP-C, from an elongated string of molecules to a folded, or "closed," chain. The cMyBP-C is elongated when it revs up and is closed when it brakes.

Phosphorylation helps the protein accelerate and downshift smoothly so, when it's in high gear, it won't brake too quickly and make a hard stop or jerky movement. Without phosphorylation, it's a bumpy ride, with the heart not functioning as well.

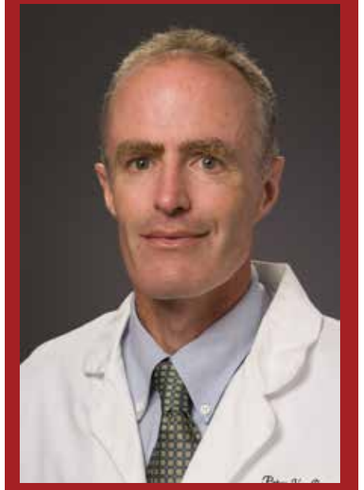
Many HCM cases stem from cMyBP-C mutations where phosphorylation levels are low. The new study shows that, even if the protein is normal, the lack of phosphorylation leads to the same problem – the heart never relaxes and struggles to fill with enough blood to pump adequately.

These findings suggest a possible new therapy, a chemical way to provide phosphorylation and, essentially, keep the engine tuned. Pharmaceutical companies are now paying attention to cMyBP-C, Warshaw says.

The team's next step is to determine the reason why phosphorylation changes the structure of cMyBP-C. "To just say that it happens isn't enough," Warshaw says. "We want to know why."

HEART FAILURE RESEARCH CONTRIBUTES TO IMPROVED PATIENT CARE

Martin LeWinter, M.D.



Peter Van Buren, M.D.

The origin of a common abnormality in heart failure patients called diastolic dysfunction remains a mystery, and cardiologists have no current therapies to treat it. Professor of Medicine **Martin LeWinter, M.D.**, and Associate Professor of Medicine **Peter Van Buren, M.D.**, are working to change this situation.

Diastolic dysfunction, marked by the left ventricle's inability to relax properly and adequately fill with blood before it pumps, primarily occurs in patients with a history of high blood pressure. In a recent *Circulation* study coauthored by LeWinter and Van Buren, they examined the effects of high blood pressure and other factors contributing to this problem by comparing three groups of patients – those with high blood pressure with and without heart failure and those with neither high blood pressure nor heart failure.

"We looked at the mechanisms of why the heart stiffens or fails to relax normally in these patients," says LeWinter, who is internationally known for his work in heart failure. "It turns out it's a really complicated business."

Some of these patients are elderly, have high blood pressure and occasionally consume too much salt, leading to acute heart failure with severe trouble breathing, says Van Buren. Other patients have metabolic syndrome – a combination of overweight, diabetes and high blood pressure – but often only show heart failure symptoms like shortness of breath during exercise.

By obtaining heart biopsies in patients undergoing coronary bypass surgery, the researchers identified, for the first time, molecular indicators of left ventricular stiffness in human subjects with high blood pressure, confirming previous studies in animal models. The study suggests the potential for early diagnosis and intervention to reduce long-term mortality.

"If we are both lucky and good, we will receive a grant to effectively treat these people," LeWinter says, who wrote a proposal with colleague Philip Ades, M.D., director of UVM's cardiac rehabilitation program. The researchers hope to examine the benefits of a sustained exercise and diet program for reducing diastolic dysfunction in patients with high blood pressure – before they develop heart failure.

By obtaining heart biopsies in patients undergoing coronary bypass surgery, the researchers identified, for the first time, molecular indicators of left ventricular stiffness in human subjects with high blood pressure.

This work enhances the UVM Medical Center's reputation as a leader in treatment of heart failure. A 2015 *U.S. News & World Report* hospital ratings report ranked UVM Medical Center as "high-performing" in heart failure care, following an evaluation of more than 4,500 U.S. institutions. UVM's low rates of readmission and infections were strengths. Only 10 percent of the hospitals earned this rating.

UVM's success in cardiology, LeWinter says, has even more to do with making sure patients get appropriate treatment with the right medications in the right amounts.

Van Buren is seeking funding to study torsemide, a drug he prescribes that he thinks might work better than furosemide. Both are diuretics that help the kidneys excrete excess water and salt in the urine.

Harold Dauerman, M.D.

DAUERMAN TEAM FINDS TAVR PROVIDES MARKED IMPROVEMENT FOR PATIENTS

Early findings from CoreValve® Pivotal Trial-related research conducted by CVRI board member **Harold Dauerman, M.D.**, UVM professor of medicine and interventional cardiologist, and colleagues was presented at a moderated poster session during the American College of Cardiology Scientific Sessions and Expo held in Chicago, Ill. in April 2016.

This new research, which examined a group of aortic stenosis patients with reduced left ventricular (LV) ejection who were treated with Transcatheter Aortic Valve Replacement (TAVR) technology, a therapy that received FDA approval in June 2015.

Aortic stenosis is a condition in which the heart's aortic valve is narrow, or does not fully open, causing decreased blood flow and increased work for the heart, often leading to chest pain and ultimately, heart failure. Approximately one-third of patients suffer from symptomatic aortic stenosis have reduced left ventricular ejection fraction (LVEF).

The TAVR procedure involves attaching an artificial aortic heart valve to a wire frame, which is then guided by a thin, flexible tube – a catheter – to the heart. When it gets to the appropriate location in the heart, the wire frame expands, allowing the new aortic valve to open and begin to pump blood.

The researchers studied 156 patients from the CoreValve extreme-risk/high-risk trials who had an LVEF measurement of 40 percent or less. Via cardiac ultrasound, patients were assessed at baseline, post-TAVR procedure, at discharge, and 30 days, six months and one year post-procedure. The team found that early LVEF recovery, which was defined as "an absolute increase of 10 percent or more in EF," occurred in more than 62 percent of the patients, generally prior to discharge, and was sustained through the first year in 70 percent of the trial participants.

