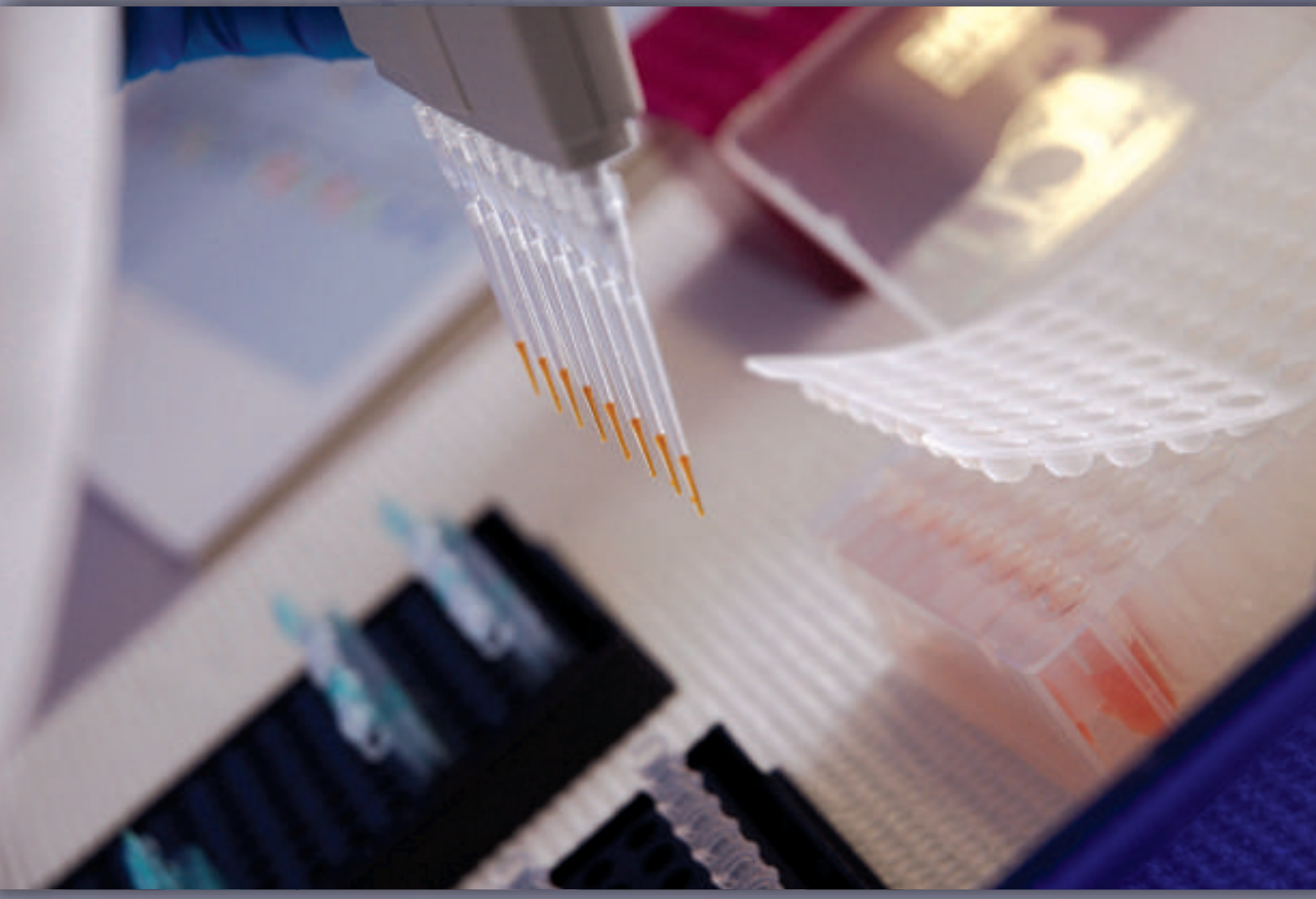
MAYO CLINIC

Cardiovascular Research 2008



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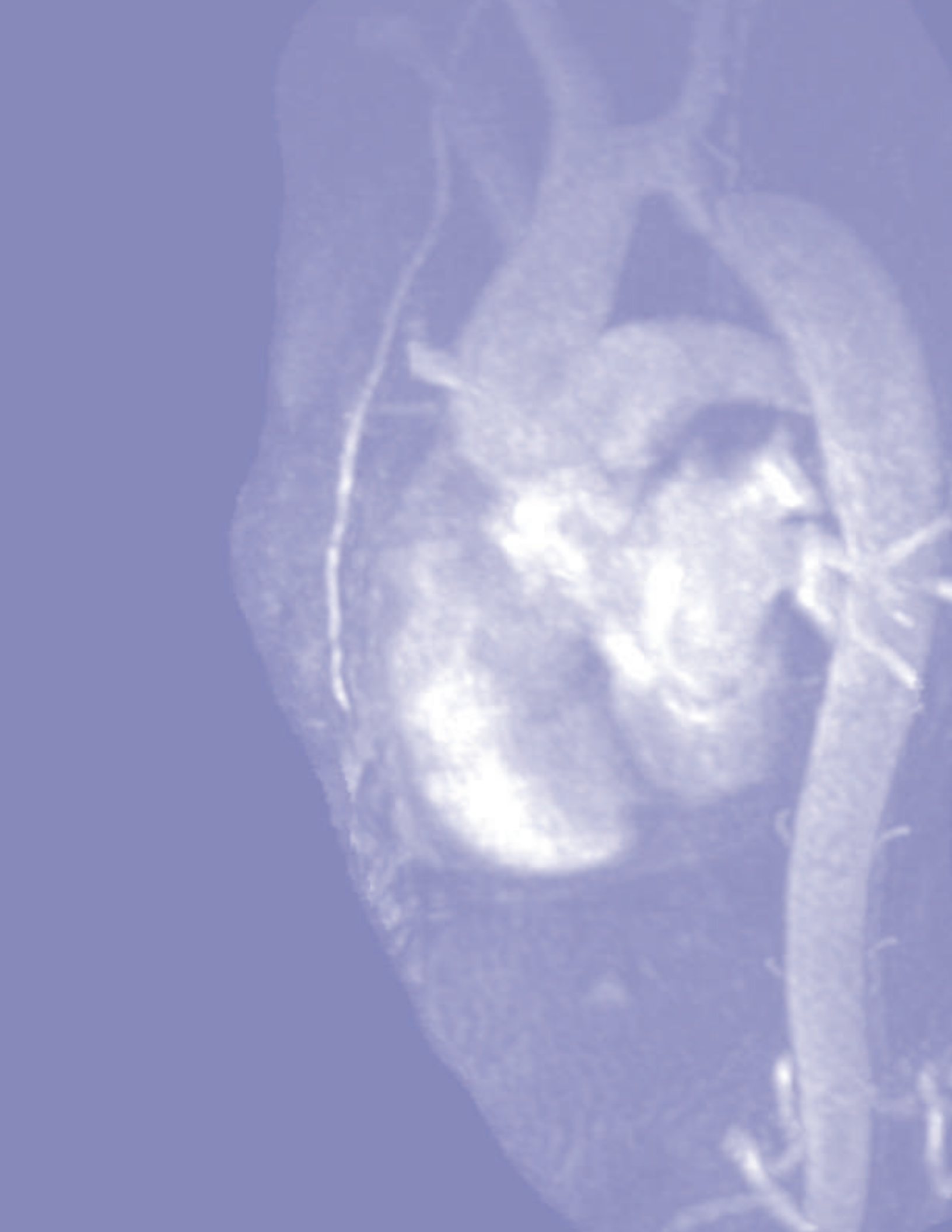

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Dear Colleague:

On behalf of the Division of Cardiovascular Diseases and our colleagues in the Divisions of Cardiovascular Surgery and Pediatric Cardiology, I would like to take this opportunity to welcome you to Cardiovascular Research 2008. The mission of Cardiovascular Research at Mayo Clinic Rochester is to understand, optimally treat, ultimately predict, and cure cardiovascular disease. The Cardiovascular Research Committee consists of a well-integrated, broadly defined group of investigators with particular strengths in ischemic heart disease, heart failure, and arrhythmiogenesis. This booklet provides a glimpse into this widely varied research community that extends from basic molecular sciences to clinical epidemiology.

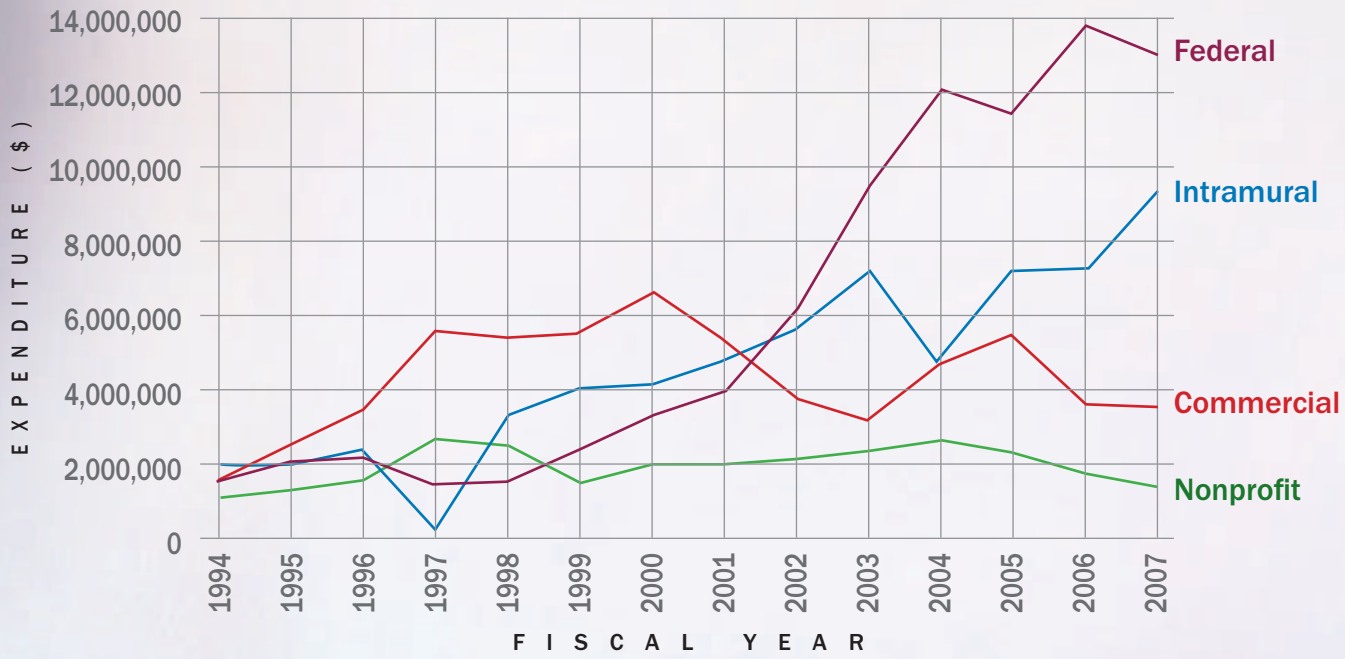
The community represented in this booklet is actively involved in education of undergraduates, medical students, graduate students, residents, and postdoctoral fellows. The group hosts visiting scientists from all over the world. If you are interested in contacting any of the investigators whose work is described in this booklet, please do not hesitate to use the contact information provided on the back cover.

