Cardiovascular Research Center at Icahn School of Medicine at Mount Sinai Translational Mission

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The Cardiovascular Research Center (CVRC) at Icahn School of Medicine at Mount Sinai was established in 2007 and is focused on advancing our knowledge of cardiovascular diseases and translating these discoveries into effective therapies. The CVRC is currently housed in The Leon and Norma Hess Center for Science and Medicine, a state-of-the-art clinical and research facility in New York's Upper East Side. The Center is part of the Mount Sinai Health System, comprised of the Icahn School of Medicine at Mount Sinai and 7 other hospital campuses throughout the New York Metropolitan Area.

Since its inception, the CVRC has grown to include ≈75 members composed of physicians, physician-scientists, postdoctoral fellows, research scientists, and technicians. Our team of lead investigators and researchers work across platforms to investigate cardiac and stem cell biology, tissue engineering, vector biology, cardiac physiology, electrophysiology, vascular diseases, metabolic disorders, imaging, and clinical trials. Close collaboration and shared vision among the investigators glean fundamental insights into cardiovascular physiology and pathobiology, which illuminate potential avenues for therapeutic treatment.

The Center currently has 2 full professors, 5 associate professors, 10 assistant professors, and 4 instructors in medicine/cardiology. In 2017, total National Institutes of Health funding increased to >14 million dollars. In addition to 15 R01s, 3 K awards, and an F30, the CVRC is home to 3 Transatlantic Leducq Foundation grants, 4 American Heart Association postdoctoral fellowships, 4 American Heart Association Scientist Development grants, an American Heart Association Strategically Focused Research Network, a Department of Defence Concept Award, and a National Institutes of Health S10 Shared Instrument grant. We have also recently acquired funding from 2 biotechnology companies. Figure shows the junior and senior investigators at the Cardiovascular Research Center.

The faculty has a broad range of interests including (1) gene therapy for heart failure, (2) gene-based therapies for arrhythmias, (3) tissue engineering & 3-dimensional bioprinting, (4) post-translational modifications in heart failure, (5) exosomes in cardiac repair, (6) modified RNA as a novel platform for cardiac regeneration, (7) diabetic cardiomyopathy, (8) adeno-associated vector (AAV) biology, (9) atherosclerosis and vascular biology, (10) fibromuscular dysplasia (FMD), (11) metabolomics and proteomics, and (12) large animal models of cardiovascular diseases.

Leadership

The Center is the brainchild of Dr Valentin Fuster and Dr Roger J. Hajjar. Their vision was to create a world-class research center with the resources and infrastructure to tackle the most pressing issues in cardiovascular disease. Dr Fuster is Physician-in-Chief at The Mount Sinai Health System, as well as Director of Mount Sinai Heart. In addition, Dr Fuster is the General Director of the National Center for Cardiovascular Investigation in Madrid, Spain.

The CVRC is directed by Dr Roger J. Hajjar, MD, and under his leadership, it has grown into a vibrant center of discovery and treatment. The CVRC is under the umbrella of the Cardiovascular Institute and is closely aligned with Mount Sinai Heart, with vast inpatient and outpatient clinical services that treat a complete range of cardiovascular disorders and promote cardiovascular health. In addition to directing the Center, Dr Hajjar is the Arthur & Janet C. Ross Professor of Medicine and a clinically trained cardiologist and heart failure/transplant specialist. His laboratory has extensive experience studying cardiac physiology in both in vitro and in vivo models with a long-standing research program targeting signaling pathways in cardiac hypertrophy and heart failure. His group has developed a number of methodologies for cardiac gene transfer, and these techniques have been adopted by a large number of investigators in the field. Furthermore, he has used multi-imaging modalities to characterize the various models of cardiovascular diseases and the effects of various gene transfer experiments on the physiological function in these models.

Overview of Research at the CVRC

The CVRC is a center with a diverse faculty whose background varies significantly. They include clinical cardiologists, interventional cardiologists, cardiac surgeons, biomedical engineers, electrophysiologists, vascular biologists, immunologists, and proteomic experts. The diversity of the faculty provides the perfect forum for multidisciplinary approaches across various projects. In fact, most of the individual programs within the Center have components from many of the laboratories and draw upon the expertise of different principal investigators.