Dauerman and his team concluded that "Nearly two thirds of patients with reduced LVEF will have a marked early improvement after TAVR. Early LVEF recovery is associated with improved clinical outcomes and is most likely among patients with higher baseline aortic valve gradients."

Scholarly Events

The Cardiovascular Research Institute of Vermont (CVRI) brings outstanding scientists in cardiovascular medicine to the University of Vermont as Visiting Professors. These visits include a major lecture and a series of interactions with trainees and junior investigators.

CVRI RESEARCH SEMINARS

September 22, 2015

Mysteries of the Endothelium, More Secrets Unraveled

GAUTUM CHAUDHURI, M.D., Ph.D.

Professor and Chair, Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles

October 2, 2015

In Vivo Diagnosis of Plaque Erosion: Insights from Optical Coherence Tomography

IK-KYUNG JANG, M.D., Ph.D.

Professor of Medicine at Harvard Medical School and Interventional Cardiologist, Division of Cardiology, Massachusetts General Hospital

February 5, 2016

Translating Effective Lifestyle Interventions into Practice: Lessons from the Hopkins-Healthways Collaboration

LAWRENCE APPEL, M.D., M.P.H.

The C. David Molina, M.D., M.P.H. Professor of Medicine, Epidemiology, Nursing, and International Health and Director of the Welch Center for Prevention, Epidemiology and Clinical Research at The Johns Hopkins University School of Medicine

April 24-25, 2016

Genetics of Cardiomyopathies

ALI J. MARIAN, M.D.

Professor and Director, Center for Cardiovascular Genetic Research, The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, University of Texas Health Science Center at Houston

May 13, 2016

Optimizing Cardiac Rehabilitation Participation

RANDAL THOMAS, M.D.

Professor of Medicine, Cardiovascular Diseases at Mayo Clinic and Vice-Chair, Clinical Cardiology Council, American Heart Association

Spring 2016

Multiscale Computational Modeling of Cardiac Electrophysiology

GUNNAR SEEMANN, DR.-ING.

Associate Professor, Institute of Biomedical Engineering, Karlsruhe Institute of Technology, Germany

2015-2016 SOBEL VISITING PROFESSOR

Honoring Burton E. Sobel, M.D., Founding Director of the CVRI

May 23-25, 2016

Genetic Forms of Heart Failure; Genetic Screening; and Small Molecule Therapies Targeted to Contractile Proteins

CHRISTINE SEIDMAN, M.D.

The T.W. Smith Professor of Medicine & Genetics and Director of the Brigham & Women's Cardiovascular Genetics Center

2015-2016 ALPERT VISITING PROFESSOR

Honoring Norman Alpert, Ph.D., Professor and Chair of the UVM Department of Molecular Physiology and Biophysics from 1966 to 1995

Spring 2016

W. JONATHAN LEDERER, M.D., Ph.D.

Professor of Physiology and Director of the Center for Biomedical Engineering and Technology, University of Maryland

The CVRI presented its first Cardiovascular Medicine Community Clerkship in the College of Medicine's Larner Team-Based Classroom on February 1, 2016. This event showcased to several dozen community leaders the ways that cardiovascular patients in the Vermont community and beyond are being better served by advances in treatment, and presented a broad view of some of the leading-edge research taking place in UVM laboratories and at the bedside in the UVM Medical Center.

Connecting Our Scholars

The Cardiovascular Research Institute of Vermont encompasses the full range of scholarship, from young scientists and physicians at the start of their careers to our Distinguished Investigators with decades of notable work to their credit. Through travel awards, research seminars, and an Early Career Advisory Committee available to them, junior investigators who are affiliated with the CVRI have plenty of rich opportunities to interact and learn from their more experienced colleagues.

CVRI TRAVEL AWARDS

The International Society on Thrombosis and Haemostasis 61st Annual Congress
Toronto, Canada – June 2015

Nels Olson, Ph.D.
Postdoctoral Fellow, Laboratory for Clinical Biochemistry Research, Department of Pathology and Laboratory Medicine
ORAL PRESENTATION: Relationships of circulating coagulation factor VIIa (FVIIa) with common single nucleotide polymorphisms and risk of incident ischemic stroke: the Cardiovascular Health Study

Society of General Physiologists 69th Annual Meeting and Symposium
Woods Hole, MA – September 2015

Osama Harraz, Ph.D.
Postdoctoral Associate, Department of Pharmacology
POSTER PRESENTATION: Regulation of endothelial TRPV4 channel activity in the cerebral circulation

Heart Failure Society of America 19th Annual Scientific Assembly
National Harbor, MD – September 2015

Patrick Hohl, D.O., M.P.H.
Fellow, Cardiovascular Disease, Department of Medicine – Cardiology
POSTER PRESENTATION: Echocardiographic measurements predictive of LVEF recovery

10th World Congress for Microcirculation
Kyoto, Japan – September 2015

Fabrice Dabertrand, Ph.D.
Assistant Professor, Department of Pharmacology
POSTER PRESENTATION: Novel intact *ex vivo* preparation of pressurized intracerebral arterioles and capillaries reveals conducted upstream vasodilation following application of neurovascular coupling agents onto capillaries

Thomas Longden, Ph.D.
Assistant Professor, Department of Pharmacology
POSTER PRESENTATION: Retrograde regenerative electrical signaling through capillary KIR channels regulates blood flow into the brain

Albert Gonzales, Ph.D.
Postdoctoral Fellow, Department of Pharmacology
POSTER PRESENTATION: Pericytes exhibit asymmetric control of blood flow at capillary bifurcations

Daniel Collier, Ph.D.
Postdoctoral Associate, Department of Pharmacology
POSTER PRESENTATION: Extracellular histones activate endothelial calcium signals

SCHOLARLY ACTIVITY

Biophysical Society 59th Annual Meeting
February 2015 – Baltimore, MD

David M. Warshaw, Ph.D.
Crossing the Bridge between Muscle Contraction and Intracellular Cargo Transport

