

## Heart Center of SAHZU Transforming Into an Innovative Institute

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With a long tradition of innovation, the Heart Center of the Second Affiliated Hospital of Zhejiang University School of Medicine (SAHZU) is striving to be a leader in health care for cardiovascular diseases through multidisciplinary research and collaboration.

### Introduction of the Hospital

SAHZU is a not-for-profit tertiary care public hospital founded in 1869 by the British Church Missionary Society with a mission of Spreading Benevolence and Saving People. It has 2 sites, the Jiefang Road Campus and the Riverside Campus, with a total capacity of 3200 inpatient beds, and is the major medical center in southeast China. In 2013, SAHZU was accredited by Joint Commission International as an Academic Medical Hospital Center and passed recertification in 2016. SAHZU served ≈135 200 inpatients and 4.18 million outpatients last year. In addition, ≈113 300 surgeries were performed.

### History and Structure of Heart Center

Innovation has a long tradition at our center. In the 1960s, the Cardiothoracic Surgery Department started research of prosthetic valves and produced the first generation of metal ball-like prosthetic valves in China. In the 1970s, a pioneering epidemiological study on cardiovascular diseases in China was performed on a population of fishermen by the Department of Cardiology. In the 1980s, the Cardiology Department started the first percutaneous cardiac intervention program in our Province. In the 1990s, the first partial left ventriculectomy in a patient with valvular cardiomyopathy was successfully performed by the Cardiothoracic Surgery Department. In the 2000s, Jianan Wang initiated the translational research of stem cell transplantation for congestive heart failure.

Currently, the Heart Center is composed of the Departments of Cardiology, Cardiovascular Surgery, Cardiovascular Interventional Center, Cardiovascular Imaging, and the Cardiovascular Key Laboratory of Zhejiang Province. The personnel is composed of a team of innovative cardiologists, cardiac surgeons, radiologists, anesthesiologists, and nurses work closely together to provide state-of-the-art care to our patients. Each year, ≈9000 diagnostic and therapeutic procedures are performed in the catheter laboratory with cutting-edge interventional techniques, such as transcatheter aortic

valve replacement (TAVR), mitral clip, imaging- and physiology-guided transradial coronary intervention for complex lesions, hybrid treatment for coronary heart disease, and catheter ablation for cardiac arrhythmias with magnetic navigation system.

### Mission and Leadership

Facing the challenge of the rapidly growing burden of cardiovascular diseases and an aging population, the mission of our Heart Center in SAHZU is dedicated to serve our society with innovating science, promoting education and leading the future. As the major cardiovascular research center in Zhejiang Province, the physicians and scientists are devoted to conducting rigorous research and various clinical trials, exploring new medications and technologies under the guidance of Jian'an Wang, the Chief of the Heart Center. As a leader and physician-scientist, Wang had a clear vision for the Heart Center, which is developing and applying new cutting-edge technologies to solve unmet clinical needs. He is the first physician-scientist in China to perform a clinical trial using stem cell therapy to treat acute myocardial infarction patients, use TAVR for patients with isolated aortic regurgitation, and treat patients with congestive heart failure with hydrogel implant Algisyl-LVR in the Asia Pacific region. In view of his outstanding performance in cardiovascular sciences, Wang has won many awards including the National Science and Technology Progress Award, which is the highest honor for scientists in China.

### Basic Research

Basic research constitutes a major component in the Heart Center of SAHZU. The Myocardial Cell Therapy Team focuses on safety, efficacy, and potential mechanisms of stem cell-based therapy in heart failure, based on serial studies from rodent models to nonhuman primate models to clinical trials. The research interest of the Atherosclerosis and Aortic Aneurysm Pathophysiology Team includes studies on the pathological mechanism of atherosclerosis and aortic aneurysms, especially on the relationship between renin-angiotensin system and vascular remodeling, as well as the role of nicotine in atherosclerosis. Finally, the Myocardial Mitochondrial Function Team focuses on experimental studies to better understand the mitochondrial biology, especially

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how mitochondrial signaling and mitochondrial dynamics were involved in both adaptation and maladaptation processes under the conditions of stress, such as ischemia and heart failure (Figure 1).

