

THE HEART OF TRANSLATIONAL RESEARCH

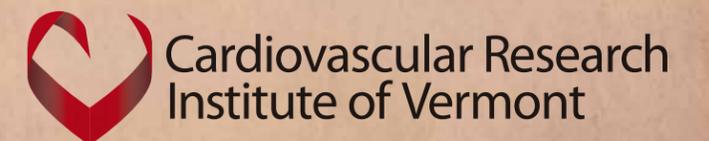
THE RENEWAL OF THE CARDIOVASCULAR RESEARCH INSTITUTE OF VERMONT

Though there's cutting-edge research happening there, don't look for the Cardiovascular Research Institute of Vermont (CVRI) on a map of the University of Vermont campus; you won't find it, and not because it's housed elsewhere in the state. Like the circulatory system itself, which branches throughout the human body, supporting its components literally from head to toe, the CVRI has a subtle presence throughout dozens of laboratories, supporting research across a wide range of disciplines at the University. Through the work of its affiliates, it is at the forefront of cardiovascular research — not only in the United States, but worldwide.

In 2002, Burton Sobel, M.D., with an \$8 million endowment in hand, formed a nonprofit cardiovascular research organization under the aegis of the College of Medicine's Department of Medicine. The CVRI was subsequently formed in 2008. Its mission was generally outlined by a dedication to reductions in the incidence, morbidity, and mortality of heart and vascular diseases through improving prevention, diagnosis, and treatment. In July 2013, David Schneider, M.D., F.A.C.C., F.A.H.A., was appointed director, shortly after Dr. Sobel's death. "Burt Sobel was a force, and the Cardiovascular Research Institute was really his baby to do cardiovascular research," says

Schneider. So as it has been rebirthed in this process there was a real direct effort to make the base less narrow. At the urging of the College's dean, Rick Morin, that base has been redesigned "specifically to be broad, to reach out to many different areas and to different types of research and then to amplify that," says Schneider. Today its reach extends across disciplines and research areas by providing funding and support to established senior investigators, as well as to those who are just beginning their careers. The CVRI encompasses the broadest possible definition of cardiovascular research, embracing everything from bench to translational research to clinical applications and including under its umbrella disciplines that range from cardiology to pharmacology, even psychology and engineering. While those who are associated with the CVRI are loosely referred to as "members," there is no real membership per se, no application process or criteria other than the engagement in research that is related to cardiovascular health.

The first year of the revamped CVRI was outwardly quiet, but behind the scenes it was evolving and growing. That began with the formation of a board of directors, whose six members were chosen from across the University and appointed to three-year terms.





Professor of Medicine David Schneider, M.D., has directed the Cardiovascular Research Institute of Vermont since 2013, and is seen here in his laboratory at UVM's Colchester Research Facility.

Their first task was to generate a charter that laid out the governance, mission, and initiatives of the CVRI; that was adopted in January 2014, and for Schneider and his board, it wasn't just an item on a checklist.

"We really want to live our mission, which is fostering cardiovascular research," says Schneider. "And the two prongs to that are highlighting the excellence in research that's going on here and nurturing the next generation."

EXCELLENCE IN RESEARCH

Schneider first worked with Sobel while completing his cardiology fellowship at Washington University in St. Louis. That program was structured so that the first two years were spent on research and the second two involved clinical work, a translational approach that appeals to Schneider to this day. At Washington University Schneider analyzed the fibrinolytic system, which makes the

proteins that dissolve blood clots that form in response to injury, and then looked at the balance between the activator and plasminogen activator inhibitor-1 (PAI-1) in patients who are diabetic or have other insulin-resistant states. Schneider's research became fully translational when clinical trials were used to look at how insulin, glucose and fatty free acids affect the production of the protein.

"The research I'm involved in today and the research of the cardiology division are really designed to improve care," says Schneider. "There's some research that just understands how things work, but as a clinician, it makes sense that I try to always connect mine to the clinical side, and that's what I've tried really hard to do throughout my career."

"WE REALLY WANT TO LIVE OUR MISSION, WHICH IS FOSTERING CARDIOVASCULAR RESEARCH ... HIGHLIGHTING THE EXCELLENCE IN RESEARCH THAT'S GOING ON HERE AND NURTURING THE NEXT GENERATION."