Experimental Biology 2015
April 2015 – Boston, MA

Benedek Erdos, M.D., Ph.D.
Novel Method for Investigating Impaired Blood Pressure Regulation Following Subarachnoid Hemorrhage in Conscious Rate

Japanese Circulation Society
April 2015 – Osaka, Japan

Mary Cushman, M.D., M.Sc.
Diabetes and Heart Failure in the United States

Brain 2015
June 2015 – Vancouver, BC

Marilyn J. Cipolla, Ph.D.
Increased Tone of Brain Arterioles during Early Post-ischemic Reperfusion

American Society for Preventive Cardiology Annual Cardiovascular Disease Prevention Conference
July 2015 – Boca Raton, FL

Mary Cushman, M.D., M.Sc.
Is it Time to Take on Inflammation?

Transcatheter Cardiovascular Therapeutics – TCT 2015
October 2015 – San Francisco, CA

Harold L. Dauerman, M.D.
Antithrombins for PCI in Acute Coronary Syndromes and Pharmacology for PCI and TAVR

2015 International Conference on Coronary Artery Disease
November 2015 – Florence, Italy

Harold L. Dauerman, M.D.
Regional Systems of Care for STEMI

American Heart Association 2015 Scientific Sessions
November 2015 – Orlando, FL

Markus Meyer, M.D.
Human Diastolic Heart Failure

Mary Cushman, M.D., M.Sc.
Chronic Venous Insufficiency: Silent and Disabling

Mary Cushman, M.D., M.Sc.
Epidemiology of Post-thrombotic Syndrome: Who is Most at Risk?

Mary Cushman, M.D., M.Sc.
Plenary Session, Improving Outcomes in Women's Cardiovascular Health: Women and Venous Thromboembolism: Understanding Risk

Mary Cushman, M.D., M.Sc.
Rationale and Structure of Workplace Wellness Programming. Creating and Maintaining Ideal Health using AHA's Simple Seven

13th Annual Update in Pulmonary Hypertension
December 2015 – Cambridge, MA

William Hopkins, M.D.
The Left Ventricle in WHO Group 2 PH: What's Wrong?

Distinguished Investigators

CVRI has recognized six University of Vermont faculty as Distinguished Investigators, acknowledging the long-term high impact of their work in cardiovascular research. Appointed for a period of five years, the inaugural group was named in April 2014.

Philip Ades, M.D.
Professor of Medicine

Joseph E. Brayden, Ph.D.
Professor of Pharmacology

Martin M. LeWinter, M.D.
Professor of Medicine

George Osol, Ph.D.
Professor of Obstetrics, Gynecology and Reproductive Sciences

Russell Tracy, Ph.D.
Professor of Pathology

Kathleen M. Trybus, Ph.D.
Professor of Molecular Physiology and Biophysics

Research Funding: Highlights

Understanding the causes and consequences of cardiovascular disease, from the molecule to the patient to populations to policy, drives a robust research enterprise at the University of Vermont, and represents a significant portion of the $85 million in funding received by the College of Medicine in 2015. Grant funding comes from Federal, State, Corporate and Non-Profit sources; below is a sampling of recent awards.

Cardiac Muscle

National Institutes of Health Funding

P01 HL059408-11
Cardiac Myosin-Binding Protein C: Molecular Mechanisms of Actomyosin Modulation
PI: David M. Warshaw, Ph.D.
$10,274,400

NIH/NIA R01 AG033547
Muscle Disuse and Contractile Dysfunction in the Elderly
PI: Michael Toth, Ph.D.
$1,893,112

R01 HL126909-01
Cardiac Myosin-Binding Protein C: Molecular Modulation Actomyosin Function
PI: David M. Warshaw, Ph.D.
$1,887,024

NIH 5R01 HL122744
Sarcolemmal Calcium Extrusion Defect in Patients with Diastolic Dysfunction
PI: Markus Meyer, M.D.
$1,800,000

NHLBI U10 HL110342
Heart Failure Research Network – Vermont, New York and Quebec Regional Clinical Center
PI: Peter VanBuren, M.D.
$1,150,000

NHLBI R01 HL118524
Myofilament Based Mechanisms of Diastolic Dysfunction in HFpEF
PI: Martin LeWinter, M.D.
$1,044,000

NIH PPG – University of Texas (Houston) Health Science Center
Mutations in Smooth Muscle Contractile Proteins: Pathways to Vascular Diseases

Project 1: Molecular Mechanisms of ACTA2 Missense Mutations
PI: Kathleen Trybus, Ph.D.
$390,444

R01
Mutational Studies of Processive Myosin Motors
PI: Kathleen Trybus, Ph.D.
$349,562

R21 AI117476
Reconstitution of the Class XIV Myosin Glideosome from the Malaria Parasite
PI: Kathleen Trybus, Ph.D.
$234,000

NIH/Renova Therapeutics 13761
Adenovirus Vector Type 5 (Ad5.hAC6o) Expressing Human Adenylyl Cyclase Type 6 Administered via Intracoronary Catheterization
PI: Matthew Watkins, M.D.
$26,000

R01 HL127028
Transition for Risk Factors to Heart Failure: Prevalence, Pathogenesis, and Phenomics
Subcontract PI: Russell Tracy, Ph.D.
$6,676

Clinical Trials/Industry Support

Medtronic
SURTAVI: TAVR vs Surgical AVR for Patients at Intermediate Risk
Local PI: Harold Dauerman, M.D.
$200,000

Pacing-Induced Remodeling in a Swine Model of Left Ventricular Hypertrophy III
PI: Markus Meyer, M.D.
$50,000

Pacing-Induced Remodeling in Patients – A Safety and Feasibility Study
PI: Markus Meyer, M.D.
$65,000

CoreValve® Expanded Use and Continued Access Transcatheter Aortic Valve Replacement Registries
Local PI: Harold Dauerman, M.D.
$873,500 for 92 patients