Sincerely,

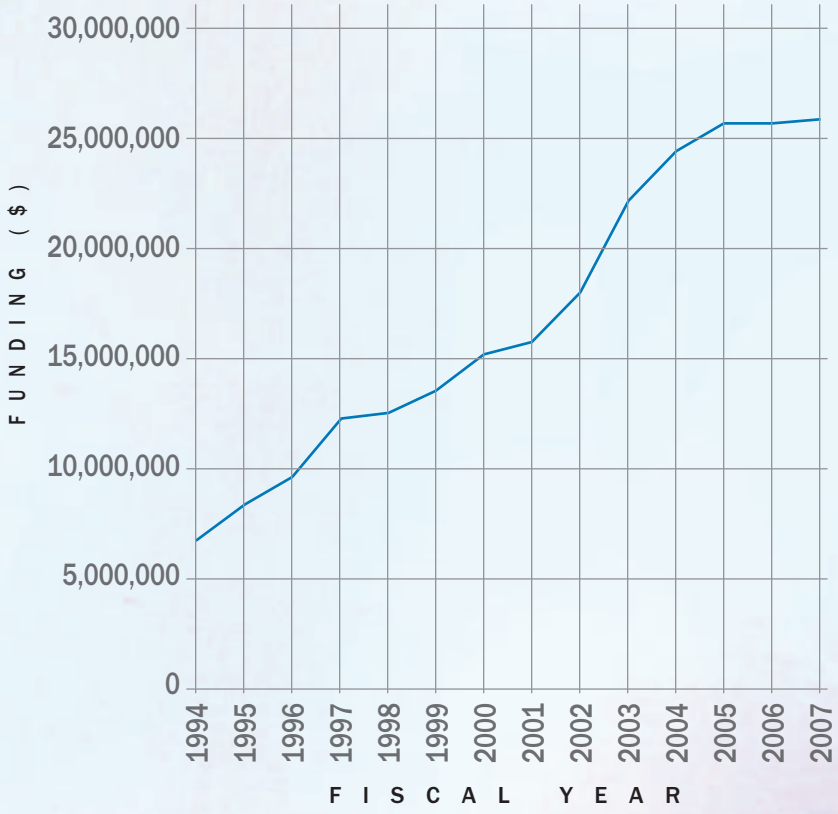
Robert Simari

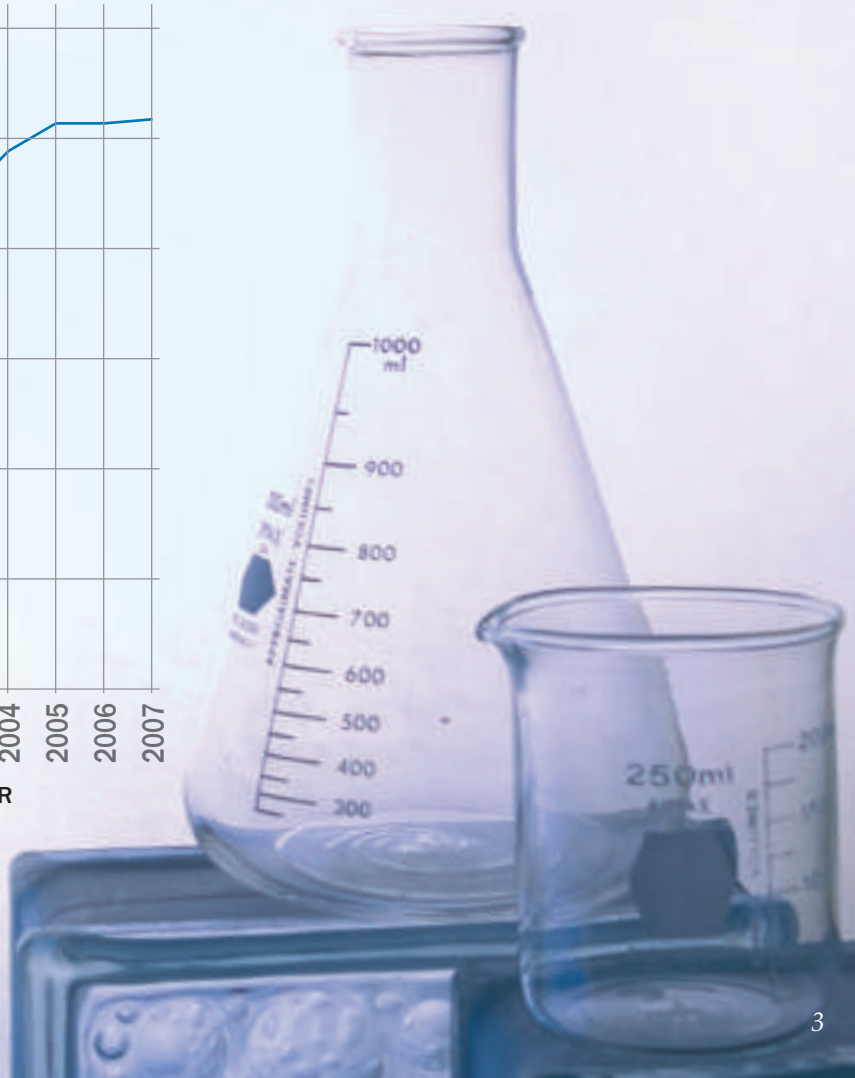
Robert D. Simari, MD
Professor of Medicine
Vice Chair for Cardiovascular Research

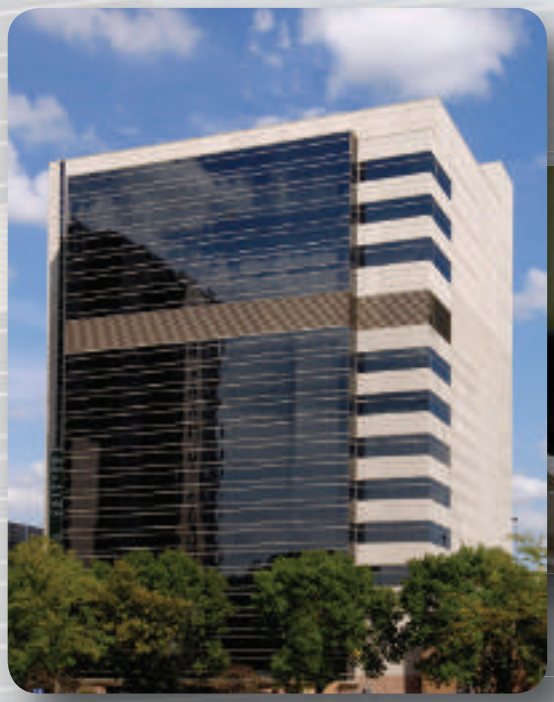
Total Cardiovascular Research Expenditures by Source



Total Cardiovascular Research Funding by Year



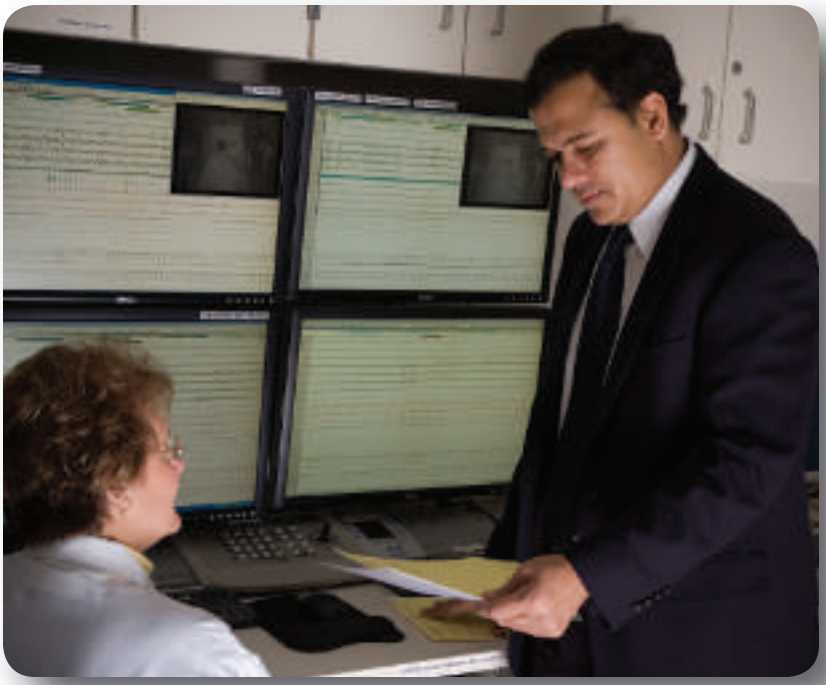




In August 2007, the Judd Leighton Cardiovascular Research Laboratories were dedicated on the fourth and fifth floors of the Vincent A. Stabile Building. These state-of-the-art research laboratories are used by basic and translational cardiovascular scientists. Judd Leighton's relationship with Mayo Clinic encompassed close friendships and a strong philanthropic spirit that continues through his foundation.

Robert Simari MD, vice chair for cardiovascular research (right), and Alexander Schirger, MD (second from right), and members of the Judd Leighton Foundation board tour new laboratory facilities.

Publications by Mayo Clinic Cardiovascular Staff



VIREND K. SOMERS, MD, DPHIL

Dr Somers's research interests relate to the links between sleep disorders, obesity, and cardiovascular disease. His research techniques include population studies, patient-oriented research, and molecular studies of disease mechanisms. Ongoing studies are evaluating the inflammatory, vascular, metabolic, and molecular consequences of fat gain in healthy individuals; identifying the mechanisms by which sleep apnea and sleep deprivation may induce cardiac and vascular events; exploring the links between sleep and the early morning surge in cardiovascular and cerebrovascular events; and defining the mechanisms leading to increased cardiovascular risk in National Football League players and other professional athletes.

Funding for his research program is provided by several grants from the National Institutes of Health as well as predoctoral and postdoctoral awards from the American Heart Association.

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Kara T, Wolk R, Somers VK. Sleep apnea and cardiac disease. In: Murphy JG, Lloyd MA, editors. Mayo Clinic cardiology: concise textbook. 3rd edition. Murphy JG, Lloyd MA, editors. Rochester, MN: Mayo Clinic Scientific Press, Informa Healthcare; 2007. pp. 1035-1042.

Bruce D. Johnson, PhD

Dr Johnson's laboratory is focused on human integrative and applied physiology. Recent studies have centered around the impact of altered cardiovascular function associated with heart failure on the respiratory system. In particular, the project has included studying heart failure–related changes in lung mechanics, gas exchange, and ventilatory control and the impact on functional capacity. Novel methods have been developed to assess cardiac output, to quantify alveolar-capillary recruitment, and to measure pulmonary and airway blood flow noninvasively. His laboratory also has a strong interest in human adaptation to hypoxia-altitude and possible synergies with disease. He is funded by grants from the National Institutes of Health, the National Science Foundation, and the American Heart Association.

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Snyder EM, Beck KC, Hulsebus ML, Breen JF, Hoffman EA, Johnson BD. Short term hypoxic exposure at rest and during exercise reduces lung water in healthy humans. J Appl Physiol 2006;101:1623-1632.

Olson TP, Frantz RP, Snyder EM, O'Malley KA, Beck KC, Johnson BD. Effects of acute changes in pulmonary wedge pressure on periodic breathing at rest in heart failure patients. Am Heart J 2007;153:104.e1-104.e7.

Juan Carlos Romero, MD

Dr Romero's research covers 2 areas:

- To understand the renal mechanisms responsible for the control of blood pressure. Specific emphasis is placed on the role of the renin-angiotensin system, oxidative stress, and sodium metabolism.
- To develop a noninvasive system based on imaging provided by 3-dimensional computed tomography with high temporal resolution or magnetic resonance to evaluate renal function. This has been done in diseases that affect the kidney such as renovascular hypertension and obstructive nephropathies.

SELECTED PUBLICATIONS

Daghini E, Juillard L, Haas JA, Krier JD, Romero JC, Lerman LO. Comparison of mathematic models for assessment of glomerular filtration rate with electron beam CT in pigs. Radiology 2007;242:417-424.

Juillard L, Lerman LO, Kruger DG, Haas JA, Rucker BC, Polzin JA, Riederer SJ, Romero JC. Blood oxygen level-dependent measurement of acute intrarenal ischemia. Kidney Int 2004;65:944-950.

Reckelhoff JF, Romero JC. Role of oxidative stress in angiotensin induced hypertension. Am J Physiol Reg 2003;284:R893-R912.

Bentley MD, Ortiz MC, Ritman EL, Romero JC. The use of microcomputed tomography to study microvasculature in small rodents. Am J Physiol 2002;282: R1267-R1279.

Romero JC, Lerman LO. Novel noninvasive techniques for studying renal function in man. Semin Nephrol 2000;20:456-462.

Lilach O. Lerman, MD, PhD

Dr Lerman's research involves development and application of basic science techniques to study renal and cardiovascular physiology and pathophysiology in both animal and human models. High-resolution imaging methods are applied for exploration of physiologic processes and of adaptive responses to cardiovascular disease, such as hypertension, ischemia, hypercholesterolemia, and early atherosclerosis. Disease mechanisms are subsequently investigated using molecular biology and cell culture techniques, and potential therapeutic targets are identified using novel interventions, including drugs, revascularization, and progenitor cell delivery. The research has been supported by grants from the National Institutes of Health and the American Heart Association.

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Chade AR, Zhu X, Mushin OP, Napoli C, Lerman A, Lerman LO. Simvastatin promotes angiogenesis and prevents microvascular remodeling in chronic renal ischemia. FASEB J 2006:20:1706-1708.

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Zhu X, Rodriguez-Porcel M, Bentley MD, Chade AR, Sica V, Napoli C, Caplice N, Ritman EL, Lerman A, Lerman LO. Antioxidant intervention attenuates myocardial neovascularization in hypercholesterolemia. Circulation 2004;109:2109-2015.

DAVID J. DRISCOLL, MD

Dr Driscoll pursues epidemiological and outcome analysis of pediatric cardiac disease. Using the Mayo Clinic database, he is able to evaluate the usefulness of various diagnostic procedures and efficacy of treatment. Currently he is analyzing long-term outcomes of 538 patients who have had surgery for Ebstein anomaly.