The CVRC has a strong focus on elucidating new ways to halt or reverse cardiac pathologies. Investigators at the Center lead the field in cardiac gene therapy. Starting from

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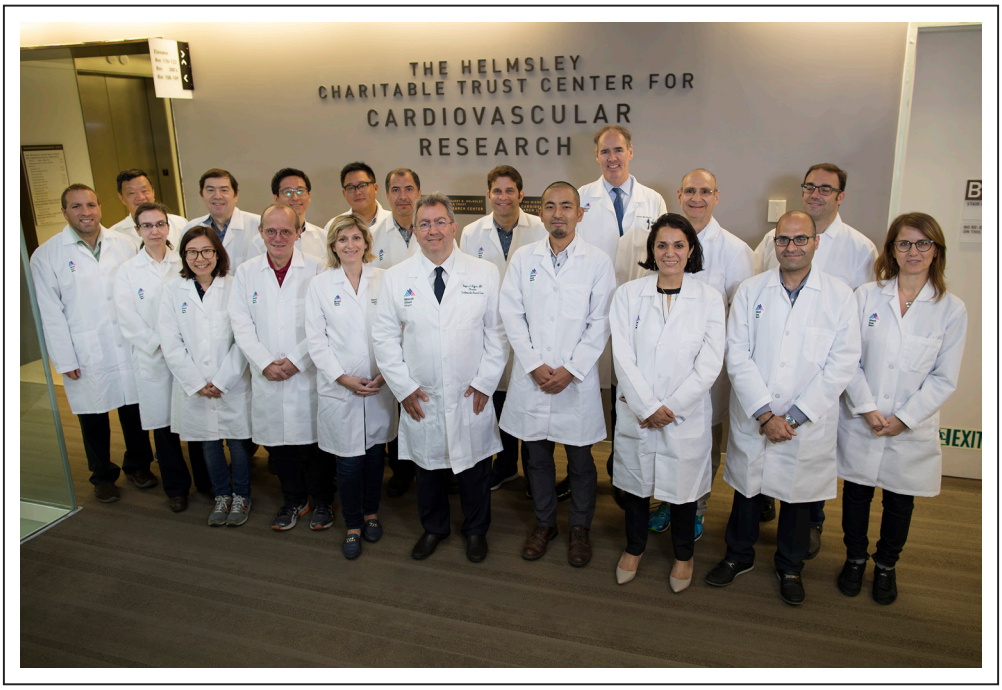

Figure. Junior and senior investigators at the Cardiovascular Research Center. Front row (left to right): Anthony Fargnoli, Irene Turnbull, Ah Young Lee, Thomas Weber, Chiara Giannarelli, Roger J. Hajjar, Kiyotake Ishikawa, Lahouaria Hadri, Fadi Akar, and Francesca Stillitano. Back row (left to right): Jiqiu Chen, Michael Katz, Changwon Kho, Dongtak Jeong, Djamel Lebeche, Lior Zangi, Jason C. Kovacic, Kenneth Fish, and Kevin Costa. Not shown: Susmita Sahoo.

the in vitro studies, our group has successfully translated AAV-mediated *SERCA2a* gene therapy to rodent and large animal studies and to clinical trials targeting chronic heart failure. Additionally, scientists are exploring the use of novel gene therapy vectors including re-engineered AAVs, modified RNA, and exosomes. Attempts to use gene therapy for various forms of heart failure, ventricular arrhythmias, pulmonary hypertension, and myocardial infarction are being examined. Gene editing is also an active area of research, and the CVRC team uses its expertise in gene therapy to accomplish this in iPS (induced pluripotent stem cell)-derived cardiomyocytes from patients with phospholamban mutations. The team also discovered a powerful small molecule that enhances the contractile function of cardiomyocytes. Finally, systems biology approaches are used to explore key signaling pathways that lead to cardiovascular diseases as represented by proteomics and metabolomics.