AdaptResponse Clinical Trial
Local PI: Joseph F. Winget, M.D.
$67,550

World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT)
Local PI: Daniel Lustgarten, M.D., Ph.D.
$399,919

Capricor, Inc.
Randomized, Double-Blind, Placebo-Controlled Phase I/II Study of the Safety and Efficacy of Intracoronary Delivery of Allogeneic Cardiosphere-derived Cells in Patients with an Anterior Myocardial Infarction and Ischemic Left Ventricular Dysfunction (ALLSTAR)
Local PI: Matthew Watkins, M.D.
$326,000

Biotronik, Inc.
Protego DF4 Post Approval Registry
PI: Daniel Lustgarten, M.D., Ph.D.
$66,812

St. Jude Medical
Quadripolar Pacing Post Approval Study
PI: Daniel Lustgarten, M.D., Ph.D.
$17,250

Boston Scientific
Evaluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL)
Local PI: Daniel Lustgarten, M.D., Ph.D.
$168,613

Quadripolar CRT-D on Currently Approved Lead SystemS (CROSS X4)
Local PI: Joseph F. Winget, M.D.
$250,000

Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy (PREVAIL) and Continued Access to PREVAIL (CAP2)
Local PI: Daniel Lustgarten, M.D., Ph.D.
$250,000

Actelion
Eisenmenger Quality Enhancement Research Initiative (ES-QuERI)
PI: William Hopkins, M.D.
$33,500

Gilead Sciences
Evaluating Ventricular Arrhythmia in Subjects With Implantable Cardioverter Defibrillator or Cardiac Resynchronization Therapy-Defibrillator (TEMPO)
PI: Daniel Lustgarten, M.D., Ph.D.
$60,387

Vascular Biology/Thrombosis

National Institutes of Health Funding

UM1 HL120877
Analysis and Characterization of Trauma-Induced Coagulopathy
Co-PIs: Kenneth Mann, Ph.D., and Mark T. Nelson, Ph.D.

Project 2: The Role of Factor Xla in TIC
PI: Saulius Butenas, Ph.D

Project 6: The Coagulation and Fibrinolysis Interface
PI: Kathleen Brummel-Ziedins, Ph.D.

Project 12: Effects of Histones, Polyphosphates (polyp) and Thrombin on Native Endothelium in Trauma
PI: Mark T. Nelson, Ph.D.
$23,769,600

NIH/NHLBI PO1 HL095488-01
Calcium Signaling in the Cerebrovascular Unit in Health and Disease
PI: Mark T. Nelson, Ph.D.

Project 1 and Administrative Core
PI: Mark T. Nelson, Ph.D.
$7,831,664

Project 2: Cav Channels, TRP Channels, and Vascomotor Function in Cerebral Arterioles
PI: Joseph Brayden, Ph.D.
$1,362,000

Project 3: Cerebrovascular Function During Ischemia and Reperfusions
PI: Marilyn J. Cipolla, Ph.D.
$1,900,000

Project 4: Impact of SAH on Parenchymal Arterioles and Neurovascular Coupling
PI: George Wellman, Ph.D.
$1,205,000

NIDA/USFDA P50 DAO36114
Tobacco Centers of Regulatory Science
PI: Steven Higgins, Ph.D.
$2,924,426

R01 1HL121706
Regulation of Myoendothelial Function by Signaling Microdomains in Hypertension
PI: Mark T. Nelson, Ph.D.
$1,923,375

R01 HL071944-05
Pre-pregnancy Phenotype and Predisposition to Preeclamplsia
PI: Ira Bernstein, M.D.
$1,881,250

R01 NS045940-10
The Role of the Blood-brain Barrier in Seizure during Pregnancy and Preeclampsia
PI: Marilyn J. Cipolla, Ph.D.
$1,667,970

R01 NS093289-01
Targeting Parenchymal Arterioles in Acute Stroke Treatment
PI: Marilyn J. Cipolla, Ph.D.
$1,653,665

NIH P20 GM103644-01A1
Vermont Center for Behavior and Health
PI: Steven Higgins, Ph.D.
$1,533,382

NIH/NINDS/NIGMS R01 NS073815
Control of Reactive Astrocytes by Notch1 and Amyloid Precursor Protein
PI: Jeffrey Spees, Ph.D.
$1,250,000

U01 NS41588
Etiology of Geographic and Racial Differences in Stroke Mortality
Sub. PI: Mary Cushman, M.D., M.Sc.
$684,296

NIH – NICHD
National Longitudinal Study of Adolescent Health – Wave V
Sub. PI: Mary Cushman, M.D., M.Sc.
$478,373

R01 HL131181-01
K+ Sensing and Electrical Signaling by Kir Channels in Brain Vasculature
PI: Mark T. Nelson, Ph.D.
$475,887

T32 HL007594
Thrombosis and Hemostasis Program for Academic Trainees
PI: Robert J. Kelm, Jr., Ph.D.
$320,958

HHS N2682015000031
Multiethnic Study of Atherosclerosis (MESA)

Task 1 and 3 Repository Maintenance
Subcontract PI: Russell Tracy, Ph.D.
$92,375

Task 2
Subcontract PI: Russell Tracy, Ph.D.
$120,085

U01 AG0504
Enabling Reduction of Low-grade Inflammation in Seniors (ENRGISE)
Subcontract PI: Russell Tracy, Ph.D.
$99,017

N01 HC95166
Multiethnic Study of Atherosclerosis (MESA) II – Laboratory Center
PI: Russell Tracy, Ph.D.
$88,014

R01 AG023629
Exceptional Survival: Trajectories to Function
Sub. PI: Mary Cushman, M.D., M.Sc.
$48,887

R01 HL059367
Epidemiology of Venous Thrombosis and Pulmonary Embolism
Sub. PI: Mary Cushman, M.D., M.Sc.
$33,723