Dr Driscoll is also completing a meta-analysis of the effect of pectus excavatum repair on short- and long-term cardiopulmonary function. He continues to collaborate in studying the genetic basis of vascular malformations.

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Bartz PJ, Driscoll DJ, Dearani JA, Puga FJ, Danielson GK, O'Leary PW, Earing MG, Warnes CA, Hodge DO, Cetta F. Early and late results of the modified Fontan operation for heterotaxy syndrome. J Am Coll Cardiol 2006;48:2301-2305.

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Husmann DA, Rathburn SR, Driscoll DJ. Klippel-Trenaunay syndrome: incidence and treatment of genitourinary sequelae. J Urol 2007;177:1244-1249.

Driscoll DJ. Socrates, epistemology, and pediatric cardiology, or should doctors think like lawyers? Congenit Heart Dis 2007;2:220-223.

Benjamin W. Eidem, MD

Tissue Doppler and strain rate imaging are novel echocardiographic techniques that enable quantitative evaluation of the motion and deformation of the myocardium. Dr Eidem's research interests have focused on the application of these exciting new advances in noninvasive imaging to the evaluation of ventricular function in fetuses, children, and adults with congenital heart disease. In particular, his research has focused on the impact of altered geometry and loading conditions on these echocardiographic parameters in both preoperative and postoperative settings. In addition, the impact of medical, interventional, and surgical therapies on short- and long-term ventricular performance has also been an important area of ongoing research in congenital heart disease.

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Jefferies JL, Eidem BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. Genetic predictors and reverse remodeling of dilated cardiomyopathy in muscular dystrophy. Circulation 2005; 112: 2799-2804.

Frank Cetta, MD

Dr Cetta has many clinical research interests in the field of pediatric cardiology. Particular areas of interest include

- placement of intra- and extra-cardiac closure devices
- heparin-induced thrombo-cytopenia in congenital heart disease
- clinical outcomes of adults with congenital heart disease
- advanced echocardiography in congenital heart disease
- long-term follow-up of patients with congenital heart disease after Fontan operation

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Porcelli R, Moskowitz BC, Cetta F, Graham LC, Eidem BW, Godwin JE, Prechel MM, Walenga JM. Heparin-induced thrombocytopenia with associated thrombosis in children after the Fontan operation: report of two cases. Tex Heart Inst J 2003;30:58-61.

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Allison K. Cabalka, MD

Dr Cabalka leads the congenital catheterization laboratory research efforts. Her interests primarily involve use of cutting-edge interventional catheterization therapy for children and adults with congenital heart disease. She also is active in the congenital echocardiography laboratory and complements her work in the catheterization laboratory with use of intracardiac echocardiography. Dr Cabalka is a champion for international humanitarian efforts to deliver quality pediatric cardiology care to emerging nations.

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Bartz PJ, Cetta F, Cabalka AK, Reeder GS, Squarcia U, Agnetti A, Aurier E, Carano N, Tachana B, Hagler DJ. Paradoxical emboli in children and young adults: role of atrial septal defect and patent foramen ovale device closure. Mayo Clin Proc 2006; 81:615-618.

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Patrick W. O'Leary, MD

Dr O'Leary's current research efforts are focused on improving understanding of the following concepts:

- The relationships between Doppler hemodynamics and clinical parameters and their relationship to pediatric patient outcomes.
- The anatomy of complex congenital cardiac malformations using multimodality imaging (including live 3-D echocardiography and intraoperative transesophageal echocardiography).
- Noninvasive assessment of myocardial systolic and diastolic function, with emphasis on the correct ventricle in patients with congenital cardiac malformations. Efforts in this area also involve correlation with the catheterization laboratory and cardiac magnetic resonance imaging center. Areas of special interest include myocardial deformation imaging (strain and strain rate evaluation) and retrospective studies aimed at outlining echocardiographic parameters that may predict patient outcomes.

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Dearani JA, O'Leary PW, Danielson GK. Surgical treatment of Ebstein's malformation: state of the art in 2006. Cardiol Young 2006;16 (Suppl 3):12-20.

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CHRISTOPHER G.A. MCGREGOR, MB, FRCS

One potential approach to address the donor shortage is xenotransplantation, which involves transplanting living organs from one species to another. The idea of conducting animal-to-human transplants is not a new one. Indeed, xenotransplantation has been tried at various times during the past 95 years. Recent scientific study has revealed that there exist specific molecular hurdles to carrying out pig-to-human xenografts and that these hurdles can be addressed in a definitive manner by the genetic engineering of animals. The success of this endeavor has stimulated the imagination of many in the field of transplantation. As well as organs, such as the heart and kidney, genetically altered animals could provide cells, for example, for the treatment of diabetes and other diseases and tissues for orthopedic (ligament and bone) and cardiac surgical (heart valves) applications.

Research studies in Dr McGregor's laboratory include

- Genetic Engineering Research. As part of the xeno-transplantation research program, he has been studying the human immune system and genetically engineering pigs so that their organs do not trigger the standard human immune response that would destroy them when transplanted. Human transgenes have been added to the pig genome as well as the knocking out of specific pig genes that lead to animal organ rejection.

- Preclinical Research. Mayo Clinic transplant scientists and physicians are studying pig cardiac xenotransplantation using genetically altered pig donors. Studies of orthopedic and cardiac surgical applications of xenotransplantation are also being pursued.

- Immunosuppression and Rejection. A major focus in the xenotransplantation laboratory is optimization of immunosuppression following xenotransplantation, with specific studies on the pathophysiology of xenograft vascular rejection.

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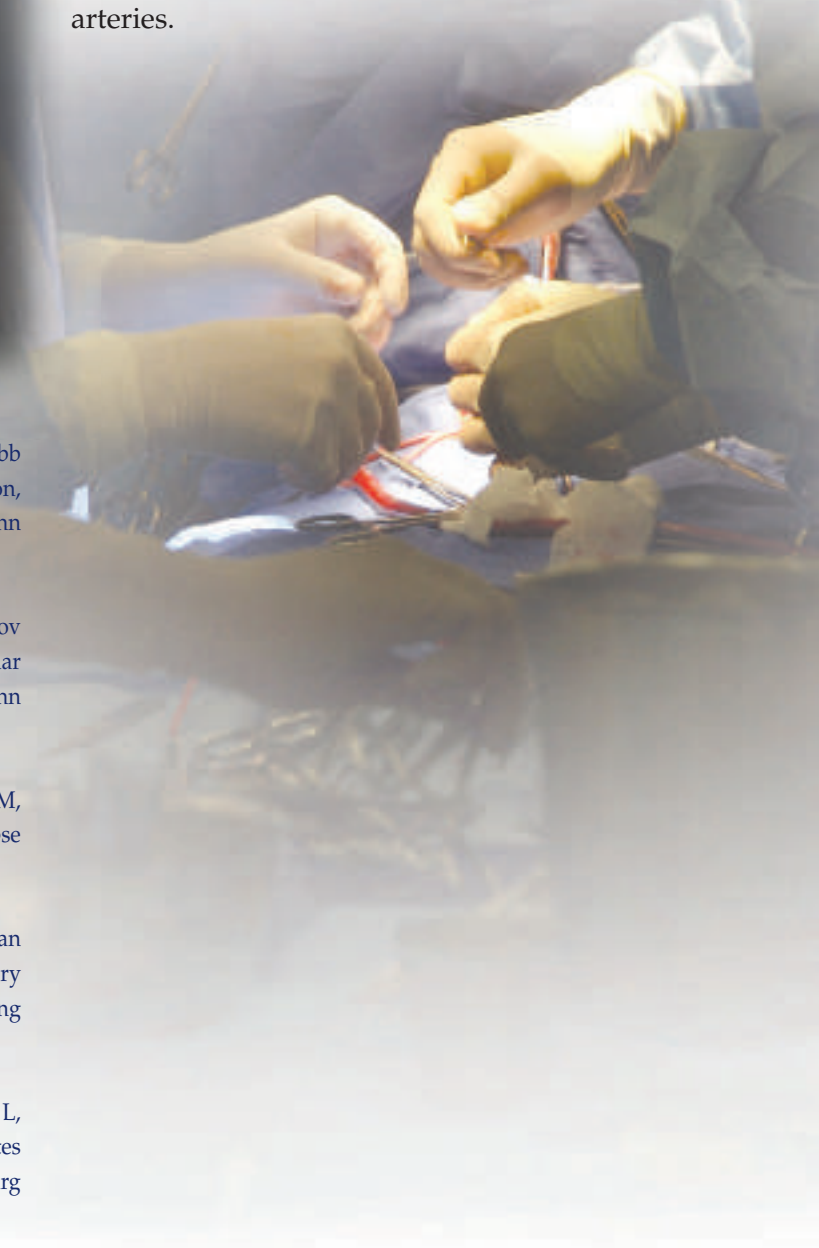
Davila E, Byrne GW, LaBreche PT, McGregor HCJ, Schwab AK, Davies WR, Rao VP, Oi K, Tazelaar HD, Logan JS, McGregor CGA. T cell responses during pig-to-primate xenotransplantation. Xenotransplantation 2006;13:31-40.

Byrne GW, Davies WR, Oi K, Rao VP, Teotia SS, Ricci D, Tazelaar HD, Walker RC, Logan JS, McGregor CGA. Increased immunosuppression not anticoagulation extends cardiac xenograft survival. Transplantation 2006;82:1787-1791.

Rao VP, Miyagi N, Ricci D, Carlson SK, Morris JC 3rd, Federspiel MJ, Bailey KR, Russell SJ, McGregor CG. Sodium iodide symporter (hNIS) permits molecular imaging of gene transduction in cardiac transplantation. Transplantation 2007;84:1662-1666.

Harold M. Burkhart, MD

Dr Burkhart's research interests focus on clinical aspects of congenital and pediatric cardiac surgery. Current projects include research on the surgical aspects of tetralogy of Fallot, coarctation of the aorta, Shone syndrome, and anomalous coronary arteries.



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De Oliveira NC, Ashburn DA, Khalid F, Burkhart HM, Adatia IT, Holtby HM, Williams WG, Van Arsdell GS. Prevention of early sudden circulatory collapse after the Norwood operation. Circulation 2004;110(11 Suppl 1):II133-II138.

Bagtharia R, Trivedi KR, Burkhart HM, Williams WG, Freedom RM, Van Arsdell GS, McCrindle BW. Outcomes for patients with an aortopulmonary window, and the impact of associated cardiovascular lesions. Cardiol Young 2004;14:473-480.

Burkhart HM, Ashburn DA, Konstantinov IE, De Oliveira NC, Benson L, Williams WG, Van Arsdell GS. Interdigitating arch reconstruction eliminates recurrent coarctation after the Norwood procedure. J Thorac Cardiovasc Surg 2005;130:61-65.

Thoralf M. Sundt III, MD

Dr Sundt's main areas of investigation include bicuspid aortic valve disease and the role of human factors in cardiovascular surgery laboratory has projects under way addressing both the clinical behavior (phenomics) and genetic basis (genomics) of bicuspid aortic valve disease with a focus on aneurysmal disease. Drawing on the large Mayo Clinic surgical database and clinical experience, he is investigating the clinical behavior of this condition, including the natural history of the aorta and the risk of ultimate aortic dissection or rupture. Additionally, he is studying the basis of this condition with the ultimate translational goal of permitting genetically tailored surgical therapy. Furthermore, studies of individuals with a family history of bicuspid aortic valve disease have led Dr Sundt to identify novel areas of interest in the human genome as potential sites of the gene ultimately responsible for this common and clinically important condition.

Recognizing the critical role of primary research in laying the foundation for change in clinical practice, the cardiovascular surgery group has established an investigative program in human factors. The activities of this group are currently focused on the operating room itself, although the scope will expand to other areas of the hospital in the future. As part of the infrastructure for primary research on human factors and its impact on error management (error prevention, error detection, and error correction) in the cardiovascular surgical operating rooms, functioning cameras have been installed in one of the cardiovascular surgical operating rooms which permitting remote viewing of cases by staff without directly interfering with the team dynamics. This work has already led to important insights into team dynamics in this setting. Dr Sundt is also in the process of establishing interinstitutional collaborations regarding human factors to augment studies and facilitate the communication of findings with others.

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Sundt TM 3rd, Mora BN, Moon MR, Bailey MS, Pasque MK, Gay WA Jr. Options for repair of a bicuspid aortic valve and ascending aortic aneurysm. Ann Thorac Surg 2000;69:1333-1337.

Absi TS, Sundt TM, Tung WS, Moon M, Lee JK, Damiano RR, Thompson RW. Altered patterns of gene expression distinguishing ascending aortic aneurysms from abdominal aortic aneurysms: complementary DNA expression profiling in the molecular characterization of aortic disease. J Thorac Cardiovasc Surg 2003;126:344-357.