Researchers in Department of Cardiology recently demonstrated that hypoxia preconditioning improved the effectiveness of mesenchymal stem cells transplantation for the treatment of myocardial infarction in nonhuman primates without increasing the occurrence of arrhythmogenic complications.<sup>1</sup> Meanwhile, the CHINA-AMI phase I trial (China Acute Myocardial Infarction) initiated by our Cardiology Department provided the first-in-man evidence that intracoronary administration of hypoxia preconditioned bone marrow mononuclear cells improved left ventricular end-diastolic volume, end-systolic volume, and adverse remodeling in patients with acute ST-segment–elevation myocardial infarction.<sup>2</sup> Furthermore, work on the role of hypoxia preconditioning in augmented therapeutic properties of mesenchymal stem cells has revealed that leptin, microRNA-211, and heparanase were respectively required for hypoxia preconditioning–driven stem cell survival, migration, and angiogenesis.<sup>3–5</sup> In the field of atherosclerosis, a recent study led by our researchers demonstrated that nicotine accelerates atherosclerosis in *Apoe*<sup>-/-</sup> mice by activating the  $\alpha 7$  nicotinic acetylcholine receptor on mast cells, and mast cell deficiency in *Apoe*<sup>-/-</sup> mice diminished nicotine-induced atherosclerosis.<sup>6</sup>

The Department of Cardiology has achieved great academic progress in recent years, and various teams in our department have published numerous studies in top-ranking research journals. The number of publications with an impact factor >5 has gradually increased since 2011, with a total of 19 papers under the support from major national grants totaling 0.64 billion Chinese Yuan, including National Program on Key Basic Research Project, National High-tech R&D Program of China, and International Key Program from the National Natural Science Foundation of China. In addition, a series of facilities have been established for preclinical and clinical studies, including a 3100 m<sup>2</sup> large animal experimental center and a 516 m<sup>2</sup> Good Manufacturing Practice standard cell therapy laboratory. These achievements place our center among the top institutions in our nation, and the success in basic research is matched by strong progress in translational and clinical projects.

### Clinical Research

The major goals of clinical research in the Heart Center of SAHZU are developing new techniques to solve common clinical problems with ideas or knowledge gained from basic or translational research.

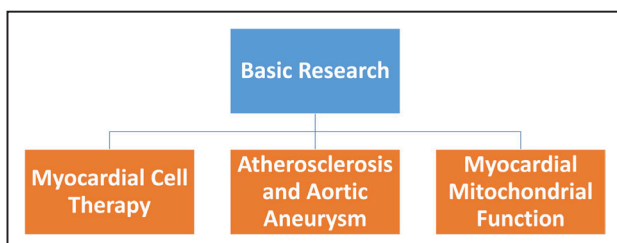


Figure 1. Areas of basic research.

### Valvular Heart Disease

In a recent retrospective study on 1394961 patients who underwent echocardiogram examination at our center between 2010 and 2015, among severe valve diseases, mitral regurgitation was the most frequent (0.68%) followed by mitral stenosis (0.38%), aortic stenosis (0.28%), and aortic regurgitation (0.27%). The prevalence of severe mitral regurgitation and aortic stenosis increased strikingly with age. Aortic valve calcification was the predominant cause of aortic stenosis, and its prevalence greatly increased with age.<sup>7</sup> Bicuspid aortic stenosis (BAV) was listed as a relative contraindication for TAVR in the 2012 European Society of Cardiology guideline on the management of valvular heart disease, because of higher prevalence of residual aortic regurgitation, valve malposition, annulus rupture, and aortic dissection compared with tricuspid aortic stenosis. However, BAV is quite common in the Chinese aortic stenosis patient population compared with its Western counterpart (33%–54% versus 13%–27%). To overcome the challenges brought by BAV, Wang designed a new domestic transcatheter aortic valve (Venus A) by strengthening the radial force and sealing technique. Also, he developed several important techniques to optimize the TAVR results for BAV, including stepwise balloon-sizing strategy to guide device selection and higher implantation. With these efforts, we achieved comparable outcomes for BAV patients receiving TAVR.<sup>8</sup> The clinical trial of Venus A was successfully finished with a good result, and the device was approved by China Food and Drug Administration in April 2017. On the basis of these results, the China TAVR Expert Panel recommended BAV as a relative indication for TAVR. Up to now, we have 11 patents in this field. In the future, we plan to continue our research in this field through close collaboration with engineers and industry partners. For example, a clinical trial of a new device, the Venibri dry valve (Venus Medtech, Hangzhou, China), will be started soon.