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

When Sobel moved to UVM, where he'd accepted the E.L. Amidon Chair of Medicine, he invited Schneider to come along. Schneider arrived in Vermont in mid-1994, and once here, his interests broadened to include thrombosis and platelet function, in the hopes of identifying an individualized therapy for patients. Working with Professor of Biochemistry Paula Tracy, Ph.D., Schneider developed an assay that used flow cytometry to look at platelet function and activation; in the years since, his focus has remained on platelets and their functioning. He's now getting started on a project with Associate Professor Kathleen Brummel-Ziedens, Ph.D., and Professor of Biochemistry Kenneth Mann, Ph.D., to find novel ways to characterize the risk of forming thrombin and causing platelet activation. Schneider believes they may have identified a new method to characterize platelet function. Brummel-Ziedens and Mann have been developing assays to better characterize an individual's likelihood of developing blood clots. Together these may someday be useful tools to best target therapies to the individual. Some of that work has evolved because of proximity — Schneider's lab is next door to Mann's — which is the kind of naturally occurring relationship the CVRI board would like to see more of.

For Marilyn Cipolla, Ph.D., F.A.H.A., a professor in the Department of Neurological Sciences and a CVRI board member, breaking down the "silos" that divide separate research efforts will be the continuing goal of the CVRI. She's hopeful they will someday have a common lab, with researchers in adjoining spaces and equipment, animals, and trainees, all of which would allow them to integrate their work in potentially important ways. "So when I do cerebrovascular disease and stroke work, which is related to the heart, if there was somebody next door to me that I could step over and talk to about their findings in atherosclerosis, I could start looking at that in my models," she says.

Cipolla's own research is focused on three areas of cerebrovascular disease: the failure of blood vessels in the brain

to reperfuse after ischemic stroke; hypertensive small vessel disease; and preventing brain injury in preeclampsia and eclampsia, particularly in developing countries, where this disorder is the leading cause of maternal death. Cipolla has collaborated on studies of preeclampsia with fellow board member Ira Bernstein, M.D., John Van Sicklen Maeck Professor and chair of the Department of Obstetrics, Gynecology and Reproductive Sciences, examining brain blood flow and brain water changes in pregnant women using MRI. Cipolla focuses on the bench end of translational research, using animal models, while Bernstein is engaged in a trial of 125 women to see who will develop preeclampsia. Although preeclampsia itself is restricted to women during pregnancy, it remains a very real concern for those who do develop it — within the last 15 years, research has found that women who have had preeclampsia, especially early in pregnancy, are at high risk for developing cardiovascular disease later in life, whether ischemic heart disease, hypertension, or heart failure. Bernstein has hypothesized that some women develop preeclampsia because they had a specific cardiovascular phenotype even before conceiving, and the hormonal and physiological challenges of pregnancy then expose that risk.

Bernstein is an example of the kind of nontraditional cardiovascular researcher

"WE'RE HAPPY TO HAVE PEOPLE WHO ARE IN OTHER COLLEGES AT UVM PARTICIPATE IN THE PROGRAMMING, BE ELIGIBLE FOR AWARDS, AND BE PART OF THE CORE CULTURE THAT'S INTERESTED IN CARDIOVASCULAR SCIENCES AND ITS IMPLICATIONS FOR HUMAN HEALTH."

— Ira Bernstein, M.D.

Schneider has in mind when he talks about the CVRI's broad base; he also engages in interdisciplinary work that is one of its hallmarks, collaborating regularly with colleagues in other departments. For one project Bernstein conducted research with Alessandra Rellini, Ph.D., associate professor in the psychology department, on the vascular aspects of female sexual response, in an effort to determine whether they are related to broader indices of cardiovascular health.

"We're happy to have people who are in other colleges at UVM participate in the programming, be eligible for awards, and be part of the core culture that's interested in cardiovascular sciences



The Cardiovascular Institute of Vermont's 2015 celebration at the UVM Davis Center in May was an opportunity to publicly recognize the leadership and researchers of the institute.

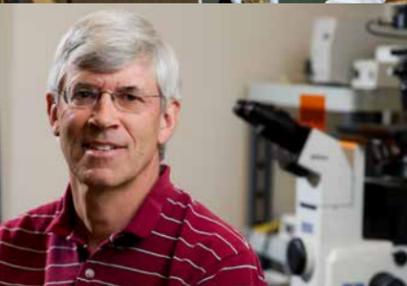
DISTINGUISHED INVESTIGATORS

INAUGURAL 2014–2015 GROUP



Philip Ades, M.D., Professor of Medicine

Dr. Ades is director of Cardiac Rehabilitation and Prevention at the UVM Medical Center. His research, which has had consistent NIH funding since 1988, focuses on the treatment and prevention of disability in older patients with coronary artery disease and patients with chronic heart failure.