Okamoto RJ, Xu HD, Kouchoukos NT, Moon MR, Sundt TM. The influence of mechanical properties on wall stress and distensibility of the dilated ascending aorta. J Thorac Cardiovasc Surg 2003;126:842-850.

Majumdar R, Yagubyan M, Sarkar G, Bolander ME, Sundt TM. Bicuspid aortic valve and ascending aortic aneurysm are not associated with germline or somatic homeobox NKX2-5 gene polymorphism in 19 patients. J Thorac Cardiovasc Surg 2006;131:1301-1305.

Joseph A. Dearani, MD

Dr Dearani's main areas of investigation include congenital heart disease, with a specific interest in late-outcome data for large numbers of patients with congenital heart disease. Drawing on a large Mayo Clinic surgical database and clinical experience, he is investigating the late results of patients with congenital heart disease who initially have surgery during childhood and live into their adult years. Many of these patients require repeat operations during adult life. Risks and benefits of reoperation and long-term survival with quality-of-life issues are the focus of these studies.

In addition, he has a special interest in the pathology of congenital heart disease, with emphasis on surgical-pathological correlation. The largest collection of cardiovascular pathology specimens in the world resides in Minnesota at both the Jesse E. Edwards Registry of Cardiovascular Disease in St Paul and at Mayo Clinic in Rochester. Drawing on this large database and collaboration, he is currently writing a textbook on the pathology of congenital heart disease.

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Stulak JM, Dearani JA, Daly RC, Zehr KJ, Sundt TM, Schaff HV. Left ventricular dysfunction in atrial fibrillation: restoration of sinus rhythm by the Cox-maze procedure significantly improves systolic function and functional status. Ann Thorac Surg 2006;82:494-501.

Suri RM, Schaff HV, Dearani JA, Sundt TM, Daly RC, Mullany CJ, Enriquez-Sarano M, Orszulak TA. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. Ann Thorac Surg 2006;82:819-827.

Richard C. Daly, MD

Dr Daly is the principal investigator at Mayo Clinic Rochester for several clinical trials, including

- the STICH trial (Surgical Treatment of Ischemic Heart Failure), a multicenter, prospective, randomized trial comparing coronary artery bypass grafting to medical therapy for patients with ischemic cardiomyopathy. The trial will also evaluate the effectiveness of surgical ventricular remodeling for ischemic cardiomyopathy.
- a multicenter, prospective, randomized trial comparing the HeartMate II and HeartMate XVE left ventricular assist devices as permanent destination therapy.
- a multicenter, prospective trial evaluating the Jarvik 2000 left ventricular assist device as a bridge to transplantation.

Dr Daly has been involved with the development of a new surgical instrument that allows mitral valve repair by placing artificial chordae tendineae into the mitral leaflets in an off-pump manner that may lead to a minimally invasive approach to repair mitral insufficiency.

He is also involved with clinical investigations into tricuspid insufficiency after heart transplantation, combined heart-and-liver or heart-and-kidney transplantation, heart transplantation with HLA mismatch and with HLA antigen-antibody mismatch, and ischemic mitral insufficiency.

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IFTIKHAR J. KULLO, MD

Dr Kullo's work is focused on validating biomarkers of cardiovascular risk including genetic and proteomic markers as well as noninvasive measures of arterial function. Three main projects are ongoing:

- Genetic bases of atherosclerotic vascular disease (grant from the National Heart, Lung, and Blood Institute). The goal of this project is to identify the genetic determinants of peripheral arterial disease using both linkage and association approaches.
- Proteomic markers of arteriosclerosis (grant from the National Heart, Lung, and Blood Institute). The goal of this project is to study the association of novel protein markers in etiologic pathways of vascular disease with quantitative phenotypes of arteriosclerotic vascular disease (coronary artery calcium, cerebral leukoaraiosis, albuminuria, and ankle brachial index).
- Physiologic markers of arterial function. The goal of this project is to evaluate the association of measures of arterial function with vascular disease phenotypes in 2 large community-based cohorts.

The motivating hypothesis of all this research is that functional arterial measures (endothelial function and arterial stiffness) provide integrated assessments of the effects of diverse vascular risk factors and are associated with structural changes of arteriosclerosis. Dr Kullo is investigating whether measures of arterial wall function improve the prediction of quantitative measures of arteriosclerosis beyond what is possible with current algorithms for risk assessment (eg, the Framingham Risk Score).

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Klos KL, Kullo IJ. Genetic determinants of HDL: monogenic disorders and contributions to variation. Curr Opin Cardiol 2007;22:344-351.

Véronique L. Roger, MD, MPH

Dr Roger's is chair of the Department of Health Sciences Research at Mayo Clinic. Her research focuses on myocardial infarction and heart failure using a community-based approach. This ongoing work integrates classical tools of large-scale, population-based epidemiology with the measurement of novel biomarkers and imaging to further understanding of the burden of heart disease. Her research is supported by several research grants from the National Heart, Lung, and Blood Institute as well as an Established Investigator Award from the American Heart Association.

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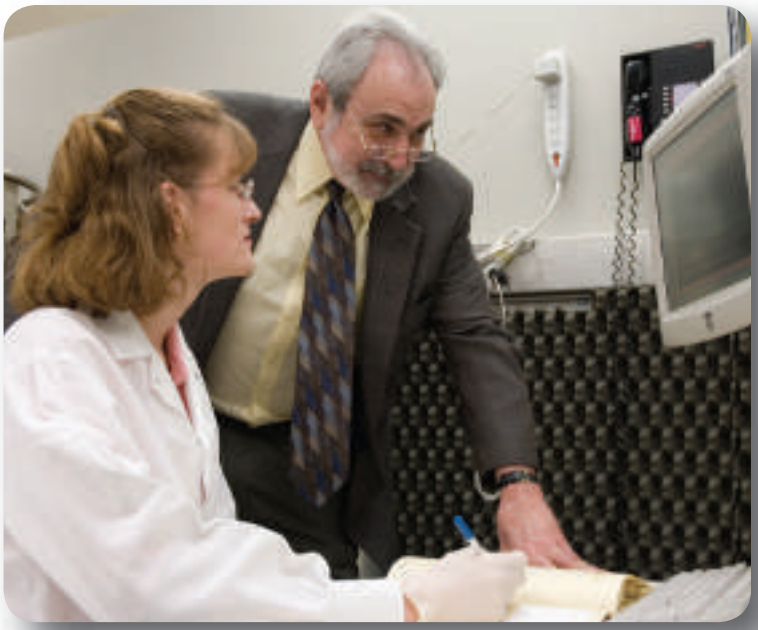
Allan S. Jaffe, MD

Dr Jaffe has spent his career investigating markers of myocardial injury, hemodynamic compromise, and hemostasis in patients with acute ischemic heart disease. He has a joint appointment in the Division of Cardiovascular Diseases and in the Department of Laboratory Medicine and Pathology where he is the medical director of cardiovascular laboratory medicine. His research involves assessment of clinical utility of markers such as troponin, creatine kinase MB, natriuretic peptides, and C-reactive protein as well as novel markers of cardiovascular abnormalities in patients with acute disease, usually ischemic heart disease and/or congestive heart failure. His research is extensively funded, and he has access through his clinical activities and that of collaborators to substantial numbers of patients.



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Henry H. Ting, MD, MBA

Dr Ting's clinical research is focused on quality improvement, health services, innovative models for health care delivery, and outcomes research. His research interests have included ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, drug-eluting stents, vascular closure devices, and percutaneous coronary intervention without on-site surgery involving large clinical registries, including the National Registry of Myocardial Infarction, American College of Cardiology National Cardiovascular Data Registry, and ACC-ACTION Registry. His work in quality improvement has used methods including Lean, Six Sigma, value network analysis, and Baldrige performance excellence criteria.

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GERALD T. GAU, MD

The focus of his research is preventive cardiology, particularly in the field of lipidology, and most recently the use of nuclear magnetic resonance technology to look at lipid particles in patients with complex lipid conditions as well as novel coronary disease risk factors.

With the National Institutes of Health, he is investigating the use of chelation therapy in high-risk coronary patients enrolled in a continuing trial to look at chelation's possible value. In the Cardiovascular Health Clinic, prevention of both primary and secondary coronary disease is his main research emphasis.

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Gau GT, Wright RS. Pathophysiology, diagnosis, and management of dyslipidemia. Curr Probl Cardiol 2006;31:445-486.

Francisco Lopez-Jimenez, MD, MSc

Dr Lopez-Jimenez's research interest includes translational research assessing the effect of obesity, metabolic syndrome, and sleep apnea on cardiovascular health. His current research is testing the added value of direct measurement of body fat and the implementation of effective weight loss techniques in clinical practice. He holds several grants supporting research on bariatric surgery and cardiovascular disease mechanisms and others supporting research on dietary interventions in metabolic syndrome.

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Lopez-Jimenez F, Bhatia S, Collazo-Clavell ML, Sarr MG, Somers VK. Safety and efficacy of bariatric surgery in patients with coronary artery disease. Mayo Clin Proc 2005;80:1157-1162.

Batsis J, Nieto-Martinez RE, Lopez-Jimenez F. Metabolic syndrome: from global epidemiology to individualized medicine. Clin Pharmacol Ther 2007;82:509-524.

Sharonne N. Hayes, MD

As director of the Women's Heart Clinic, Dr Hayes is interested in clinical research related the development, diagnosis, treatment, and prognosis of heart disease in women. She is a principal investigator in a number of clinical studies:

- Effects of Estrogen Replacement on Atherosclerosis Progression in Recently Menopausal Women: The Kronos Early Estrogen Prevention Study (KEEPS)
- Noninvasive Assessment of Endothelial Function Using Endo-PAT (Endothelial-Peripheral Arterial Tonometry) in Subjects Enrolled in KEEPS (Kronos Early Estrogen Prevention Study)
- SMART Study: Stress Echocardiography in Menopausal Women at Risk for Coronary Artery Disease
- AWARE Study (Angiogenesis in Women With Angina Pectoris Who Are Not Candidates for Revascularization)

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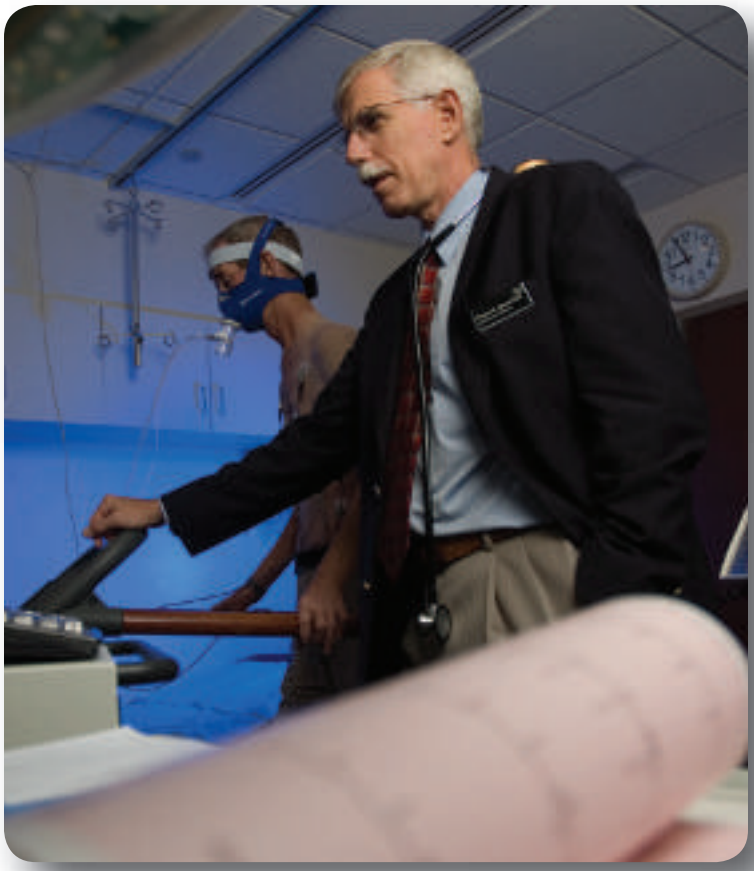
Thomas G. Allison, PhD, MPH

Dr Allison's research interests focus principally on exercise testing—in particular, the use of cardiopulmonary exercise testing for risk stratification and selection of patients with complex cardiac disease for surgical intervention. The Cardiovascular Health Clinic has a large database of exercise testing results that Dr Allison is evaluating. Mortality and other data are being analyzed to better understand predictors of clinical outcomes.

He is also interested in coronary risk factor management, especially the practical aspects of managing risk factors in clinical practice.



