

The Texas Heart Institute Part 2—Working Toward the Next Breakthrough in Cardiovascular Medicine

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In Honor of Dr Denton A. Cooley

The Texas Heart Institute (THI) has grown significantly since its inception in 1962. By taking a multifaceted approach to research and patient care, THI has stayed at the forefront of innovation in cardiovascular medicine (Table). Nothing has symbolized this more than the opening of The Denton A. Cooley Building in 2002. Thanks to a successful \$75 million campaign, this 10-story, 327 000-square-foot building, located next to St. Luke's Episcopal Hospital, was built to provide the full spectrum of cardiovascular services. It includes 12 operating rooms, a postinterventional floor, a transplantation floor, a progressive-care floor, cardiovascular recovery beds, an imaging facility, a telemedicine center, 2 floors dedicated to basic science research, a 325-seat conference center (the largest in the Texas Medical Center), a Heart Information Center, and a museum dedicated to the heart and the pioneering cardiovascular research conducted at THI.

A major focus of THI's laboratories has always been the development and testing of mechanical assist devices and cardiac substitutes. In fact, the Cullen Cardiovascular Research Laboratory, established in 1972, has been involved in the development of most of the cardiac pumps used throughout the world today, including the Heartmate II and HeartWare ventricular assist devices. Currently, research is underway to develop progressively smaller continuous-flow left ventricular assist devices and to improve heart transplantation capabilities. As part of this ongoing work, Dr O.H. Frazier, director of the Cullen Cardiovascular Research Laboratory, has performed >1400 heart transplantations and has implanted >1000 left ventricular assist devices in patients with severe heart failure—more of either procedure than has been performed by any other heart surgeon in the world.

Many other devices and techniques have also been developed at THI to improve the diagnosis and treatment of cardiovascular disease. Between 1994 and 1996, THI physician-scientists Drs Ward Casscells and James Willerson demonstrated that vulnerable atherosclerotic plaques have temperature heterogeneity that can be measured in vivo with a catheter. Together with Mr Olav Bergheim, Drs Casscells and Willerson founded the Volcano Corporation, a prominent biotech startup that produced catheters capable of detecting vulnerable atherosclerotic plaque. The first catheters produced detected the temperature

heterogeneity of atherosclerotic plaques. However, later versions added intravascular ultrasound and optical coherence tomography, allowing physicians to visualize the interior of the atherosclerotic plaque to identify anatomic components that could render the plaque dangerous. More recently, Dr Dixon and his team at THI have developed a noninvasive technique for visualizing vulnerable plaques in the heart and throughout the body. Specifically, inflammation, a hallmark of vulnerable plaques, is detected by using liposomal and nanoparticle carriers coupled with small-molecule compounds that bind with high affinity to receptors on inflammatory cells.

Over time, THI's research focus has broadened to explore other novel treatment options for cardiovascular disease, such as cell-based therapies and tissue engineering. In 2001, THI researchers began pioneering the use of stem cells for the treatment of heart failure and coronary heart disease in patients with no other treatment options. Dr Perin¹ led the first clinical study to test the safety and efficacy of treating heart failure patients with coronary heart disease and no other treatment options with their own bone marrow-derived stem cells by using a NOGA catheter, which allows the physician to identify and inject the cells directly into reversibly injured endocardium. The success of this study paved the way for larger, randomized clinical trials of stem cell therapies. A more recent clinical study conducted by Dr Perin² and his collaborators at THI and other institutions showed that allogeneic mesenchymal cells from youthful donors are not rejected when implanted; furthermore, they seem to be effective at improving left ventricular function and reducing future adverse events in patients with ischemic cardiomyopathy who had heart failure, coronary heart disease, and no other treatment options.