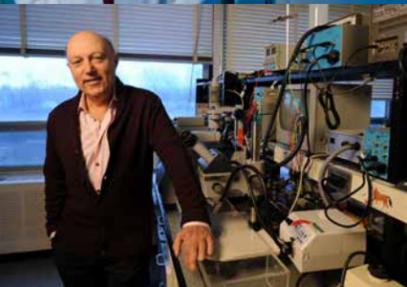
Joseph Brayden, Ph.D., Professor of Pharmacology

Dr. Brayden's laboratory investigates the ionic mechanisms of vasoconstriction, vasodilation, and communication between endothelial and smooth muscle cells in cerebral arterioles and is a pioneer in research on the electrical properties of vascular smooth muscle.



Martin LeWinter, M.D., Professor of Medicine

Dr. LeWinter is director of the UVM Medical Center's Heart Failure Program and principal investigator of UVM's NIH-funded Regional Clinical Center for heart failure research. His work focuses on myocardial and ventricular functioning and remodeling in cardiomyopathy and heart failure. He was a 2007 University Scholar.



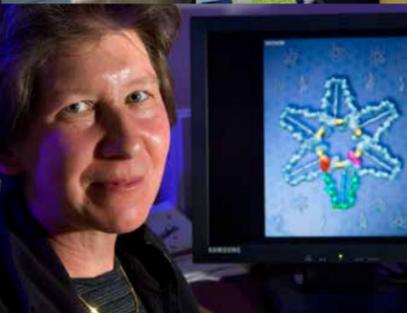
George Osol, Ph.D., Professor of Obstetrics, Gynecology & Reproductive Medicine

Dr. Osol's research is focused on vascular adaptations in pregnancy. He is program director for the NIH Center of Excellence in Women's Reproductive Health Research and a 2010 University Scholar. His work has received NIH support for more than 25 years.



Russell Tracy, Ph.D., Professor of Pathology

Dr. Tracy, interim senior associate dean for research, Laboratory for Clinical Biochemistry Research director, and 2009 University Scholar, is exploring genetic risk factors related to myocardial infarction and atherosclerosis, among other diseases.



Kathleen Trybus, Ph.D., Professor of Molecular Physiology & Biophysics

Dr. Trybus is engaged in the study of molecular motors and their cargo — specifically, myosin regulation, and the mechanisms that cause mutations in smooth muscle actin to result in vascular disease, in particular, thoracic aneurysms and coronary artery disease.

and its implications for human health," says Bernstein.

The CVRI also recognizes what it calls Distinguished Investigators, those who are "performing sustained, impactful cardiovascular research," with a five-year award. The current roster is made up of Philip Ades, M.D.; Joseph Brayden, Ph.D.; Martin LeWinter, M.D.; George Osol, Ph.D.; Russell Tracy, Ph.D.; and Kathleen Trybus, Ph.D. Their research interests span heart failure, vascular adaptation during pregnancy, thoracic aneurysms and coronary artery disease, genetics of heart disease, and weight loss in obese coronary patients, and their work is widely recognized on the international stage.

Along with the Distinguished Investigators initiative that came out of the CVRI charter, there is a concerted effort to support up-and-comers in cardiovascular research — the junior investigators, trainees, and others who are still in the early stages of their careers.

THE NEXT GENERATION

With 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 at their disposal.

"We're here to support young researchers through money and exposure," says board member Harold Dauerman, M.D., professor of medicine. Dauerman conducts clinical trial and registry research and has worked with the American Heart Association on quality improvement initiatives, and has also led national trials developing new technology and pharmacology for interventional cardiology procedures. He's an active enroller in clinical trials at the College of Medicine and regularly instructs trainees in clinical trials and registries research, and says the ability to underwrite some of a young researcher's expenses early in his or her career is crucial. That support comes in the form of travel awards and is supplemented by exposure to cardiovascular experts from outside the university.