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Randal J. Thomas, MD, MS

Dr Thomas's research work is focused on finding ways to reduce the so-called prevention gap—the gap in the use of preventive strategies of known efficacy in clinical practice. These efforts are centered on 2 main areas of study:

- Cardiovascular risk assessment, using primary and secondary database analysis from the Mayo Clinic Cardiovascular Health Clinic database, as well as other Mayo Clinic and national databases.
- Cardiovascular risk reduction, exploring ways to better define and apply appropriate preventive therapies in the clinical and community settings.

Current research protocols include a project to assess a novel risk assessment tool for vascular health (arterial augmentation index) and 2 projects aimed at identifying and reducing barriers to secondary prevention strategies for patients with cardiovascular disease.

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Thomas RJ, Witt BJ, Lopez-Jimenez F, King ML, Squires RW. Quality indicators in cardiovascular care: the case for cardiac rehabilitation. J Cardiopulm Rehabil 2005;25:249-256.

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Sharon L. Mulvagh, MD

Dr Mulvagh's research interests include risk assessment for coronary disease in women. Current active protocols include

- Effects of Estrogen Replacement on Atherosclerosis Progression in Recently Menopausal Women: The Kronos Early Estrogen Prevention Study (KEEPS)
- Noninvasive Assessment of Endothelial Function Using Endo-PAT (Endothelial-Peripheral Arterial Tonometry) in Subjects Enrolled in KEEPS (Kronos Early Estrogen Prevention Study)
- SMART: Stress Echocardiography in Menopausal Women at Risk for Coronary Artery Disease

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ARSHAD JAHANGIR, MD

Dr Jahangir has expertise in cardiac electrophysiology and gerontology and directs the CardioGerontology Research Laboratory. His basic research interests include the study of aging on cardiovascular pathophysiology, cardioprotection, and arrhythmogenesis, specifically focusing on the role of mitochondria in cardiac responsiveness to stress.

He has received several awards, including recent acknowledgment by the American Society for Clinical Pharmacology and Therapeutics, which presented him with the William B. Abrams Award for Geriatric Clinical Pharmacology. He has received research grants from the National Institute on Aging of the National Institutes of Health, the American Heart Association, and the Society of Geriatric Cardiology and several intramural awards from Mayo Clinic.

His CardioGerontology Research Laboratory studies the effect of aging on cardiac function in health and diseases and uses a multiparametric approach, applying tools from molecular biology, basic cardiac electrophysiology, imaging, pharmacology, genomics, and proteomics to study changes in heart function with aging. The focus is on transcriptional and proteomic profiling with detailed functional assessment of cellular and mitochondrial pathways regulating cardiac energetics, ion channels, and cellular excitability in animal models and cardiac tissue from young and elderly patients. The overall goal of his research is to obtain insights into the molecular basis for increased susceptibility of the aging heart to electrical instability and mechanical dysfunction and to discover novel therapeutics for the prevention and treatment of age-related cardiac disabilities.

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Liu X-K, Jahangir A, Shen WK. Dysrhythmias in older adults. In: Principles of geriatric medicine and gerontology. 6th edition. In press.

Michael J. Ackerman, MD, PhD

Dr Ackerman's research program is endowed as the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory and is dedicated to the discovery of novel disease-causing genes and the elucidation of genotype-phenotype relationships for

- the most common causes of autopsy-negative sudden death, namely, the cardiac channelopathies that include long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT)
- sudden infant death syndrome (SIDS)
- the most common cause of autopsy-positive sudden death in young people, especially athletes, namely, hypertrophic cardiomyopathy (HCM)

In addition, as director of the Long QT Syndrome Clinic, Dr Ackerman has active clinical translational research efforts devoted to identifying individuals at greatest risk for sudden death. These projects include autonomic nervous system studies and overnight sleep studies. During the past 12 months, his laboratory has published articles describing 6 novel disease-susceptibility genes for LQTS, SIDS, and HCM. In May 2007, Dr Ackerman received the 25th Young Investigator Award from the Society for Pediatric Research. In July 2007, his National Institutes of Health grant, "Cardiac Channel Mutations in Sudden Infant Death Syndrome," was renewed.

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Win-Kuang Shen, MD

The focus of Dr Shen's research program has been the disease mechanisms, therapeutic intervention, and outcomes in clinical electrophysiology and cardiac devices. The disease/condition-oriented themes include syncope, orthostatic intolerance, atrial fibrillation, and sudden cardiac death. He has long been interested in these problems in the aging and elderly populations. He continues clinical investigations on the mechanisms underlying vasovagal syncope, inappropriate sinus tachycardia, atrial fibrillation, and sudden death in familial conditions. He has developed several research databases, including databases on syncope, atrial fibrillation, and cardiac devices. He has been the principal investigator of several investigator-initiated single- and multicenter clinical trials. His most recent multicenter trial, "Pacing and AV Node Ablation Compared to Drug Therapy in Symptomatic Elderly Patients With Atrial Fibrillation Clinical Trial (PACIFIC)," has been funded for the pilot phase of the study.

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Razavi M, Luria DM, Jahangir A, Hodge DO, Low PA, Shen WK. Acute blood pressure changes after the onset of atrioventricular nodal reentrant tachycardia: a time-course analysis. J Cardiovasc Electrophysiol 2005;16:1037-1040.

Teresa S. Tsang, MD

Recognizing the continued growth of the population of older persons in the United States, many of whom suffer from age-related cardiovascular conditions, Dr Tsang's research team is dedicated to research endeavors that will enhance understanding of cardiovascular physiologic aging. Her work focuses on testing novel noninvasive techniques for the prediction and prevention of age-related cardiovascular and cerebrovascular outcomes, including atrial fibrillation, stroke, heart failure, ischemic heart disease, and cognitive dysfunction. Her team has been particularly interested in the epidemiology of atrial fibrillation and echocardiographic prediction and prevention of this and other age-related cardiovascular conditions.

Dr Tsang has conducted pilot clinical trials for modification of some of the factors leading to atrial fibrillation, such as diastolic dysfunction and left atrial remodeling. In collaboration with colleagues in neurology, she is also actively conducting studies looking at the relationship between cardiovascular risk factors and cognitive function as well as stroke.

SELECTED PUBLICATIONS

Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TSM. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119-125.

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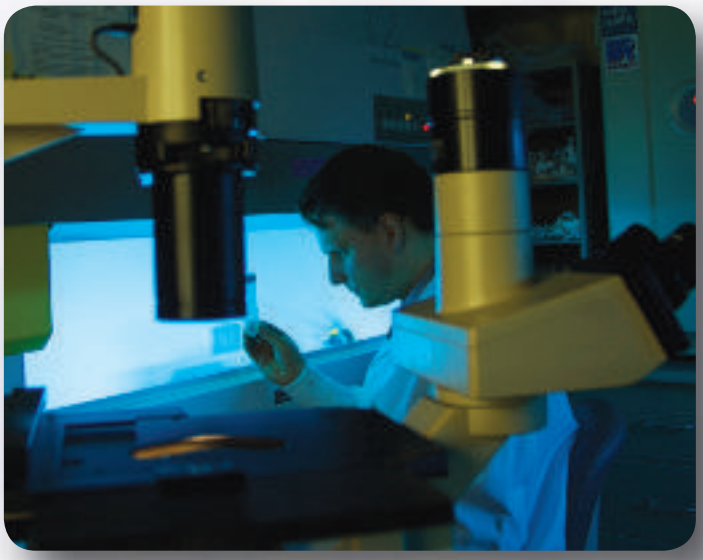
Andre Terzic, MD, PhD

Dr Terzic is director of the Mayo Clinic Marriott Heart Disease Research Program. His specific areas of interest include

- Cardioprotective and cardioregenerative medicine
- Stem cells and developmental cardiac biology
- Genetics of cardiac disease and stress tolerance in health and disease
- Bioenergetic signaling, nucleocytoplasmic communication, and ion channel biology
- Ischemic heart disease, heart failure, cardiomyopathy, and atrial fibrillation

The priority of this multidisciplinary research program is to decipher molecular pathways of stress tolerance and to identify the genetic basis of maladaptation in human disease. This ongoing work has evolved along the principles of metabolomic matrix networks and biocatalysis applied to the pathogenetics of cardiac disease, such as heart failure.

Dr Terzic's integrative research is at the interface of biophysics, biochemistry, physiology, and medicine and has led to the discovery of the vital role for membrane metabolic sensors in decoding signs of energy distress. The promise that lies ahead is in the translation of the fundamental principles of stress adaptation, established for the heart and tested in discrete patient cohorts, into broader diagnostic and therapeutic screens applied to diverse disease entities and the population at large. In particular, early genetic detection of disease susceptibility for each individual and treatment by targeted stem cell–based repair deficits provide opportunities for the further advancement of cardiovascular medicine in the decade ahead.



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Timothy M. Olson, MD

The objective of Dr Olson's research program is to identify mutations in genes that cause or confer susceptibility to mechanical dysfunction and electrical instability in the heart. His molecular genetic studies focus on 2 heritable disorders in humans: idiopathic dilated cardiomyopathy and atrial fibrillation. Experimental strategies include genetic linkage analysis to map the genomic location of novel disease genes in familial cases and hypothesis-based mutational analyses of candidate genes. These investigations utilize technologically advanced, automated systems for high-throughput DNA analysis and capitalize on genomic information derived from the Human Genome Project. The long-term objective of his research is to gain new insights into molecular mechanisms for congestive heart failure and arrhythmias and apply this knowledge to improve diagnosis, treatment, and prevention of heart disease.

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Douglas L. Packer, MD

The focus of Dr Packer's investigative efforts in the Cardiac Electrophysiology Translational Research Laboratory is to understand the mechanisms underlying atrial fibrillation and its treatment with ablative intervention. This includes the investigation of the atrial structure/activity relationships in the left atrium and pulmonary veins. His group is developing 4- and 5-dimensional imaging techniques to enhance cardiac mapping approaches, which incorporate intracardiac ultrasound, computed tomography, and magnetic resonance image integration. Parallel studies for ventricular tachycardia/ventricular fibrillation ablation use this technology to create ablation paradigms for unstable ventricular tachycardia. He also seeks to discover cell therapies for modulating conduction during atrial fibrillation in the setting of ventricular dysfunction. With this, he hopes to design better interventional therapies for atrial arrhythmias and counter the conduction abnormalities present in cardiomyopathies. This work forms the translational basis for innovative therapies in the Clinical EP Laboratory, where Dr Packer is conducting parallel investigations. These studies are funded in part by the National Institutes of Health and the Mayo Clinic clinical investigator program.

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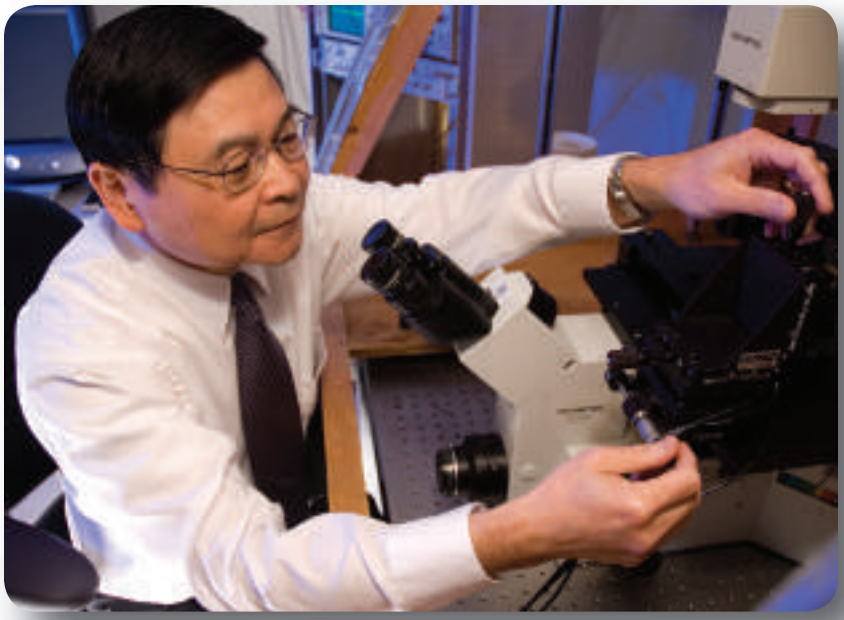
Hon-Chi Lee, MD, PhD

The major focus of Dr Lee's research is to understand the regulation of ion channels in the cardiovascular system. He uses patch clamp and microelectrode techniques to measure action potentials and ionic currents in cardiovascular tissues and cells. He also uses biochemical and molecular approaches to examine ion channel expression, cellular trafficking, membrane targeting, and the effect of mutagenesis on structure-function relationships. Specific active projects include

- Studies on the role of lipid metabolites in the regulation of potassium channels in heart and blood vessels.
- The role of endothelium-derived hyperpolarizing factors on vascular ion channel activities and on the regulation of vasoreactivity.
- New motifs of ion channel regulation, including the role of membrane microdomain targeting.
- Abnormal ion channel regulation in disease states such as diabetes and the role of reactive oxygen species on ion channel function.
- Novel approaches in the treatment of heart rhythm problems such as cellular therapy of cardiac arrhythmias.
- Use of proteomics approaches on cardiovascular diseases.