Recently, THI has begun to focus more on basic and translational science research. The Denton A. Cooley building was designed with 60 000-square feet of research space for regenerative medicine, genetic discovery, and gene manipulation studies, and several leading cardiovascular molecular biologists and regenerative medicine scientists have been recruited to THI. The contributions of these scientists, including Drs Doris Taylor, Richard Dixon, Jie Cheng, Mehdi Razavi, Robert Schwartz, James Martin, and A.J. Marian, promise to provide many new treatment options for cardiovascular

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Table. Historical Milestones of the Texas Heart Institute (2000–2017)

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| 2000 | <ul style="list-style-type: none"> • First site for clinical trials of the Jarvik 2000, a miniature, axial-flow LVAD |
| 2001 | <ul style="list-style-type: none"> • First demonstration that C-reactive protein causes vascular inflammation • 100 000th open-heart operation performed • Completed REMATCH study, which compared long-term implantation of the HeartMate electric LVAD to conventional medical therapy for heart failure • Implantation of the AbioCor total artificial heart • First in the world to treat coronary heart disease patients with heart failure and no other treatment options with their own stem cells by directly injecting them into the heart with a NOGA catheter |
| 2002 | <ul style="list-style-type: none"> • Dedication of the THI/SLEH—The Denton A. Cooley Building • HeartMate electric LVAD approved for destination therapy |
| 2003 | <ul style="list-style-type: none"> • First nationally ranked cardiovascular center in the United States to open a catheterization laboratory medical simulation training center • First implantation of a HeartMate II LVAD in the United States |
| 2004 | <ul style="list-style-type: none"> • First FDA-approved clinical trial of autologous adult stem cell therapy for congestive heart failure in the United States • First US patient to receive HeartMate II LVAD surpasses 1 y of survival with the device • THI and the University of Texas System sign a legal affiliation agreement to collaborate in cardiovascular disease research and education and the recruitment of outstanding physician-scientists |
| 2006 | <ul style="list-style-type: none"> • 1000th heart transplantation performed |
| 2007 | <ul style="list-style-type: none"> • National Institutes of Health selects THI as 1 of 5 centers for Stem Cell Study Consortium |
| 2008 | <ul style="list-style-type: none"> • James T. Willerson, MD, becomes president of THI, and Denton A. Cooley, MD, becomes president emeritus • First in United States to implant a pacemaker enclosed in an antibiotic envelope • FDA approval to use the HeartMate II LVAD as bridge to transplantation |
| 2009 | <ul style="list-style-type: none"> • THI and the University of Texas System sign an enhanced legal affiliation (Figure) |
| 2010 | <ul style="list-style-type: none"> • FDA approval to use the HeartMate II LVAD as destination therapy • Second in the United States to treat AAA with the minimally invasive Endurant AAA Stent Graft System |

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| 2011 | <ul style="list-style-type: none"> • First successful implantation of a continuous-flow total artificial heart in a human • Dr Willerson named Editor-in-Chief of the <i>Texas Heart Institute Journal</i> |
| 2012 | <ul style="list-style-type: none"> • THI chosen as the Biorepository Core Laboratory for the national Cardiovascular Cell Therapy Research Network and as one of the National Heart, Lung, and Blood Institute stem cell centers for treating patients with cardiovascular disease with stem cells after a nationwide competition • Dr Cooley publishes his memoirs, <i>100 000 Hearts</i> |
| 2014 | <ul style="list-style-type: none"> • 1000th LVAD implanted • THI develops a new working partnership with Catholic Health Initiatives • The <i>Texas Heart Institute Journal</i> begins being published online every 2 mo |
| 2015 | <ul style="list-style-type: none"> • THI and the University of Texas System renew and expand their legal affiliation |
| 2017 | <ul style="list-style-type: none"> • Dr James T. Willerson, MD, becomes president emeritus |

AAA indicates abdominal aortic aneurysm; FDA, Food and Drug Administration; LVAD, left ventricular assist device; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure; SLEH, St. Luke's Episcopal Hospital; and THI, Texas Heart Institute.