Jeff Clarke, David Seaver, Raj Chawla



Sobel Visiting Professor Joseph Loscalzo, M.D., Ph.D., chair of Medicine at Brigham & Women's Hospital and editor-in-chief of the journal *Circulation*, talks with early career committee members at the "Masters Tea" during his visit to campus in March 2015. A key goal of the CVRI is to expose young researchers to experts in the field.

The travel awards were established to cover educational travel costs for anyone early in their career who is a primary presenting author of an abstract at a regional or national meeting. It's an honor, and it also means that money that would otherwise have to be used to pay for them to participate can be earmarked for research funding instead. Since July 2014, thirteen \$2,000 awards have been made, sending assistant professors, postdoctoral fellows, residents in internal medicine, and graduate and medical students to, among other meetings, the International Society for Stem Cell Research's 2015 Annual Meeting in Stockholm; the Society for Reproductive Investigation's 62nd Annual Scientific Meeting in San Francisco; and the American Heart Association's Epidemiology, Prevention, Lifestyle and Cardiometabolic Risk 2015 Scientific Sessions in Baltimore. Kara Landry, a fourth-year medical student, received a travel award that allowed her to present her poster, "Association of Stroke

Andy Duback

"YOU WANT YOUR TRAINEES TO HAVE THE OPPORTUNITY TO MEET PEOPLE WHO ARE LEADERS IN THEIR FIELD."

— MARY CUSHMAN, M.D., M.Sc., F.A.H.A.

Risk Biomarkers With Stroke Symptoms: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort," at the latter this spring, something she says would have been impossible for her to do otherwise, given the financial constraints of school loans.

The newly established Cardiovascular Research Institute seminars, meanwhile, bring nationally established cardiovascular investigators to UVM to not only expose UVM investigators to their work, but promote interaction with UVM junior investigators and trainees. Through the Sobel Visiting Professorship and the Alpert Visiting Professorship, two world-renowned researchers are invited for an extended stay, allowing time for colloquia, grand rounds, and one-on-one meetings

and dinners. A week or two before such visits, the CVRI's Early Career Advisory Committee holds a Journal Club meeting at which attendees discuss two or three of that visiting professor's papers, an activity that allows for cross-departmental introductions while allowing participants to familiarize themselves with the invitee's work ahead of time.

The Early Career Advisory Committee itself is at the heart of the CVRI's support of the future of cardiovascular research and medicine. Its eight members, selected by application to the board, represent a broad array of departments and levels of expertise — they range from fourth-year medical students to early career-level faculty members in Microbiology, Molecular

Genetics and Obstetrics, Gynecology and Reproductive Sciences. In addition to coordinating events such as the Journal Club for their peers, committee members participate in the planning of the visiting professorships and report regularly to the CVRI board on issues, concerns, and needs faced by their early career colleagues.

Michael Previs, Ph.D., is an assistant professor in the Department of Molecular Physiology and Biophysics and the advisory committee's chair. Although the group is so new it's only met a few times, already, says Previs, "it's been an excellent opportunity to meet other young scientists in the UVM community and increase awareness for their involvement in cardiovascular research." Landry, the committee's sole medical student member, notes another advantage as she heads into a neurology residency at UVM Medical Center.

"I'm definitely interested in a research career, and I know that these next four years are going to be focused on learning how to be a strong clinician," she says. "But I also want to stay connected to research and basic sciences. Being part of this committee will allow that."

The committee is shepherded by Mary Cushman, M.D., M.Sc., F.A.H.A., director of the Thrombosis and Hemostasis Program, professor of medicine in the Hematology/Oncology Division, professor of pathology, and a CVRI board member for whom mentoring has long been a professional passion. She says that inviting early career individuals to dinners with visitors and to research and progress sessions — where they are welcome to present their work and get feedback — is important on several levels.

"You want your trainees to have the opportunity to meet people who are

leaders in their field," says Cushman. "They might help them get their next job, or they could develop a collaboration. It also teaches them how to interact with scientists outside our institution."

Cushman's own work revolves around observations of substantial populations over time to identify risk factors for cardiovascular disease and stroke, particularly those related to genetic markers. As a steering committee member of the REGARDS (REasons for Geographic And Racial Differences in Stroke) study, now in its twelfth year, Cushman has helped enroll and follow 30,000 individuals nationwide. She's also an active investigator in the Multi-Ethnic Study of Atherosclerosis (MESA), and has had continuous NIH funding at the faculty level for 18 years.

