

The Davis Heart and Lung Research Institute Building a Sustainable Platform for Translation

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The Dorothy M. Davis Heart and Lung Research Institute (DHLRI) at the Ohio State University (OSU) in Columbus, Ohio, has evolved over the past decade to serve as a platform to translate discovery from the laboratory to new practices in the clinic. Governing concepts for this evolution have been focused mission, leadership and investigator accountability, cross-disciplinary collaboration, and ultimately patient-centered discovery.

Introduction and Mission

The DHLRI is one of the largest and most comprehensive Institutes/Centers at the OSU and among the largest freestanding Institutes in the country devoted to cardiovascular, pulmonary, renal, and metabolic disease. The DHLRI was born from the multidisciplinary, programmatic study of heart, lung, and kidney disease at OSU in the late 1990s. In 2000, the DHLRI opened the doors of its new freestanding home—one of the most advanced interdisciplinary facilities on the Ohio State campus (Figure A). In 2001, ~40 DHLRI investigators published 114 manuscripts. Over the past 16 years, the DHLRI has expanded its scientific scope and research footprint across OSU. Beyond serving as the research arm of OSU Heart and Vascular Center (HVC), the DHLRI now serves >700 faculty, staff, and trainees and generated >600 manuscripts in 2016. In 2017, the DHLRI continues to strive to fulfill its overarching mission to develop innovative strategies to diagnose, prevent, and treat cardiovascular, pulmonary, renal, and metabolic diseases. Numerous core laboratories within the DHLRI offer innovative technologies to support all aspects of basic and clinical research. The clinical care provided nearby at the Richard M. Ross Heart Hospital and OSU Wexner Medical Center offers first-hand perspectives on how research is involved in the prevention, detection, and treatment of disease.

While the DHLRI has its home base in the original 96 000 square foot Institute (Figure), DHLRI-associated science is now performed at 6 different sites with a total space footprint of >200 000 square feet. Through strategic partnerships and new mechanisms to ensure investigator accountability, productivity in the DHLRI has significantly increased over the past decade. Grant submissions have increased from 158 in 2010 to 688 in 2016 (numbers now incorporate College of Medicine Grants Management Office),

the quantity and quality of manuscripts has improved, and extramural research funding to the Institute has increased. Today, within the College of Medicine, the DHLRI serves as home for researchers in the Divisions of Cardiovascular Medicine, Pulmonary Medicine, Endocrinology, Nephrology, Rheumatology, Palliative Medicine, and Human Genetics in the Department of Internal Medicine. Within Surgery, both Divisions of Vascular Surgery and Cardiothoracic Surgery are integrated within the Institute. Further, College of Medicine faculty in Physiology & Cell Biology, Plastic Surgery, Pathology, Radiology, Family Medicine, Emergency Medicine, Anesthesiology, Sports Medicine, Biochemistry and Pharmacology, Microbial Infection and Immunity, Pediatrics, and Health and Rehabilitation Sciences are associated with the DHLRI. Beyond the College of Medicine, investigators in the Colleges of Pharmacy, Engineering, Nursing, Public Health, Arts & Sciences, Dentistry, Education and Human Ecology, Food, Agricultural, & Food Sciences, and Veterinary Medicine are active DHLRI members. The breadth of investigators conducting work from molecule to human provides a rich environment for translational discovery and accelerates the ability of the organization to rapidly pivot scientific priorities toward emerging areas (eg, impact of novel cancer therapies on myocardial function, role of air pollutants on vascular and myocyte function, ex vivo lung perfusion, familial hypercholesterolemia). Thus, while not serving as the academic home for faculty, the DHLRI works each day with leadership in each College, Department, and Division to build translational research teams to address clinically relevant questions.