American Heart Association Funding

Hydrogen Peroxide and Age-Related Sympathetic Nervous System Dysregulation
PI: Benedek Erdos, Ph.D., M.D.
$308,000

Mechanisms of EGF Receptor Activation Leading to Decreased Cerebral Blood Flow after Subarachnoid Hemorrhage
PI: Masayo Koide, Ph.D.
$308,000

Founders Affiliate Summer Undergraduate Research Fellowship Award
Molecular Basis of Vascular Gene Repression by Purine-Rich Element Binding Protein B
PI: Robert J. Kelm, Jr., Ph.D.
$5,000

Funding from Other Agencies

Fondation Leducq
Pathogenesis of Small Vessel Disease of the Brain
North American Coordinator:
Mark T. Nelson, Ph.D.
$6,000,000

Naval Health Research Center
NHRC BAA 13-001
Complex Systems Approachs to Characterizing Trauma Induced Coagulopathy
PI: Kathleen Brummel-Ziedins, Ph.D.
$2,613,270

European Union Horizon 2020
Small Vessel Disease in a Mechanistic Perspective: Targets for Intervention – Affected Pathways and Mechanistic Exploration for Prevention of Stroke and Dementia
PI: Mark T. Nelson, Ph.D., for WP1; Co-PI for WP2, WP3, WP4, WP5
$616,909

Totman Medical Research Trust
Cerebrovascular Research
PI: Mark T. Nelson, Ph.D.
$150,000

British Heart Foundation
Imaging Small Artery Endothelial Calcium Signals in Human Obesity: Does Damage to TRPV4 Channel Function Explain Endothelial Dysfunction? Clinical Research Training Fellowship at UVM for Majid Ahmed.
Co-PIs: Adam S. Greenstein, Ph.D., and Mark T. Nelson, Ph.D.
£164,006

Preeclampsia Foundation
Vision Award
The Role of Blood Brain Barrier Efflux Transporters in Seizure during Pregnancy
PI: Erica Hammer, M.D.
$25,000

Clinical Trials/Industry Support

Medtronic
SIMPLICITY HTN-3: A randomized trial of renal denervation versus maximal medical therapy for severe hypertension
Local PI: Harold Dauerman, M.D.
$100,000

Abbott Vascular
ABSORB 3: A Randomized Trial Comparing a Fully Bioresorbable Drug Eluting Polylactic Acid Polymer Coronary Stent Versus a Permanent Everolimus Eluting Coronary Stent
Local PI: Harold Dauerman, M.D.
$44,500

Sanofi
Odyssey Outcomes Trial
Local PI: Friederike Keating, M.D.
$56,000

Boston Scientific
Outcomes with the Promus PREMIER Bare Metal Stent in Women and Minorities (PLATINUM Diversity)
Local PI: Matthew Watkins, M.D.
$36,000

Janssen Pharmaceuticals, LLC
Novel Markers of Thrombotic Risk
PI: David J. Schneider, M.D.
$372,000

AstraZeneca
TIGRIS: Long-Term rIsk, Clinical manaGement and Healthcare Resource Utilization of Stable Coronary Artery dISease in Post Myocardial Infarction Patients
Local PI: David J. Schneider, M.D.
$38,580

Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study (ARTEMIS)
Local PI: Prospero Gogo, Jr., M.D.
$25,600

Platelet Activation, Reactivity, and Inflammation after Coronary Bypass Surgery in Patients Treated with Ticagrelor or Clopidogrel
Local PI: David J. Schneider, M.D.
$100,000

Medinol, Ltd
BIONICS (BioNIR Ridaforolimus Eluting Stent In Coronary Stenosis) Study
PI: Edward Terrien, M.D.
$60,387

DiaDexus
Lipoprotein Associated Phospholipase A2(Lp-PLA2) Activity and the Risk of Stroke, Coronary Heartdisease and Cognitive Decline in REGARDS
PI: Mary Cushman, M.D., M.Sc.
$67,003

Research Publications: Highlights

Across our academic medical center campus, throughout the region, and around the world, teams of physicians and scientists are dedicated to reducing the incidence, morbidity, and mortality of heart and vascular diseases through improving prevention, diagnosis and treatment. We are pleased to present a sampling of publications from our University of Vermont colleagues engaged across a wide range of cardiovascular research.

Cardiac Muscle

AbouEzzeddine OF, Haines P, Stevens S, Nativi-Nicolau J, Felker GM, Borlaug BA, Chen HH, Tracy RP, Braunwald E, Redfield MM. Galectin-3 in heart failure with preserved ejection fraction: a RELAX trial substudy (phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure). JACC Heart Fail. 2015;3:245-52.

Ades PA. Temporal trends and factors associated with cardiac rehabilitation referral among patients hospitalized with heart failure: awaiting the uptick. J Am Coll Cardiol. 2015;66(8):927-9.

Bates OR, Suki B, Spector PS, Bates JH. Structural defects lead to dynamic entrapment in cardiac electrophysiology. PLoS One. 2015;10(3):e0119535.

Borlaug BA, Lewis GD, McNulty SE, Semigran MJ, LeWinter M, Chen H, Lin G, Deswal A, Margulies KB, Redfield MM. Effects of sildenafil on ventricular and vascular function in heart failure with preserved ejection fraction. Circ Heart Fail. 2015;8(3):533-41.

Callahan DM, Tourville TW, Miller MS, Hackett SB, Sharma H, Cruickshank NC, Slauterbeck JR, Savage P, Maughan DW, Ades PA, Beynnon BB, Toth MJ. Chronic disuse alters skeletal muscle structure in older adults: sex-specific differences and relationships to contractile function. Am J Physiol Cell Physiol. 2015;308(11):C932-43.

Callahan DM, Tourville TW, Slauterbeck JR, Ades PA, Stevens-Lapsley JE, Beynnon BD, Toth MJ. Reduced rate of knee extensor isometric torque development in knee osteoarthritis is associated with intrinsic muscle contractile deficits. Exp Gerontol. 2015;72:16-21.