Mark Nelson, Ph.D., F.A.H.A., University Distinguished Professor, chair

of the Department of Pharmacology, and CVRI board member, also has NIH funding — a \$12 million program project grant with Cipolla, Brayden, and George Wellman, Ph.D., to look at the regulation of arterials in the brain in both healthy individuals and those who have suffered a stroke or subarachnoid hemorrhage. Nelson also received a multi-million dollar Fondation Leducq Transatlantic Networks of Excellence grant in October 2012 and is the North American coordinator of an international study of the pathogenesis of small vessel disease of the brain, a major contributor to stroke and dementia.

Board member, David Warshaw, Ph.D., chair of the Department of Molecular Physiology and Biophysics, is also the recipient of an NIH program project grant.

"There aren't many at NIH, and to have two of them within the CVRI is a feather in the cap of the university," Warshaw says of such awards. Warshaw's grant brings together private investigators from five institutions to study genetic mutations in cardiac contractile proteins. He was recently published in the inaugural issue of *Science Advances* for his findings on a critical protein that is responsible for the efficient functioning of the heart's contractions. For Warshaw and Nelson and their colleagues who focus on elements of basic science, translational work is the only way to go.

"One of the big mandates is to try to move basic science into the clinics as quickly as possible," says Warshaw. "The only way that will happen is if we have physicians and basic scientists communicating with each other and working hand in hand, both at the bench and at the bedside. And I think the Cardiovascular Research Institute is that connection."

Nelson observes that the CVRI is the continuation of a long university tradition of outstanding cardiovascular research with premier investigators, many of whom received funding from the NIH's National Heart, Lung and Blood Institute, and notes that any grant proposal review that

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— DAVID WARSHAW, PH.D.

considers environment has historically found that cardiovascular research is a particular strength of UVM and the College of Medicine. Looking ahead, Nelson would like to see a tenfold increase in the CVRI's endowment, to allow the University to remain in the top ten percent of cardiovascular research arenas.

"Our center is one instrument through which we can invest in the future by making things happen," he says. "We need to be heavily investing in cutting-edge technology and people so we can keep the momentum going."

Growth is continuing — as recently as March, the CVRI established a leadership council, composed of seven individuals who are community leaders but not directly affiliated with UVM or the Medical Center. They will be tasked with highlighting CVRI-related activities and raising money to fund additional research. Schneider says he'd like the leadership council to create forums for investigators to talk about their work with the community at large — locally, and then regionally and beyond.

"I think many of the investigators within the University of Vermont are classic New England in that they tend to do hard work, and they're oftentimes respected and acknowledged more when they get on a plane and go someplace else," says Schneider. So the leadership council's first step will be to get the word out "to let people in Vermont be proud of what they have going on here."

It's nearly impossible to summarize the breadth of cardiovascular research that's happening around UVM and the College of Medicine in a given day, the findings that are made at the microscopic and the clinical levels.

Heart disease remains the number-one killer both in the United States and globally; and, as people live longer, doctors are seeing more of it. Heart failure, says Schneider, is essentially epidemic right now. But the new therapies continue to offer hope. By way of example, he mentions Dauerman's work on aortic stenosis, the thickening of valves that occurs fairly commonly later in life. Improvements in technology using a catheter have made it easier to replace valves in people in their 80s and 90s who otherwise would likely have died. One patient, he says, a 90-year-old, was headed for hospice care when she and her daughter heard a public service announcement about the new procedure. They made an appointment immediately, and three years later, she's living independently. She stops by annually to visit with Dauerman and express her gratitude.

"The research that we're doing has a tremendous impact," says Schneider. "It's pretty exciting stuff." He looks down the road, but for now no further than maybe five years, when he hopes to see the junior investigators maturing and becoming part of the fabric of the CVRI, perhaps on their way to being named Distinguished Investigators. Other initiatives on the horizon include grant reviewing; funding of cardiovascular work; and serving as a clearinghouse for departmental expertise, services and equipment, although on some levels that's currently happening. With that broad new base established, the Cardiovascular Research Institute is already perfecting the art of collaboration. **VM**



The Cardiovascular Research Institute of Vermont Board of Directors. From left: David Schneider, M.D., Harry Dauerman, M.D., Marilyn Cipolla, Ph.D., David Warshaw, Ph.D., Mark Nelson, Ph.D., Ira Bernstein, M.D., and Mary Cushman, M.D., M.Sc.