Rapid Bench-to-Bedside Translation

One of the limiting steps in developing new therapeutic approaches is the slow translation from bench to bedside. In the CVRC, this is streamlined by a sophisticated number of core laboratories including platforms for in vitro, small animal, and large animal testing along with expertise in clinical trial design. When promising therapies are discovered at the bench, small animal experiments can be designed and started, while the next steps have already been planned and initiated. These processes substantially reduce the amount of time for new therapies to reach clinical trials. Feedback from a multidisciplinary team is useful in determining the appropriate end points for designing studies.

The CVRC houses an independent clinical catheterization laboratory headed by Dr Kiyotake Ishikawa where large animal models of cardiovascular diseases are studied. The Cardiology Laboratory for Translational Research has several unique large animal models that closely mimic human cardiac diseases. These models are used for studying physiology, biology, imaging, and efficacy of therapeutic approaches. Recent successful demonstration of intra-airway gene therapy in preventing the progression of pulmonary hypertension, and a new viral vector–based heart failure therapy in pigs are expected to translate into clinical trials in the near future. The proximity of the Lab allows for daily catheter procedures and echocardiography, as well as pressure–volume loop evaluations. Nearby, there is access to state-of-the-art imaging modalities in the Translational and Molecular Imaging Institute including magnetic resonance imaging and positron emission tomography. This laboratory has been critical in conducting preclinical studies that have allowed Food and Drug Administration approval for the Center's clinical gene therapy trials.

Clinical Trials

Gene Therapy

The Center has continued to target calcium cycling proteins in the heart. Recently, scientists have been successful in delivering the constitutively active form of I-1 protein (protein phosphatase inhibitor-1) directly into damaged heart cells and targeting PP1 (type 1 protein phosphatase), a critical negative regulator of calcium cycling and contractility. A phase 1 trial using re-engineered adeno-associated vector carrying *I-1c* has been approved by the Food and Drug Administration and will begin enrollment. A trial using inhaled AAV1. *SERCA2a* gene therapy in patients

with pulmonary arterial hypertension is being planned. A novel platform using modified RNA is being developed at the CVRC for application in various cardiovascular diseases and therapeutic application, most notably cardiac regeneration.

FAMILIA

The FAMILIA study (Family-Based Approach to Promotion of Health Project 2), part of the American Heart Association's National Center Research Program Winter 2014 Center Strategically Focused Prevention Research Network, is led by Dr Fuster and has enrolled 3- to 5-year-old children to test a family-based approach for the promotion of cardiovascular health. More than 600 preschool children and their 600 parents or caregivers from 12 to 15 Head Start schools in Harlem, New York, have been recruited using a 2:1 (2 intervention/1 control) cluster randomization of the schools. The preschool children receive an intensive 37-hour educational program as the intervention for 4 months. For the adults, those in the intervention group are randomly assigned to 1 of 2 intervention programs: individual-focused or peer-to-peer. The primary outcome in children will be a composite score of knowledge (K), attitudes (A), habits (H), related to body mass index *Z* score (B), exercise (E), and alimentation (A) (KAH-BEA), using questionnaires and anthropometric measurements. For adults, the primary outcome will be a composite score for behaviors/outcomes related to blood pressure, exercise, weight (W), alimentation (A; diet), and tobacco (T; smoking; Fuster-BEWAT score). Saliva has been collected from the children for single nucleotide polymorphism genotyping, and blood has been collected from adults for RNA sequencing to identify network models and predictors of primary prevention outcomes.