Carrick RT, Bates OR, Benson BE, Habel N, Bates JH, Spector PS. Prospectively quantifying the propensity for atrial fibrillation: a mechanistic formulation. PLoS One. 2015;10(3):e0118746.

Couch ME, Dittus K, Toth MJ, Willis MM, Guttridge DC, George JR, Barnes CA, Gourin CG, Der-Torossian H. Cancer cachexia update for head and neck surgeons. Part I: Diagnostic advances, clinical markers and cardiac dysfunction. Head Neck. 2015;37: 594-604.

Couch ME, Dittus K, Toth MJ, Willis MM, Guttridge DC, George JR, Barnes CA, Gourin CG, Der-Torossian H. Cancer cachexia update for head and neck surgeons. Part II: Pathophysiology and treatment. Head Neck. 2015;37:1057-72.

Dittus K, Lakoski S, Savage PD, Kokinda N, Toth MJ, Stevens D, Woods K, O'Brien P, Ades PA. Exercise-based oncology rehabilitation: leveraging the cardiac rehabilitation model. J Cardiopulm Rehab Prev. 2015;35: 130-9.

Estes JD, Reilly C, Trubey CM, Fletcher CV, Cory TJ, Piatak M, Jr., Russ S, Anderson J, Reimann TR, Star R, Smith A, Tracy RP, Berglund A, Schmidt T, Coalter V, Chertova E, Smedley J, Haase AT, Lifson JD, Schacker TW. Antifibrotic therapy in siv infection preserves cd4 t cell populations and improves immune reconstitution with antiretroviral therapy. J Infect Dis. 2015;211:744-54.

Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, Tang WH, Dunlap ME, LeWinter MM, Mann DL, Felker GM, O'Connor CM, Goldsmith SR, Ofili EO, Saltzberg MT, Margulies KB, Cappola TP, Konstam MA, Semigran MJ, McNulty SE, Lee KL, Shah MR, Hernandez AF; NHLBI Heart Failure Clinical Research Network. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients (EXACT-HF). Circulation. 2015;131:1763-71.

Harhay MO, Kizer JR, Criqui MH, Lima JA, Tracy R, Bluemke DA, Kawut SM. Adipokines and the right ventricle: the MESA-RV study. PLoS One. 2015;10(9):e0136818.

Imazio M, Gaita F, LeWinter MM. Evaluation and treatment of pericarditis: a systematic review. JAMA. 2015;314:1498-506.

Kiernan MS, Joseph SM, Katz JN, Kilic A, Rich JD, Tallman MP, Van Buren P, Lyons JJ, Bethea B, Eckman P, Gosev I, Lee SS, Soleimani B, Takayama H, Patel CB, Uriel N, Evolving Mechanical Support Research Group (EMERG) Investigators. Sharing the care of mechanical circulatory support: collaborative efforts of patients/caregivers, shared-care sites, and left ventricular assist device implanting centers. Circ Heart Fail. 2015;8:629-35.

Lewinter C, Doherty P, Gale CP, Crouch S, Stirk L, Lewin RJ, LeWinter MM, Ades PA, Kober L, Bland JM. Exercise-based cardiac rehabilitation in patients with heart failure: a meta-analysis of randomized controlled trials between 1999 and 2013. Eur J Prev Cardiol. 2015;22(12):1504-12.

LeWinter MM, Palmer BM. Updating the physiology and pathophysiology of cardiac myosin binding protein-C. Circ Heart Fail. 2015;8(3):417-21.

LeWinter MM. My approach to patients with acute pericarditis. Trends Cardiovasc Med.2015;25:168-9.

LeWinter, MM. Colchicine and beyond: new options for the treatment of pericarditis.Trends Cardiovasc Med. 2015;25:137-9.

Lu H, Fagnant PM, Bookwalter CS, Joel P, Trybus KM. Vascular disease-causing mutation R258C in ACTA2 disrupts actin dynamics and interaction with myosin. Proc Natl Acad Sci USA. 2015;112:E4168-77.

Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, Lobel R, Winget J, Koehler J, Liberman E, Sheldon T. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. Heart Rhythm. 2015;12(7):1548-57.

Macheret F, Bartz TM, Djousse L, Ix JH, Mukamal KJ, Zieman SJ, Siscovick DS, Tracy RP, Heckbert SR, Psaty BM, Kizer JR. Higher circulating adiponectin levels are associated with increased risk of atrial fibrillation in older adults. Heart. 2015;101 (17):1368-74.

Meyer M, McEntee RK, Nyotowidjojo I, Chu G, LeWinter MM. Relationship of exercise capacity and left ventricular dimensions in patients with a normal ejection fraction. An exploratory study. PLoS One. 2015;10(3):e0119432.

Miller MS, Bedrin NG, Ades PA, Palmer BM, Toth MJ. Molecular determinants of force production in human skeletal muscle fibers: effects of myosin isoform expression and cross-sectional area. Am J Physiol Cell Physiol. 2015;308:C473-84.

Nock NL, Owusu C, Flocke S, Krejci SA, Kullman EL, Austin K, Bennett B, Cerne S, Harmon C, Moore H, Vargo M, Hergenroeder P, Malone H, Rocco M, Tracy R, Lazarus HM, Kirwan JP, Heyman E, Berger NA. A community-based exercise and support group program improves quality of life in African-American breast cancer survivors: a quantitative and qualitative analysis. Int J Sports Exerc Med. 2015; 1(3).

Pandrea I, Landay A, Wilson C, Stock J, Tracy R, Apetrei C. Using the pathogenic and nonpathogenic nonhuman primate model for studying non-AIDS comorbidities. Curr HIV/AIDS Rep. 2015;12(1):54-67.

Previs MJ, Prosser BL, Mun JY, Previs SB, Gulick J, Lee K, Robbins J, Craig R, Lederer WJ, Warshaw DM. Myosin-binding protein C corrects an intrinsic inhomogeneity in cardiac excitation-contraction coupling. Sci Adv. 2015;1(1):e1400205.