Building Translational Partnerships

The DHLRI is fully integrated with all 3 academic missions (research, education, and service/patient care). Partnerships in all 3 areas have provided a catalyst to expand the scope and impact of the DHLRI portfolio. Most significant to the translational mission of the Institute is its integration with the OSU HVC/Richard M. Ross Heart Hospital. Directed by Thomas Ryan, MD, the Ross Heart Hospital is a 150-bed facility that combines the latest technology with patient-focused care. When the Ross Heart Hospital opened in 2004, it was one of the nation's first comprehensive academic hospitals dedicated to cardiovascular care. Today, the Ross Heart Hospital is still

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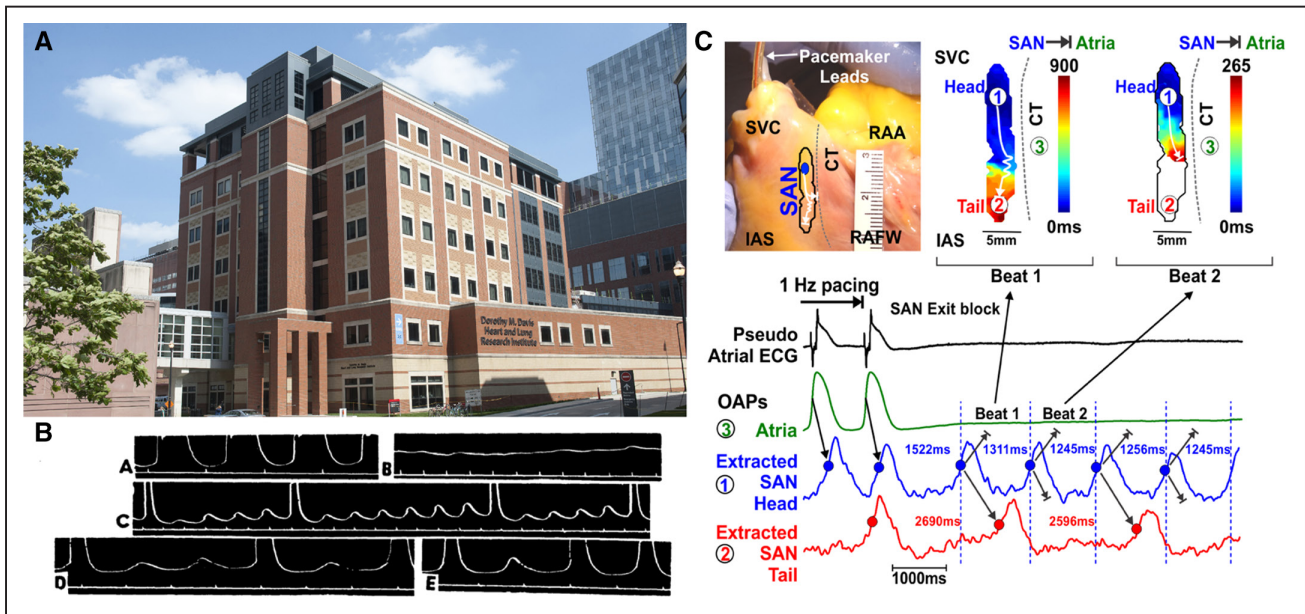


Figure. The Dorothy M. Davis Heart and Lung Research Institute. **A**, Freestanding Institute serves as platform for translational discovery. **B**, The first demonstration of sinoatrial node exit block during parasympathetic stimulation on an isolated sinus venous preparation of the turtle by a single monophasic action potential recording from Bozler in 1943.² **C**, Demonstration of sinus node exit block during atrial pauses in diseased human heart from Csepe.³ White arrow, intranodal conduction. Atrial ECG indicates atrial electrogram; CT, crista terminalis; IAS, interatrial septum; OAP, optical action potential; RAA, right atrial appendage; RAFW, right atrial free wall; SAN, sinoatrial node; and SVC, superior vena cava.

making headlines as a leader in its field. Each floor of the Ross Heart Hospital is focused on a specific type of care (eg, electrophysiology, heart failure, cardiovascular surgery), thus, allowing the cultivation of multidisciplinary teams to provide optimal patient care. Further, these teams form the nidus for clinical/translational research studies. In 2016, the Ross Heart Hospital had >30 000 outpatient visits and 8700+ adjusted admissions, with strategic growth over the past decade in the areas of electrophysiology (increased 162%), heart and lung transplant (increased 138%), and ventricular assist devices (increased 224%). Because of a myriad of clinical/research partnerships, it is not surprising that the growth of research in the DHLRI has paralleled the expansion of heart and vascular clinical services at Ohio State.