Fibromuscular Dysplasia

Investigators at the CVRC work closely with the clinicians at Mount Sinai Heart. This model of seamless collaboration is well exemplified in the DEFINE-FMD study (Defining the Basis of Fibromuscular Dysplasia; NCT01967511), which is headed by Dr Jason Kovacic. The aim of DEFINE-FMD is to use disease-relevant samples from patients with FMD and matched healthy control subjects to DEFINE the molecular and cellular basis of this poorly understood disease. As suggested by the name fibromuscular dysplasia, it is likely that fibroblast cells play an important role in the disease pathobiology. In the DEFINE-FMD study, we are collecting DNA, plasma, serum, fibroblast cells (via skin punch biopsy), and culture supernatant from rigorously phenotyped FMD patients and healthy controls. Healthy controls are also carefully screened and matched to FMD patients by sex, race/ethnicity, age, and other factors. All fibroblasts are grown from skin biopsy samples under carefully standardized conditions. Fibroblast RNA is then harvested for high-throughput transcriptomic analysis. The DEFINE-FMD data sets have already proven their utility for disclosing the molecular basis of this disease and in an international collaboration were leveraged to help validate and study the first gene associated with this disease. As of September 2017, 310 subjects have been enrolled, and recruitment is ongoing.

Fostering Next-Generation Researchers

The vision at the CVRC is 3-fold: (1) to create a physical infrastructure populated by investigators pursuing innovative cardiovascular research, (2) to nurture a pipeline of early career-independent translational and clinical cardiovascular investigators, and (3) to initiate new training and career development programs while creating new outreach endeavors targeting high-school students and undergraduates from under-represented minorities in the surrounding area of Mount Sinai. The philosophy is to instill in trainees an understanding of the metrics required for career progression and, through close mentorship, to enable trainees to acquire professional survival skills (eg, grant writing and project management) in the progression toward professional independence.

Excellent researchers are the key to promote best science. Although actively recruiting world-renowned scientists, the CVRC also nurtures early career researchers within the institute to foster the next generation of researchers. Several of principal investigators within the CVRC were postdoctoral fellows and became independent. Long-term interactions enable these early-stage investigators to have close collaborations with each other while, at the same time, establishing their own laboratories. The training program, coupled with a Molecular and Cellular Cardiology T32 Training Grant through the National Heart, Lung, and Blood Institute, reached its 22nd year in 2017 and supports 8 postdoctoral trainees each year. The T32 program is composed of faculty preceptors in several departments and provides support to postdoctoral researchers.

International Collaborations

The CVRC has been in close collaboration with a number of internationally well-known investigators and institutions. Leaders in the cardiology field are invited to deliver lectures on cutting-edge science. New ideas are generated during these discussions with the visiting professors and collaborative projects ensue. Postdoctoral fellows frequently spend time in collaborating investigators laboratories learning new techniques, and we, in turn, provide the same opportunities for others. These exchanges offer worldwide network building for postdoctoral fellows.

What We Foresee

With increasingly longer life spans, the social and economic burdens associated with heart failure and vascular disease are expected to grow significantly in the next couple of decades. The world-class team of scientists and collaborators at the CVRC are dedicated to developing targeted therapies for cardiovascular diseases that will result in treatments for the ailing heart and the promotion of cardiac health and longevity. These therapeutic endeavors will be achieved through collaboration with the pharmaceutical industry and biotechnology endeavors. A number of faculty members at the CVRC have indeed become founders of new start-ups that are advancing the technologies that have been discovered in their laboratories. Some examples include start-ups that are focused on

1. gene therapy for heart failure and pulmonary hypertension,
2. engineered bio-artificial human heart prototypes using state-of-the-art stem cells bioengineering approaches for drug testing, and

3. advancing small-molecule treatment targeting newly discovered pathways in heart failure.

Challenges

Cardiovascular research faces multiple challenges in the United States, namely, decreased funding along with a dwindling numbers of talented physicians and physician-scientists. In the next decade, despite these obstacles, the CVRC will continue to focus on building a solid infrastructure while incorporating the most advanced techniques and methodologies. The CVRC strives to be a center in which investigators will always have the freedom to address the most pressing questions in cardiovascular biology. Cardiovascular medicine has witnessed tremendous progress over the past 25 years, resulting in significant improvements in patient care and survival. The next 25 years promise more breakthroughs and better treatments for the millions of lives affected by heart disease. The CVRC is uniquely positioned to play a key role in this mission.

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Disclosures

None.

Reference

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