Rao KS, Aronshtam A, McElory-Yaggy KL, Bakondi B, VanBuren P, Sobel BE, Spees JL. Human epicardial cell-conditioned medium contains HGF/IgG complexes that phosphorylate RYK and protect against vascular injury. Cardiovasc Res. 2015;107(2):277-86.

Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ, Felker GM, Cole RT, Reeves GR, Tedford RJ, Tang WH, McNulty SE, Velazquez EJ, Shah MR, Braunwald E; NHLBI Heart Failure Clinical Research Network. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med. 2015;373:2314-24.

Savage PD, Rengo JL, Menzies KE, Ades PA. Cardiac rehabilitation after heart valve surgery: comparison with coronary artery bypass graft patients. J Cardiopulm Rehabil Prev. 2015;35(4):231-7.

Seecheran N, Ittleman F, Dauerman H. Left ventricular outflow tract embolization and balloon assisted recapture of a SAPIEN XT prosthesis during transcatheter aortic valve replacement. Catheter Cardiovasc Intervent. 2015;doi: 10.1002/ccd.26255.

Tischler MD. Ischemic mitral regurgitation: can we identify who is at risk? Coron Artery Dis. 2015;26(8):637-8.

Zakeri R, Levine JA, Koepp GA, Borlaug BA, Chirinos JA, LeWinter M, VanBuren P, Dávila-Román VG, de Las Fuentes L, Khazanie P, Hernandez A, Anstrom K, Redfield MM. Nitrate's effect on activity tolerance in heart failure with preserved ejection fraction trial: rationale and design. Circ Heart Fail. 2015:8:221-8.

Zile MR, Baicu CF, S Ikonomidis JS, Stroud RE, Nietert PJ, Bradshaw AD, Slater R, Palmer BM, Van Buren P, Meyer M, Redfield MM, Bull DA, Granzier HL, LeWinter MM. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. Circulation. 2015;131:1247-59.

Vascular Biology/Thrombosis

Ackerman S, Watkins MW, Kostial AF, Rabinowitz T. Urgent assessment of decision-making capacity in a patient with schizophrenia and an evolving myocardial infarction who is refusing care. Psychosomatics. 2015;56(1):89-93.

Ades PA, Savage PD, Marney AM, Harvey J, Evans KA. Remission of recently diagnosed type 2 diabetes mellitus with weight loss and exercise. J Cardiopulm Rehabil Prev. 2015;35(3):193-7.

Ades PA. A lifestyle program of exercise and weight loss is effective in preventing and treating type 2 diabetes mellitus: why are programs not more available? Prev Med. 2015;80:50-2.

Agarwal I, Arnold A, Glazer NL, Barasch E, Djousse L, Fitzpatrick AL, Gottdiener JS, Ix JH, Jensen RA, Kizer JR, Rimm EB, Siscovick DS, Tracy RP, Wong TY, Mukamal KJ. Fibrosis-related biomarkers and large and small vessel disease: The cardiovascular health study. Atherosclerosis. 2015;239(2):539-46.

Altman RD, Strand V, Hochberg MC, Gibofsky A, Markenson JA, Hopkins WE, Cryer B, Kivitz A, Nezzer J, Imasogie O, Young CL. Low-dose Solumatrix diclofenac in the treatment of osteoarthritis: a 1-year, open-label, Phase III safety study. Postgrad Med. 2015;127:517-28.

Auer PL, Nalls M, Meschia JF, Worrall BB, Longstreth WT Jr, Seshadri S, Kooperberg C, Burger KM, Carlson CS, Carty CL, Chen WM, Cupples LA, DeStefano AL, Fornage M, Hardy J, Hsu L, Jackson RD, Jarvik GP, Kim DS, Lakshminarayan K, Lange LA, Manichaikul A, Quinlan AR, Singleton AB, Thornton TA, Nickerson DA, Peters U, Rich SS; National Heart, Lung, and Blood Institute Exome Sequencing Project. Rare and coding region genetic variants associated with risk of ischemic stroke: the NHLBI Exome Sequence Project. JAMA Neurol. 2015;72(7):781-8.

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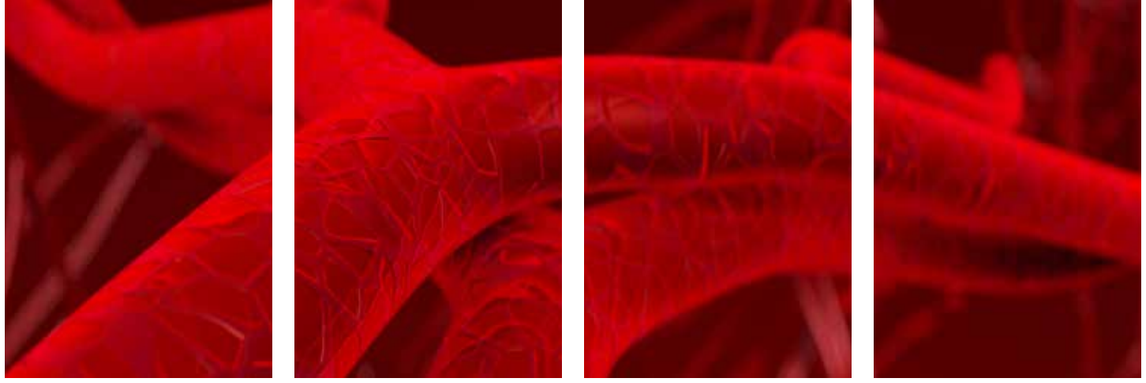

Research Publications: A Sampling *(continued)*

Badejo OA, Chang CC, So-Armah KA, Tracy RP, Baker JV, Rimland D, Butt AA, Gordon AJ, Rinaldo CR, Jr., Kraemer K, Samet JH, Tindle HA, Goetz MB, Rodriguez-Barradas MC, Bedimo R, Gibert CL, Leaf DA, Kuller LH, Deeks SG, Justice AC, Freiberg MS. CD8 (+) T-cells count in acute myocardial infarction in HIV disease in a predominantly male cohort. BioMed Res Int. 2015;2015:246870.