Most relevant for bench-to-bedside translation, the DHLRI is tightly aligned with and serves as home to the Clinical Trials Management Organization led by William T. Abraham, MD (Director, Division of Cardiovascular Medicine). The Clinical Trials Management Organization, built to provide experienced clinical research infrastructure, evolved from a platform established to serve HVC clinical trials and now employs 118 staff with comprehensive services to currently manage >800 clinical trials and translational research studies. In 2016, >200 of the investigator-led and industry-sponsored studies were associated with the HVC. Notable recent trials have focused on the development of device therapies for arrhythmias and heart failure, including the emerging arena of interventional heart failure, leveraging the internally collaborative research environment among cardiovascular subspecialists. For example, OSU led enrollment in the REDUCE LAP-HF randomized trial (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure), a collaborative effort between interventional

cardiologists and heart failure specialists. The results of this trial are pending. OSU also played a pivotal role in the development and evaluation of a novel implanted transvenous phrenic nerve neurostimulation system for the treatment of central sleep apnea, a collaborative effort among sleep medicine specialists, electrophysiologists, and heart failure specialists, with results recently published in the *Lancet*.¹ Beyond the Clinical Trials Management Organization, translation of research to the clinic is supported by the OSU Center for Clinical and Translational Science.

DHLRI: Building on a Rich History of Discovery

DHLRI investigators continue to build on a legacy of translational findings at Ohio State. For example, Emil Bozler, PhD (1901–1995) seeded an entire field of smooth muscle physiology and was one of the first in the world to describe the basis of inherent rhythmicity of cardiac muscle—identifying the localized pacemaker prepotential in the sinus node in 1943 (Figure B).² Nearly 3 quarters of a century later, in the same laboratories, Vadim Fedorov, PhD, is using explanted human donor hearts and next-generation imaging modalities to develop new platforms to enhance our understanding of human sinus node dysfunction (Figure C).³ Further, nearly every week, explanted human heart tissue continues to populate one of the fastest growing human cardiovascular tissue repositories (directed by Paul Janssen, PhD, and Philip Binkley, MD)—providing critical samples for >20 laboratories with research interests in valve disease, contraction/relaxation, arrhythmia, diabetes mellitus, hypertrophy, and heart failure.⁴ DHLRI investments in the areas of regenerative medicine, muscle inflammation, and pulmonary inflammation have resulted in significant scientific translational growth and the organization of the Center for

Regenerative Medicine and Cell-Based Therapies (Director, Chandan Sen, PhD). Current strengths include membrane repair, therapies for cardiac damage associated with muscular dystrophy, and wound healing. Moreover, in line with the combined HVC/DHLRI strategic plan, investment in the areas of heart failure, vascular biology, and arrhythmia has formed platforms for future growth and support for the cross-disciplinary disciplines of advanced imaging, women's health, adult congenital cardiology, and genetics. In line with this plan, the DHLRI began populating a new $\approx 35\,000$ square foot floor in 2016 devoted to heart failure and arrhythmia research. Finally, research in metabolic disease and downstream pathologies will continue to be an area for investment for the DHLRI, given the striking global disease trends. To aid in this growth, researchers have access to advanced technologies in animal and cellular imaging, cell biology, genetics, bioinformatics and statistics, flow cytometry, mass spectrometry, metabolic profiling, and animal physiology/surgery.