### Imaging- and Physiology-Guided Percutaneous Coronary Intervention

Optimization of percutaneous coronary intervention (PCI) results through physiology and imaging guidance is an important area of interest. In a prospective, multicenter, randomized controlled trial of POST-dilatation to improve outcomes in ST-segment–Elevation Myocardial Infarction patients undergoing



Figure 2. Western Zhejiang Heart Institute.

primary PCI after thrombus aspiration with optical coherence tomography assessment (POST-STEMI), we found that post-dilatation can be safely performed in ST-segment-elevation myocardial infarction patients to improve stent strut apposition after sufficient manual thrombus aspiration without adverse effect on the final blood flow. Another ongoing multicenter international trial that our institution is participating in, FLAVOUR (Fractional Flow Reserve and intravascular ultrasound (IVUS) for Clinical Outcomes in Patients With Intermediate Stenosis), compares clinical outcomes between imaging- and physiology-guided intervention strategy in patients with intermediate stenosis in 9 Korean and Chinese Hospitals. Fractional flow reserve (FFR)-guided PCI strategy for coronary artery disease has proved its benefit over angiography-guided PCI or medical treatment by previous randomized clinical trials. Recent clinical studies and meta-analysis also showed that IVUS-guided PCI strategies could also reduce the incidence of major clinical events after drug-eluting stent implantation. However, there has been no randomized study to compare the outcomes of FFR-guided versus IVUS-guided PCI in patients with intermediate coronary artery stenosis. In this regard, the randomized comparison between physiology (FFR)-guided strategy and imaging (IVUS)-guided PCI will provide valuable insights to enhance the patient's clinical outcomes with fewer number of intervention.

### Network and Education

SAHZU has 9 affiliated hospitals and has collaborated with over 200 hospitals and 31 community clinics across the country through telemedicine. As Chief Editor of the national textbook of Internal Medicine and the Vice President of the Chinese Society of Cardiology, Wang has a strong passion in medical student, physician, and patient education. As a leading figure in the use of TAVR in China, he and his team have treated many patients from 18 provinces nationwide and helped hospitals in 14 provinces to set up their TAVR programs. He was invited to Kolaj Hospital in south India to proctor their first TAVR procedure. He trained 79 medical teams from all over the country, which were willing to start a TAVR program. Furthermore, our center hosts a variety of medical education courses and conferences for practicing physicians, including the Qianjiang International Cardiovascular Conference which attracts over 4000 attendees from China and abroad each year, and the China Valve Hangzhou, a meeting dedicated to transcatheter valve therapy.

International communication and cooperation is a very important strategy for our center to improve the level of research and education. We set up a long-term cooperative basic research projects with Harvard University and Alabama University. The Center also offers training opportunities for overseas fellows and residents and established a joint cardiology fellowship training program with the University of California, Los Angeles. Each year, 2 to 4 cardiology fellows from University of California, Los Angeles receive 2 to 4 weeks of training in interventional cardiology at our center.

### Future Perspective

The main challenge facing the Heart Center of SAHZU in the coming years is to promote multidisciplinary and inter-departmental research. A brand new Western Zhejiang Heart Institute, funded by SAHZU and the local government, is currently under construction with a total floor space of 75 000 m<sup>2</sup> (Figure 2). It will be home to a specialized cardiovascular hospital, a multidisciplinary innovation center, a sample bank, and a data center. A group of elite physicians, researchers, engineers, and statisticians will be recruited to work together in an interdisciplinary approach. We are committed to finding the solution for cardiovascular diseases and will continue to nurture and inspire the passion of innovation. Together, the Heart Center of SAHZU strives to be a leader in innovation and health care for our society in the future.

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### Disclosures

None.

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