disease. For example, researchers led by Dr Schwartz have shown that it is possible to convert cultured human skin fibroblasts and adipocytes into immature contractile heart muscle cells within several weeks through the overexpression of 2 transcription factors (ETS2 and MESP1).³ In the future, it may be possible to create patches with these cells to help repair and regenerate injured hearts. THI scientists led by Dr Taylor are also optimizing methods to decellularize organs, such as hearts, livers, and kidneys, and then restore their normal function by reperfusing them with stem cells. One day, these techniques may be used to create whole transplantable organs from the recipient's own stem cells to reduce the likelihood of rejection. Another area of preclinical study is determining how the Hippo stop growth pathway regulates cardiac growth and development. In murine hearts, Hippo is expressed within 2 weeks of life to prevent overgrowth of the heart, but THI scientist Dr Martin and his team showed that inhibiting the Hippo pathway in mice either before an infarct is experimentally induced or several weeks thereafter causes the area of injury to completely regenerate, suggesting that this pathway could be a novel therapeutic target for treating heart disease.⁴

THI has also become involved in multiple community outreach projects. In 2010, Dr Willerson created the Center for Women's Heart and Vascular Health. Dr Stephanie Coulter, director of the Center, has been committed to conducting research in this field and educating women about their risk of heart and vascular diseases. Community projects include heart health screenings, public lectures, and educational programs and support groups for women. Another prominent community-based



Figure. Signing of an enhanced affiliation agreement between the Texas Heart Institute (THI) and the University of Texas (UT) System in 2009. Top row from left to right: UT System Executive Vice Chancellor for Health Affairs Kenneth Shine, MD; UT Health President Larry Kaiser, MD; and THI Board of Trustees Chairman Meredith Long. Bottom row from left to right: THI President Emeritus and Surgeon-in-Chief Denton Cooley, MD; THI President and Medical Director James Willerson, MD; and UT System Chancellor Francisco Cigarroa, MD (Published with permission from the Texas Heart Institute).

endeavor has been the screening of junior high school students in Harris County for cardiovascular abnormalities that could lead to sudden cardiac death, usually during sports-related activities. Using a generous grant from the Richard and Nancy Kinder Foundation, THI physician-scientists developed a mobile magnetic resonance imaging van, which has been used to perform the screenings at local schools. These exams can be done in 20 to 25 minutes without needles or breath holding, allowing for the noninvasive detection of 4 of the cardiovascular problems that cause sudden death in children. By 2017, 5200 children had been screened, and at least 700 were found to have various cardiovascular abnormalities, placing them at some degree of risk for adverse events.

In 2014, THI developed a new working partnership with Catholic Health Initiatives, a faith-based Catholic healthcare system based in Denver, Colorado, that includes >100 community hospitals throughout the United States (including several in Texas). As part of this transition, a new THI board was established, consisting of former THI board members and several Catholic Health Initiatives representatives, with the chairman being a THI designate in perpetuity. On March 2, 2017, Dr James Willerson became president emeritus of THI. In his new role, he will be the face of THI to the external community (locally, nationally, and internationally). In addition, he will continue to participate in cardiovascular research, provide patient care, and help educate young physicians training in cardiovascular medicine.

Throughout THI's 55-year history, many people have contributed to the Institute's success. The Board of Trustees—which comprises outstanding business and civic leaders—has supplied

effective leadership and generous financial assistance. The physicians on THI's Professional Staff have provided exceptional patient care, helped to educate succeeding generations of heart specialists, and stimulated new discoveries. In addition, all of THI's employees, many of whom have been with THI for >20 years, have contributed to THI's mission through their dedication, determination, and enthusiasm. THI has also benefited from the extraordinary generosity of thousands of benefactors.

The motivating force behind all of the innovations and medical advancements achieved at THI has always been the desire to improve patient care and prevent cardiovascular disease. As long as cardiovascular disease remains a threat to human life, these efforts will continue.

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