Training the Next Generation of Researchers

Steered by its Education Committee, the DHLRI is committed to mentoring the future leaders of biomedical research. The DHLRI is active in education and has established new programs for trainee and faculty development, laboratory management, and grant writing. Implemented in 2011, the DHLRI Early Career Development Series has hosted nearly 30 formal sessions, with topics ranging from time management, grant writing, negotiating, personnel management, and responsible conduct in research. DHLRI investigators are now closely involved in the training and academic development of junior physician-scientists and researchers through a new series of training sessions by the Education Committee focused on National Institutes of Health K-series grants. Faculty are also mentored by the College of Medicine Center for Faculty Advancement, Mentoring, and Engagement (FAME; Founded and Directed by Philip Binkley, MD, Robert Bornstein, PhD, and Heather Brod, MA) that has centralized and galvanized faculty training. This program offers regular courses to DHLRI researchers on grant writing, research mentoring, and personnel development. DHLRI is also home to 2 National Institutes of Health training grants (T32). Directed by Mark Wewers, MD, the first is focused on the molecular mechanisms of lung inflammation. The second training grant, codirected by Vidu Garg, MD, and Peter Mohler, PhD, integrates both didactic and laboratory training between Nationwide Children's Hospital and OSU in the areas of congenital and acquired cardiovascular disease. Additional training is provided through weekly Research in Progress seminars, a biannual Discovery Series that hosts preeminent national researchers, and an annual Research Day. Finally, faculty and trainees participate in ≈ 75 annual continuing medical education events, as well as the Schottenstein Lecture. This biennial lecture recognizes a scientist who has made extraordinary and sustained leadership contributions to improving health care. Past winners include Roberto Bolli, MD, FAHA (2015), Garret FitzGerald MD (2013), Christine Seidman, MD (2011), and Pascal Goldschmidt, MD (2009).

Leadership and Administrative Structure

In 2011, Peter Mohler, PhD, was named the fifth Director of the DHLRI. In addition to DHLRI vision and oversight, Dr Mohler and Executive Director Lorri Fowler, MBA, FACMPE, manage daily operations, with oversight from an Advisory Board representing leadership from colleges and departments/divisions supported by the Institute. Leadership decisions are further distributed to multiple committees that manage research space, education, research cores, and shared equipment, thus, ensuring shared, transparent, and accountable oversight of resources. Long-term financial sustainability has been a key initiative of leadership for the past 6 years. For example, philanthropic support alone has grown $\approx 90\%$ since 2013. This support, along with federal, state, university, medical center/college, and industry resources, has help to provide a balanced portfolio necessary to support the Institute's growth. Further, leadership has evolved a comprehensive infrastructure to manage the growing needs of the investigator population (building services, grants management, etc). The Business Office supports the finances of DHLRI and includes a Fiscal Officer and Fiscal Associate who monitor the day-to-day financial needs, as well as annual budgets, large equipment purchases, and maintenance contracts. The Informatics Team support the ever-growing need for secure and seamless clinical and research data sharing and storage. Finally, the DHLRI has worked with College of Medicine to create the Grants Management Office that provides pre- and postaward management to non-Cancer faculty across the Medical Center. In 2011, 3 full-time staff supported pre- and postaward management at OSU. Today, the Grants Management Office is staffed by 15 professionals to serve the complex needs of single- and multi-investigator proposals and grant awards.

Partnerships for the Future

With the HVC, the DHLRI is active within the community to advance the mission of biomedical science at OSU, as well as to improve the health of Central Ohio. A significant platform for this engagement is the OSU HVC Wellness Series, initiated in 2013. Regular events include evening lectures on research and disease prevention, community health screening, a community garden to promote heart-healthy nutrition, running/walking events, and finally an annual TriFit Triathlon/Duathlon. To date, ≈ 8000 individuals have participated in the TriFit, providing funding for 19 DHLRI pilot research projects. In addition to these events, investigators are actively engaged with local and national partners, including Ohio State Athletics, Lifeline of Ohio, American Heart Association, Mended Hearts, and the Saving Tiny Hearts Society. Further, members are active on international scientific boards, review panels, and editorial boards, and many have started their own companies to pursue translation of discoveries to the clinic.

The future for DHLRI is ripe with opportunities, as well as significant challenges. While experiencing growth over the past decade, future success is certainly not guaranteed in the current volatile research and healthcare climate. Sustainability requires that Ohio State continue to leverage its

clinical strengths, particularly in the strategic focus areas of the HVC, the College of Medicine, and the Medical Center. Further, like all research centers/institutions, growth must be focused, purposeful, and cognizant of national healthcare and research trends. Recently, the Centers for Disease Control and Prevention published that for the first time since 1993, the average life expectancy in the United States decreased (0.1 years), with an uptick in deaths related to cardiovascular disease.⁵ These data support the necessity of translational research organizations like the DHLRI to pursue novel discoveries, diagnostics, and therapies.

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Disclosures

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