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Wang X-L, Fu A, Raghavakaimal S, and Lee H. Proteomic analysis of vascular endothelial cells in response to laminar shear stress. Proteomics 2007;7:588-596.

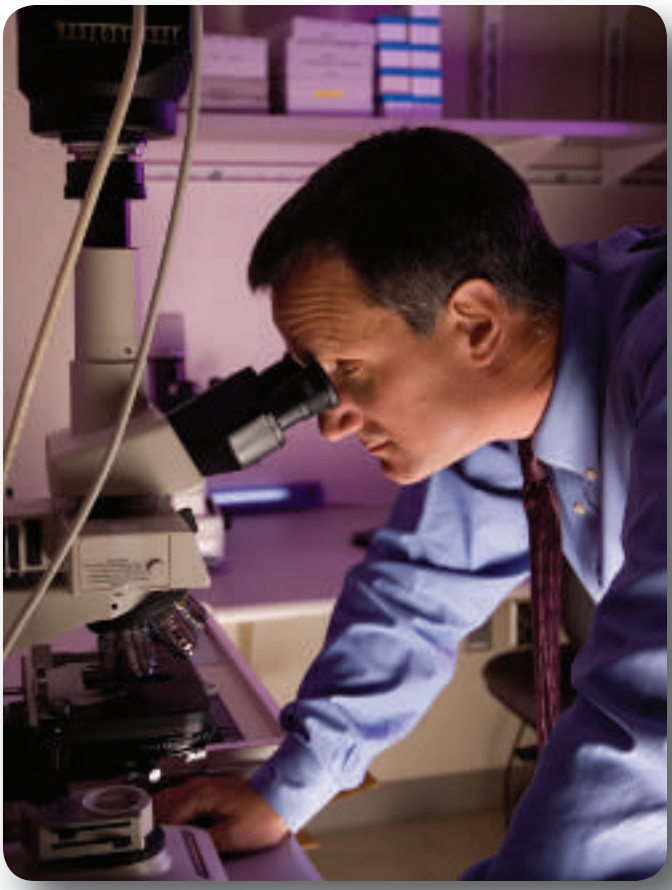
Robert D. Simari, MD

The focus of research in Dr Simari's laboratory is to define the biologic response to vascular injury and to utilize these mechanisms to develop novel biologic therapeutics. The laboratory has multiple National Institutes of Health–funded projects to support both major areas. In 1 protocol, for example, laboratory members have established unique murine models to study the role of the tissue factor pathway on vascular form and function. These models include tissue-specific overexpression and tissue-specific deletion of tissue factor pathway inhibitor. These mice allow Dr Simari to define how the tissue factor pathway is regulated in development and disease with a specific interest in thrombosis. This study was funding by the National Heart, Lung, and Blood Institute (NHLBI).

Dr Simari is interested in the role of circulating progenitor cells in the response to vascular injury. He has established a model by which he delivers autologously derived endothelial progenitors following vascular injury. Sources of cells currently being tested include blood, bone marrow, and fat. This study is also funded by NHLBI.

He is applying knowledge of circulation progenitors to the field of left ventricular (LV) dysfunction in collaboration with Drs John Burnett, Horng Chen, and Margaret Redfield as part of a program project grant on natriuretic peptides. They have demonstrated regulation of circulating progenitors in the setting of LV dysfunction and are developing means to deliver cells to reverse the process. They have also discovered a novel form of BNP, the result of alternative splicing which has unique biologic effects.

Dr Simari was recently named the national chair of the Cardiovascular Cell Therapy Research Network funded by the NHLBI, which provides an opportunity to participate in a unique multicenter network to perform cell therapy studies for LV dysfunction.



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Birgit Kantor, MD

Dr Kantor's research work is at the interface of vascular biology of atherosclerosis and cardiac imaging. She has a special interest in diabetic patients who are at increased risk of developing heart disease. Since 2000, she has been extramurally funded and is currently principal investigator on a National Institutes of Health (NIH) consortium agreement entitled "Collaterals in Aging: Enhanced by Genetic/Cell Therapy" and on a recent NIH grant entitled "In Vivo Localization of Vulnerable Plaque." In these grants, she applies dual-energy CT and microscopic CT to small and large animal models to study mechanisms of ischemia.

She is a member of 2 NIH national study sections and serves on 2 Mayo Clinic clinical research committees.

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Frank V. Brozovich, MD, PhD

How changes in the regulation of cardiac and smooth muscle contractile proteins contribute to the human cardiovascular disease is unclear. The objective of this research program is to identify changes in protein structure and/or cell signaling that result in abnormal contractility, including hypertension and congestive heart failure. The methods in the laboratory include transgenic, molecular biological, biochemical, and biophysical experimental techniques. Using these techniques, experiments focus on identifying alterations in signaling pathways that contribute to cardiovascular disease processes and on defining the role of alternative exon splicing in the regulation of protein-protein interaction necessary for muscle contractility. The laboratory's long-term objective is to identify new targets for rational drug design for the treatment of hypertension and congestive heart failure.

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Charanjit S. Rihal, MD, MBA

Dr Rihal's clinical and research interests are in the areas of coronary and structural heart disease. Dr Rihal has completed numerous outcomes analyses of the term results of coronary interventional procedures and has served as investigator in national studies such as Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D). He currently is principal investigator of a series of studies examining markers of platelet activation in acute coronary syndromes. Dr Rihal is interested in the development of novel devices and approaches for therapeutic procedures and has performed preclinical and clinical research into novel interventional approaches to the percutaneous treatment of valvular heart disease. His interests also include the management of technologically intensive practices, and he has published on economic outcomes following interventional procedures.

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David R. Holmes, Jr, MD

The focus of his research has been on the interventional treatment of both coronary artery disease and structural heart disease, with the specific aim of developing new technology and then evaluating the outcomes of these new therapeutic options. Specific current projects include 1) occlusion of the left atrial appendage for stroke prevention in patients with atrial fibrillation, 2) implantable devices for early detection of ST-segment elevation myocardial infarction, and 3) development and testing of new stent designs with new polymer coatings.

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Abhiram Prasad, MD

Dr Prasad is an interventional cardiologist with an interest in acute cardiac care. His research focuses on acute coronary syndromes. Specifically, he has ongoing research protocols investigating the role of endothelial antagonists and remote ischemic preconditioning during percutaneous coronary intervention. The studies are designed to investigate potential novel therapies to reduce myocardial injury during percutaneous coronary intervention and at the time of reperfusion therapy for myocardial infarction. In addition, he has a research interest in stress-induced cardiomyopathy, also known as apical ballooning syndrome. A Mayo Clinic registry has been established for this novel syndrome. Another avenue of investigation is outcomes research among patients undergoing percutaneous coronary intervention.

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Patricia J. M. Best, MD

The focus of Dr Best's research is to better understand the role of specific cardiovascular risk factors, including renal disease and female sex, on the development of coronary artery disease. Her interests extend also to subsequent outcomes, including myocardial infarction and percutaneous coronary intervention. Dr Best's ongoing clinical studies include the following:

- Does Chronic Thiazolidinedione Therapy Improve Endothelial Function and Preserve Renal Function in Nondiabetic Patients With Chronic Kidney Disease?
- Differences in Epicardial Plaque and Microvascular Function in Women With an Acute Myocardial Infarction
- Coronary Artery Microvascular Dysfunction in Women: A Genomic Approach to the Problem

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Amir Lerman, MD

The broad objective of Dr Lerman's research program is the detection, prevention, and treatment of early coronary atherosclerosis from cells to patient populations. The major focus of the program is on the role of the endothelium in the regulation of vascular tone in health and in disease and the role of the endothelium as well as the endothelial-derived factors and cells in vascular injury and repair.

The program is divided into several areas. The first part is focused on the basic mechanisms and animal studies. In this area, Dr Lerman is using animal models of early atherosclerosis such as hypercholesterolemic, hypertensive, and combined hypertensive/hypercholesterolemic pigs. Animal studies are done in vivo and in vitro to elucidate the role of the endothelium in regulation of vascular tone in coronary perfusion in these animal models.

The second part of the program is translation of these findings to human studies. This work is supported by the National Institutes of Health, the American Heart Association, and the US Department of Defense. It is focused on the role of the endothelium in the regulation of coronary vascular tone in humans. Patients who are undergoing comprehensive evaluation of coronary blood flow, coronary

vascular resistance, and coronary endothelial function in the cardiac catheterization laboratory have the opportunity to participate in various studies. New physiologic technology such as Doppler pressure and combined pressure flow wires as well as novel imaging techniques such as intravascular ultrasound, virtual histology, and intravascular magnetic resonance imaging are integrated into the program. Currently, several randomized studies are under way to address the role of the endothelial progenitor cells in vascular injury and repair in these patients.

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RICK A. NISHIMURA, MD

Dr Nishimura's research interests concern cardiac hemodynamics. His current work includes the evaluation of diastolic function using both invasive and noninvasive approaches. He is seeking to understand the mechanisms by which patients develop elevated filling pressures and potential treatment mechanisms.

Dr Nishimura has a longstanding interest in the hemodynamic consequences of hypertrophic cardiomyopathy. Current protocols include those evaluating the effect of clinical interventions on the natural history of the disease.

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Steve R. Ommen, MD

Dr Ommen's research efforts focus on the clinical aspects of the management of hypertrophic cardiomyopathy (HCM). Mayo Clinic has a longstanding history of treating HCM dating back nearly 5 decades and has the largest clinical database of HCM patients in the world. Current research efforts include further elucidation of pathophysiology involving both invasive and noninvasive hemodynamic assessment, evaluation of autonomic function, and electrophysiologic and demographic determinants of sudden cardiac death. Dr Ommen's work is also focused on assessment of the natural history of HCM, with particular focus on subsets of HCM, a disease that is notable for its vast heterogeneity in clinical expression.

Mayo Clinic's Cardiomyopathy Clinic has long been recognized as leader in the management of left ventricular outflow tract obstruction, a feature present in approximately 70% of HCM patients. The group strives to study and report the outcomes of surgical and nonsurgical treatment modalities and to continue to refine optimal patient selection criteria for various therapeutic modalities. Working in tandem with the Windland Smith Rice Sudden Death Genomics Laboratory at Mayo Clinic Rochester, Dr Ommen has a keen interest in the genetic underpinnings of HCM, how genetics influence each of the other aspects already mentioned, and most importantly, how understanding genetics translates into the care of each individual patient.

SELECTED PUBLICATIONS

Valeti US, Nishimura RA, Holmes DR, Araoz PA, Glockner JF, Breen JF, Ommen SR, Gersh BJ, Tajik AJ, Rihal SS, Schaff HV, Maron BJ. Comparison of surgical septal myectomy and alcohol septal ablation with cardiac magnetic resonance imaging in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2007;49:350-357.

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Garvan C. Kane, MD, PhD

The emphasis of Dr Kane's work is deciphering mechanisms of cardiovascular stress tolerance with a particular focus on pulmonary hypertension, cardiac function, and heart failure from the animal to population level. Cardiac adaptation to imposed stress is critical for organ and host survival with maladaptive processes underlying pathologic disease states, including pulmonary arterial hypertension and congestive heart failure. Prior studies have elucidated critical proteins in the cardiovascular stress response that, through integration with central metabolic cellular pathways, facilitate optimal stress adaptation through orchestration of ionic and energetic balance. Specifically, a membrane metabolic sensor, the ATP-sensitive potassium channel that assimilates changes in cellular energetic status with membrane excitability was found to be vital in the cardiovascular response to hemodynamic stressors, including systemic hypertension and the systemic sepsis response. Such studies form the basis of ongoing investigation of novel potential therapeutic targets for these diseases. Current work focuses on the syndrome of pulmonary arterial hypertension, typified by pathogenic abnormal vascular remodeling and a maladaptive myocardial response, which invariably dictates the outcome in patients with pulmonary hypertension. Understanding homeostatic pathways in the pulmonary vasculature and right ventricular myocardium under (patho)physiologic stress will provide novel targets for pulmonary vascular therapeutics.

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Sudhir S. Kushwaha, MD

Dr Kushwaha's research has been focused on coronary physiology of the transplanted heart and strategies for the prevention of cardiac allograft vasculopathy. He has initiated the use of sirolimus as primary immunosuppression for cardiac transplant recipients for the purpose of preservation of renal function and attenuation of allograft vasculopathy. Using intracoronary ultrasound attenuation of coronary intimal proliferation has been demonstrated in cardiac transplant recipients treated with sirolimus.