Balbi M, Ghosh M, Longden TA, Jativa Vega M, Gesierich B, Hellal F, Lourbopoulos A, Nelson MT, Plesnila N. Dysfunction of mouse cerebral arteries during early aging. J Cereb Blood flow Metab. 2015;35(9):1445-53.

Balbi M, Koide M, Schwarzmaier SM, Wellman GC, Plesnila N. Acute changes in neurovascular reactivity after subarachnoid hemorrhage in vivo. J Cereb Blood Flow Metab. 2015 Dec 16. pii: 0271678X15621253.

Belalcazar LM, Lang W, Haffner SM, Schwenke DC, Kriska A, Balasubramanyam A, Hoogeveen RC, Pi-Sunyer FX, Tracy RP, Ballantyne CM, Look ARG. Improving adiponectin levels in individuals with diabetes and obesity: Insights from Look Ahead. Diabetes Care. 2015;38(8): 1544-50.

Chava S, Terrien E, Schmoker J, Tischler M, Dauerman HL. Management strategies for acute coronary occlusion associated with CoreValve transcatheter aortic valve replacement. J Thromb Thrombolysis. 2015;40(2):198-202.

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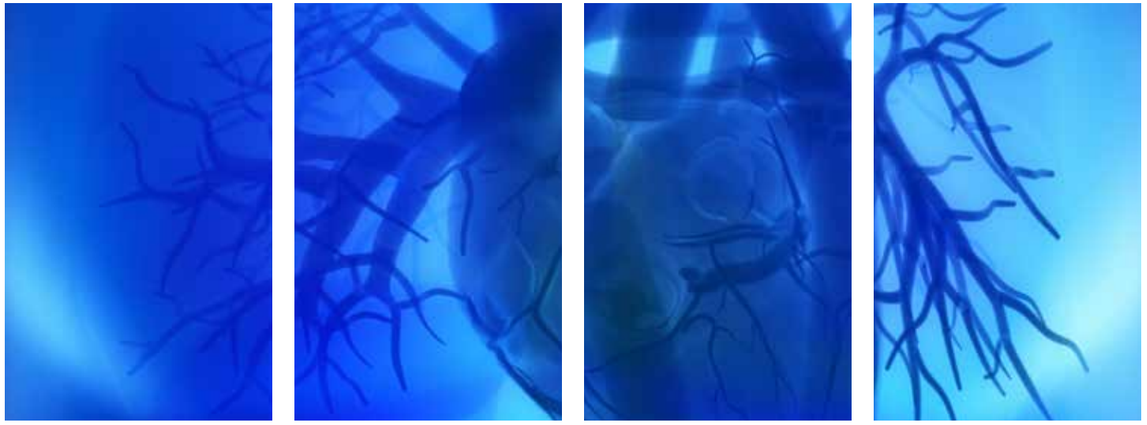

In Memory of

Norman R. Alpert, Ph.D.

1922–2004

Chair and Professor, University of Vermont College of Medicine
Department of Molecular Physiology & Biophysics
1966–1995

Dr. Alpert was an outstanding teacher, internationally renowned investigator of cardiac hypertrophy, and founder of BioTek Instruments, Inc. The Norman R. Alpert Research Prize was established in 2014 at the University of Vermont to honor his commitment to training emerging talent in the biosciences. The prize is awarded annually for the best peer-reviewed research article by a graduate student in the University of Vermont Cellular, Molecular, and Biomedical Sciences Program.

Dr. Alpert attended both Wesleyan and Columbia Universities. He received his Ph.D. in Biophysics from Columbia University in 1951. He then joined the Department of Physiology at the University of Illinois where he ascended in rank from assistant professor to full professor by 1965.

In 1966 he moved to the University of Vermont to become chair of the Department of Physiology and Biophysics. During his tenure as chair, he created one of the pre-eminent departments of cardiovascular and muscle physiology.

Dr. Alpert published 140 articles ranging from respiratory metabolism to the step size of a single cardiac myosin molecule.

Scientifically, his contributions to understanding the molecular compensatory mechanisms associated with cardiac hypertrophy were significant. In collaboration with Louis Mulieri, Ph.D., he developed an elegant thermopile system to investigate the relationship between energy utilization and contractility of cardiac muscle. This ingenious system utilized sensors coated with antimony and bismuth to accurately measure energy utilization as heat production when a cardiac muscle strip was electrically stimulated. The device proved an important tool in differentiating and quantifying the rates of energy utilization during crossbridge cycling (actomyosin ATPase activity) and Ca2+ cycling by the sarcoplasmic reticulum (Ca2+ ATPase activity). These pioneering studies were the basis for the present understanding of the physiology of crossbridge and Ca2+ cycling kinetics in normal and failing hearts.

Dr. Alpert always felt it important that a scientist give back to the scientific community by being an involved citizen, and he held an important role in the growth and success of several organizations, such as the International Society for Heart Research (ISHR), for which he served as president (1993–1994). He was also vice president of the International Academy of Cardiovascular Sciences, and founding member of the Vermont Academy of Science and Engineering. He was a co-organizer of the first International Conference of Muscle Energetics, held in Burlington, Vermont in 1977, where it returned in 1984 and 2001. Dr. Alpert also organized one of the most successful ISHR meetings, which was held in Burlington, Vermont in 1992. He also served as the editor of the *Journal of Molecular and Cellular Cardiology* (1992–1998) and as an associate editor of *American Journal of Physiology–Heart and Circulation* (1981–1987).

—David M. Warshaw, Ph.D.

From left: Drs. Schneider, Dauerman, Cipolla, Warshaw, Nelson, Bernstein and Cushman.

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