Ongoing studies include assessment of endothelial function in cardiac transplant recipients converted to sirolimus and comparing them with patients on standard cyclosporine-based immunosuppression; factors contributing to the development of allograft vasculopathy; and left ventricular remodeling after cardiac transplantation. Among Dr Kushwaha's other research interests are diastolic dysfunction and pulmonary hypertension and the use of left ventricular assist devices for the treatment of end-stage heart failure.

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Horng H. Chen, MB, BCh

The focus of his research has been the local and circulating neurohormonal systems that contribute to heart failure and the development of novel therapeutic and diagnostic strategies. Dr Chen has successfully completed laboratory studies looking at the natriuretic peptides, vasopeptidase inhibitors, endothelin, the renin-angiotensin-aldosterone system, and adrenomedullin in congestive heart failure. More importantly, he has translated these laboratory studies to clinical studies where new therapeutic potential for the treatment and possible prevention of heart failure is being applied. He is a project leader on a program project grant, "Biology and Therapeutics of Cardiovascular Peptides in Disease." Dr Chen's project concerns the cardiorenal physiology and experimental therapeutics of stage B human heart failure.

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Barry A. Borlaug, MD

Dr Borlaug's research focuses on the pathophysiologic mechanisms causing heart failure, specifically heart failure with preserved systolic function (often referred to as "diastolic heart failure"). This disease affects about half of all Americans with heart failure, particularly older patients and women, and there is no proven treatment. Achieving a greater understanding of what causes these patients' symptoms and disability may help health care providers better define optimal treatment strategies.

Dr Borlaug's active studies in patients with heart failure with preserved systolic function are examining the impact of increased vascular stiffening on cardiac functional reserve and exercise performance and performing gold standard invasive hemodynamic assessment of ventricular systolic and diastolic performance at rest and during the acute stress of exercise in the cardiac catheterization laboratory. Increased vascular stiffening is a part of normal aging but seems to be accelerated in patients with hypertensive heart disease, diabetes, kidney disease, and heart failure. He is additionally pursuing research examining the effects of vascular stiffening and pressure wave reflections on symptoms and functional capacity in patients with heart failure with mildly depressed systolic function.

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Lyle J. Olson, MD

Dr Olson's broad research interest is cardiopulmonary interactions in heart failure. His research goals include continued commitment to prospective, mechanistic, patient-oriented research focused on ventilatory control in human heart failure. Ongoing and future studies will investigate the regulation of breathing at rest, during exercise, and with sleep to clarify the interaction between cardiac dysfunction and the ventilatory control system in the pathogenesis of periodic breathing. This work may lead to advances in clinical practice, including new methods for the screening and detection of sleep-disordered breathing in patients with heart failure and for surveillance of heart failure decompensation.

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John C. Burnett, Jr, MD

Dr Burnett is the Marriott Family Cardiovascular Research Professor and director of the Cardiorenal Research Laboratory. His research is focused on the heart as an endocrine organ with a special emphasis on integration of the heart and kidney in cardiorenal homeostasis. A special focus is on the cardiac natriuretic peptide system in cardiorenal regulation as it relates to the pathobiology, novel diagnostics, and innovative therapeutics of heart failure, hypertension, and acute myocardial infarction. With a long history of funding by the National Institutes of Health, his research group has demonstrated in cell systems, animal models, and humans that these peptides of cardiovascular origin may preserve cardiorenal structure and function via the second messenger cGMP in cardiovascular disease.

His group has elucidated mechanisms that mediate resistance to natriuretic peptides using state-of-the-art mass spectrometry and cell biology. Studies reveal altered molecular forms of the native natriuretic peptides with reduced biological actions that mediate resistance to native circulating natriuretic peptides and thus contributing to the clinical phenotype of heart failure and hypertension.

Most recently, Dr Burnett's laboratory has designed and synthesized novel new-generation natriuretic peptides as well as novel delivery systems, making them orally available. To complement targeting particulate guanylyl cyclases and cGMP with the natriuretic peptides, the group is also targeting soluble guanylyl cyclase (sGC) and cGMP signaling with highly innovative direct sGC agonists, representing an additional new paradigm in cardiovascular therapeutics. These molecules are now in clinical trials and offer an exciting new possibility for therapeutic use of the natriuretic peptides.

Finally, integrating the strategy of novel drugs based on the natriuretic peptides, the laboratory is engaged in the new field of theragnostics. Here they are developing innovative genetic, protein, and imaging biomarkers that will aid in identifying patients with early cardiorenal disease that would benefit from natriuretic peptide therapy. This area will represent a new strategy for individualizing protein therapy in preventing and delaying the progression of cardiovascular disease.

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Margaret M. Redfield, MD

Dr Redfield's research program includes laboratory-based translational and preclinical research, clinical research, and population-based studies. Her broad area of interest is heart failure. Specific areas of focus include

- the epidemiology, pathophysiology, and therapeutics of diastolic heart failure
- the epidemiology, pathophysiology, and therapeutics of cardiorenal failure
- the natriuretic peptides
- device therapy of systolic heart failure

Dr Redfield is director of the Mayo Heart Failure Clinical Program, codirector of the Mayo Cardiorenal Research Laboratory, and codirector of Mayo's NIH Cardiovascular Research Training Program. The heart failure program at Mayo Clinic is 1 of the 9 in the NIH Heart Failure Clinical Research Network. Her program is funded by the National Institutes of Health and Mayo Clinic.

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Carmen M. Terzic, MD, PhD

The major barrier in the treatment of cardiovascular disease is the inability of the myocardium for self-renewal. On the basis of the emerging principle that replacement of injured tissue by healthy tissue could rescue a failing phenotype, Dr Terzic's laboratory has focused on developing a stem cell–based strategy to repair diseased cardiac tissue. She has been able to direct embryonic stem cells toward cardiogenesis and optimize their properties for cardiac commitment. Dr Terzic has developed techniques by which direct injection of embryonic stem cells in a murine model of cardiac infarction engrafts and repopulates the diseased heart with cardiac cells derived from the embryonic stem cells. The ultimate goal is to establish cardiovascular regenerative medicine as a new therapeutic modality for heart disease.

Dr Terzic also uses embryonic stem cells to study cardiac cell differentiation and the role of nuclear transport. Transport across the nuclear envelope is vital, and deficiency in the nuclear localization of transcription factors has been related to congenital abnormalities, including cardiac defects. A case in point is the lethal defect in cardiac development described recently in embryos lacking calreticulin, a multifunctional calcium-binding chaperone protein. The mechanisms responsible for calreticulin-mediated regulation of nuclear function and the contribution of calreticulin in cardiogenesis are poorly understood. Dr Terzic has established a stem cell–based model of calreticulin gene knockout (crt-/-) and obtained data suggesting a contribution of calreticulin in securing the structural and functional competence of nuclear pores and therefore differentiation. Using state-of-the-art techniques, including laser confocal microscopy, atomic force microscopy, proteomic and genomic analysis, gene transfection, and point mutation, she has obtained insight into molecular events associated with nucleocytoplasmic communication critical for cardiovascular differentiation.

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Faustino RS, Terzic A, Nelson T, Perez-Terzic C. Nuclear transport: target for therapy. Clin Pharmacol Ther 2007;81:880-886.

Xiaolei Xu, PhD

The mission of the Zebrafish Genetic Laboratory is to use the power of genetics and genomics to gain insights into the molecular mechanisms of human heart diseases. Ongoing projects include efforts to establish embryonic zebrafish models for studying cardiac remodeling and congenital heart diseases as well as cardiomyopathy and heart failure.

In the laboratory, Dr Xu and colleagues combine bioinformatics and comparative genomics to help determine which genes are of interest for studies related to human heart diseases. These "in silico" analyses are followed up with in vivo experiments using morpholino-mediated reduction in gene expression, transgenic zebrafish, and insertional mutagenesis screening to help determine the functions of the encoded proteins. The ultimate goal of these studies is to perform mutagenesis or small-molecule screens using zebrafish models to identify novel therapeutic strategies or drugs for the treatment of congenital heart diseases and heart failure.

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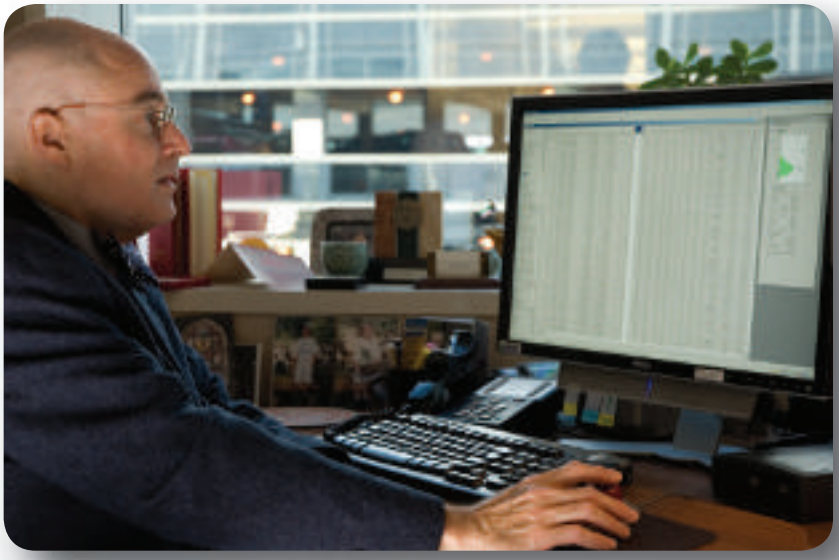
Richard J. L. Rodeheffer, MD

The focus of Dr Rodeheffer's research has been on the epidemiology of cardiac structure and function in community populations. The goal has been to provide foundational data on the distribution of ventricular function parameters in naturally occurring populations and to assess the relationship between ventricular structure and function and symptoms of cardiovascular disease. The longitudinal study of 2,000 randomly chosen Olmsted County residents has allowed for analysis of changes in cardiac structure and function over time and has provided important information on changes in circulatory physiology that increase the risk of future congestive heart failure.



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MARTIN G. RODRIGUEZ-PORCEL, MD

Cardiac cell therapy has appeared as a powerful therapeutic alternative for the treatment different stages of coronary artery disease. However, many questions regarding the biology of these therapies remain answered. Molecular imaging provides a unique opportunity to address these critical questions noninvasively.

Work in Dr Rodriguez-Porcel's laboratory focuses on the use of molecular imaging modalities (eg, optical imaging, positron emission tomography, ultrasound) to better understand the biology of cardiac stem cells for cardiovascular applications. He concentrates on understanding the biological mechanisms underlying survival, proliferation, and differentiation of stem cells. Additionally, he has an interest in the use of molecular imaging to noninvasively assess atherosclerosis and its consequences.

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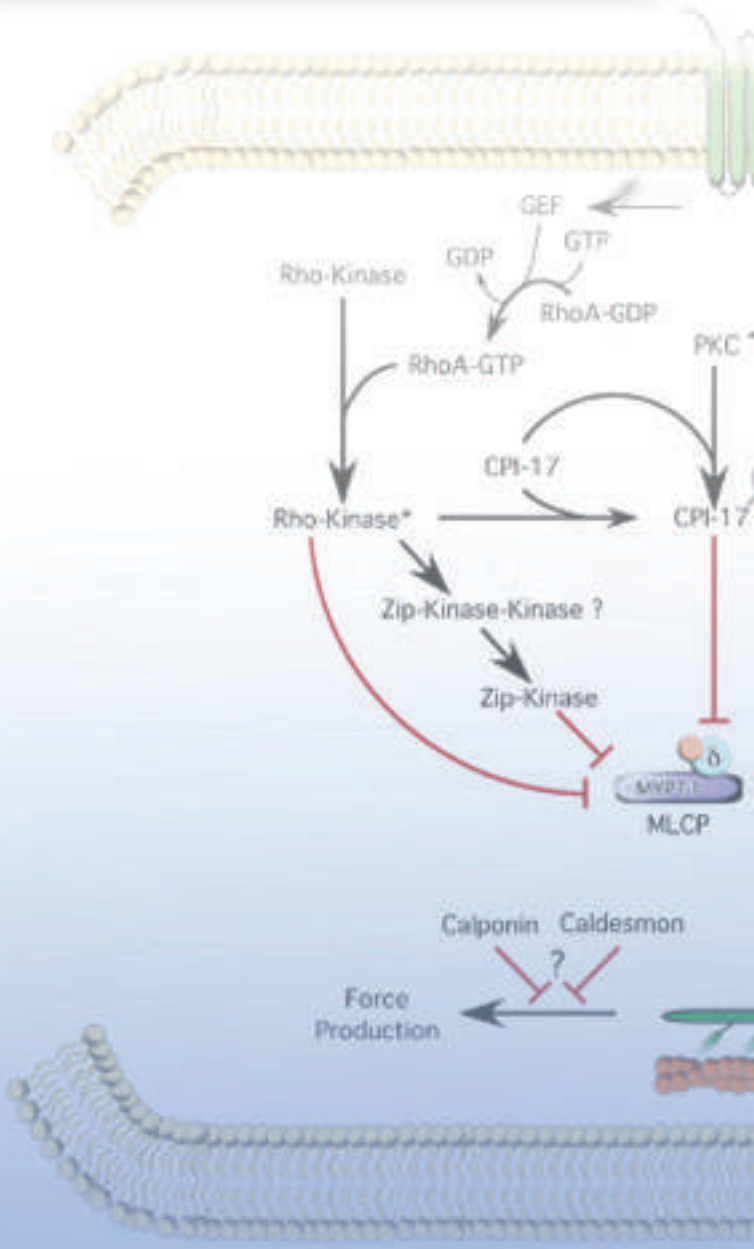
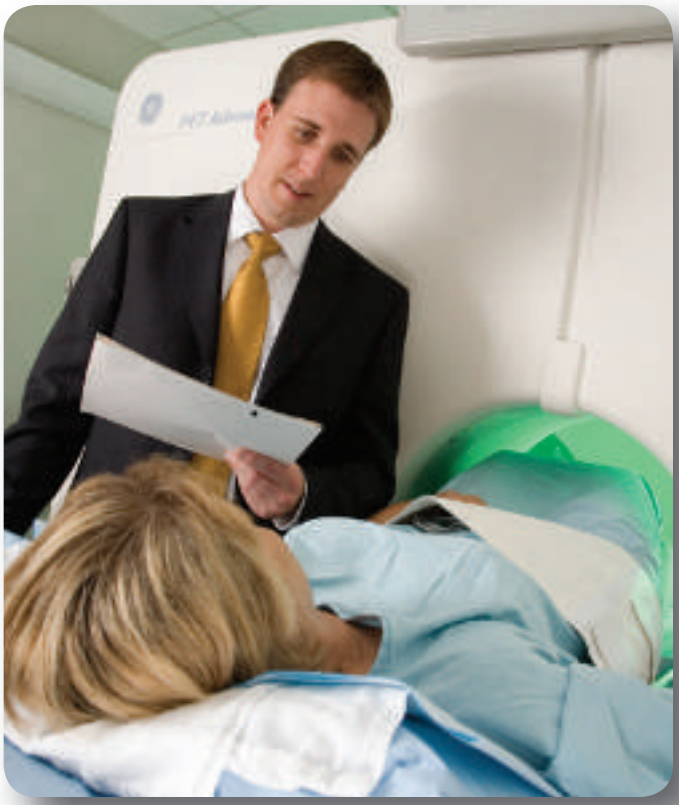
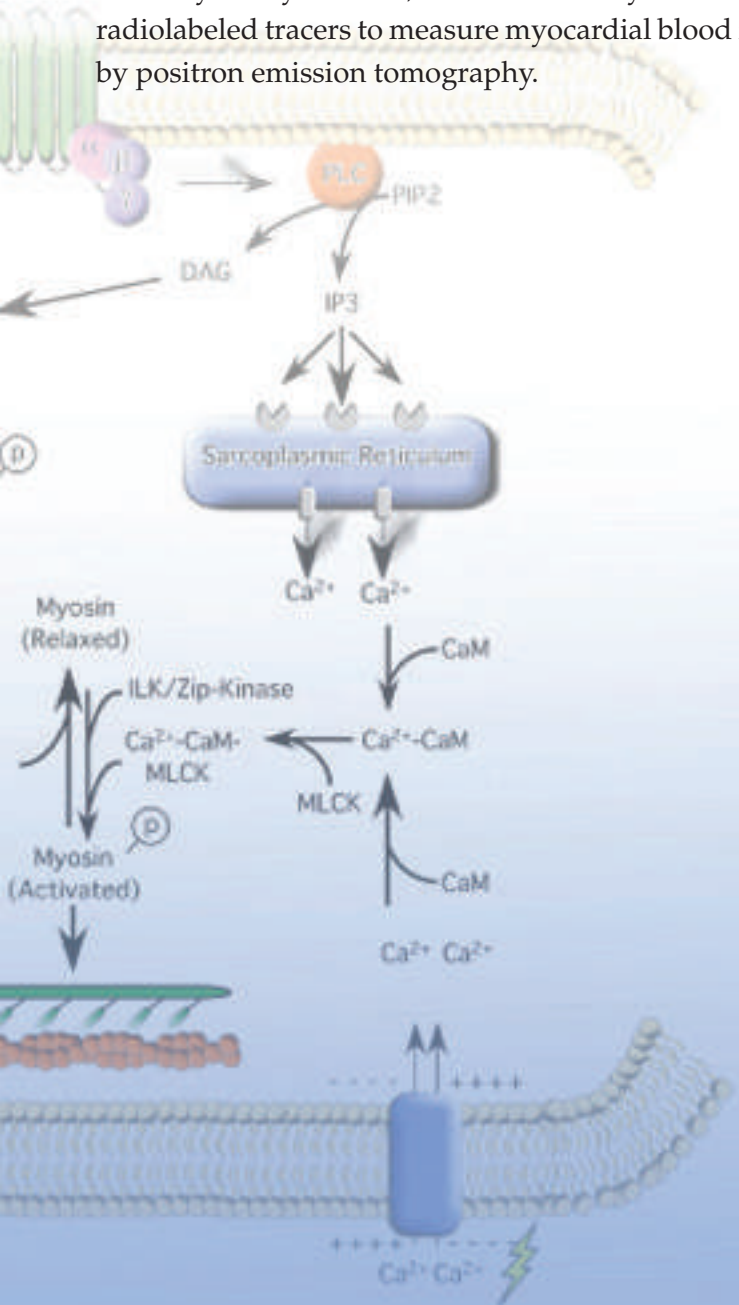


J. Wells Askew, MD

Dr Askew's research is focused primarily in nuclear cardiology with an emphasis on the value of noninvasive stress testing in specific population subsets. Recent work has included the yield of myocardial perfusion imaging in asymptomatic patients with atrial fibrillation, the yield of myocardial perfusion imaging in asymptomatic patients with coronary artery calcium, and the accuracy of different radiolabeled tracers to measure myocardial blood flow by positron emission tomography.





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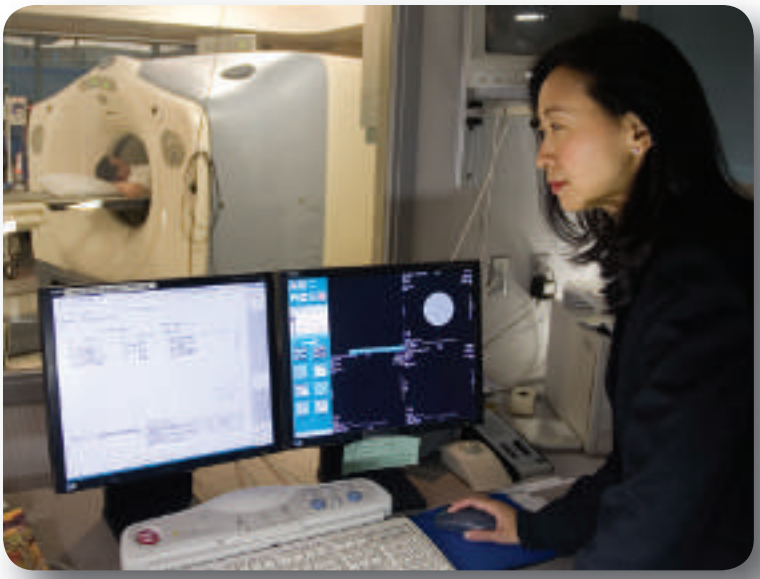

Panithaya Chareonthaitawee, MD

The focus of her research is the application of positron emission tomography (PET) imaging techniques to address pathophysiologic mechanisms of disease and the effects of interventions and therapies on these mechanisms. Currently available cardiac PET techniques include absolute quantification of myocardial blood flow and flow reserve, myocardial glucose utilization, myocardial oxidative metabolism, and cardiac sympathetic function. Her additional research focuses on the diagnostic and prognostic value of clinical PET and single-photon emission computed tomography (SPECT) studies. Her research efforts have been funded by peer-reviewed awards from Mayo Clinic, the American Heart Association, and the American Society of Nuclear Cardiology.

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Raymond J. Gibbons, MD

Dr Gibbons is a senior investigator in nuclear cardiology and myocardial infarction with more than 275 peer-reviewed publications. His recent work in nuclear cardiology has focused on the clinical value of single-photon emission computed tomography (SPECT) perfusion imaging in particular patient subsets, eg, diabetic and elderly patients, as well as its role in clinical decision-making. The Nuclear Cardiology Laboratory has served as the core laboratory for SPECT perfusion images to measure the size of myocardial infarction in more than 20 multicenter randomized trials. Recent publications from this work have reported the primary end points from these trials, as well as the results of substudies focusing on the post-hoc analysis of patient subsets, eg, diabetic patients. Most recently, Dr Gibbons has initiated a new effort in clinical research focused on the appropriateness of imaging and the proper application of published appropriateness criteria to clinical practice. The nuclear cardiology research effort that Dr Gibbons directs has been well funded by external grants for the past 15 years. The resources from these grants are available to support well-designed clinical research studies.

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Jae K. Oh, MD

Dr Oh's primary research interest is to explore clinical applications of echocardiography and its use in clinical trials. He combines his clinical interest in acute coronary care, diastolic function, cardiac hemodynamics, heart failure, aortic dissection, and pericardial diseases with the use of echocardiography in those clinical fields. He is a member of the International Registry of Acute Aortic Dissection and is active in echocardiographic education for health care providers at all levels.

Specific current research activities include

- Management and clinical outcome of patients with acute and relapsing pericarditis
- Tissue Doppler and strain imaging in cardiac resynchronization therapy and cardiac function
- Use of echocardiography in patients with acute myocardial infarction
- Evaluation of diastolic function by echocardiography at rest and exercise
- Mayo Clinic Core Echocardiography Laboratory for various clinical trials

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Patricia A. Pellikka, MD

Dr Pellikka's research is focused on the application of echocardiography and stress testing to the early detection of heart disease and for assessment of prognosis. The echocardiography laboratory annually performs more than 50,000 clinical transthoracic and transesophageal echocardiographic studies and 8,000 stress echocardiographic studies and has an active research program involving multiple areas of investigation:

- The role of echocardiography, including novel methods such as myocardial perfusion, strain, tissue Doppler, and strain rate imaging in predicting outcomes in patients with coronary artery disease and myocardial disease is being evaluated.
- Three-dimensional echocardiography is being used to quantify cardiac chamber sizes and systolic function.
- Exercise Doppler echocardiography is being used to evaluate valvular heart disease and stress-related changes in diastolic function and the relationship of these findings to clinical outcome.
- Noninvasive ultrasound modalities, including carotid intima-media thickness measurement, brachial artery reactivity, and pulse wave tonometry, are being assessed as means of detecting preclinical cardiovascular disease.
- In patients with systemic amyloidosis, a large database has been accumulated and is being evaluated to determine early markers of cardiac involvement and predictors of outcome.
- In collaboration with colleagues from oncology, carcinoid heart disease is being studied with clinical and translational models in an effort to identify means of preventing disease progression.
- Age- and sex-related changes in cardiac structure and function are being evaluated.

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Todd D. Miller, MD

The focus of Dr Miller's research is the application of nuclear myocardial imaging for the diagnosis and prognosis of coronary artery disease. The nuclear imaging techniques include stress single-photon emission computed tomographic (SPECT) imaging and quantitative infarct sizing.

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Robert P. Frantz, MD

Dr Frantz is director of the Mayo Pulmonary Hypertension Clinic and the Cardiovascular Studies Unit. His research interests include neurohumoral activation and biomarkers and prognostic modeling in heart failure and pulmonary hypertension. He is coinvestigator on a National Institutes of Health grant that includes catheterization laboratory–based investigation of genetic determinants of exercise hemodynamics and pulmonary limitations in heart failure. He is also conducting high-altitude research, including effects of sildenafil versus acetazolamide on cardiopulmonary physiology under hypoxic conditions. He is principal investigator on numerous industry-sponsored trials of investigational therapies for pulmonary hypertension, including orally bioavailable prostanoids.

Additionally, he is studying the role of implantable hemodynamic monitors in guiding therapy and understanding physiology in pulmonary hypertension and congestive heart failure. As a member of the cardiac transplant and advanced heart failure program, he is collaborating on studies of the genomic and proteomic response to left ventricular assist device implantation. He is also conducting research on the role of metabolic syndrome and inflammatory markers on the risk of coronary allograft vasculopathy.

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