Issue 4 2024

ZJU MEDICINE

SHOWCASING THE BEST OF ZHEJIANG UNIVERSITY SCHOOL OF MEDICINE

RECONSTRUCTING THE DIGITAL TREE OF LIFE

Dialogue with Prominent Scholar ZHANG Guojie

"TRIM" THE HEART AND "STRENGTHEN" LT!

Promising Therapeutic Target for Cardiovascular Disease

HOW DO INSECTS "TASTE" SWEETNESS?

Structural and Molecular Mechanisms of Sugar Receptors

ZUSM at A Glance

Zhejiang University School of Medicine (ZUSM), founded in 1912, is one of China's best and oldest higher medical education institutions. Located in Hangzhou – one of China's most picturesque cities – ZUSM is organized across the School of Basic Medical Sciences, School of Brain Science & Brain Medicine, School of Public Health, School of Nursing, 7 clinical medical schools (School of Clinical Medicine, School of Obstetrics and Gynecology, School of Pediatrics, School of Stomatology) and a healthcare partnership network composed of 8 affiliated hospitals, numerous non-directly affiliated hospitals and cooperative hospitals. It is home to more than 33,000 faculty members and over 8,800 students.

ZUSM believes that every global partner is unique and each project is irreplaceable. We are together with global partners for a better response to future medical challenges and making efforts to build a healthy future for all.

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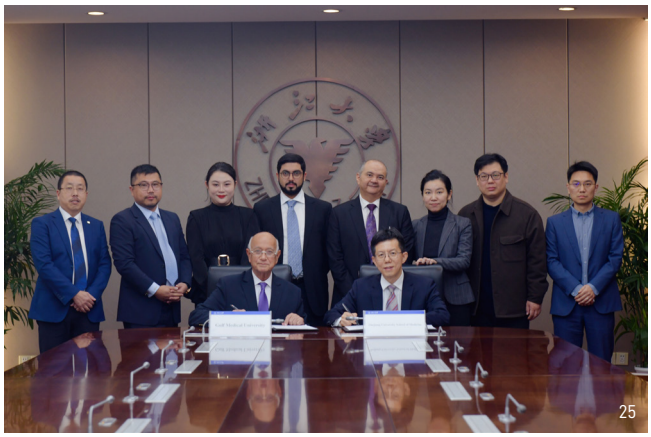


A Message from the Dean of ZUSM

HUANG Hefeng

Dean of the School of Medicine, Zhejiang University
Academician of the Chinese Academy of Sciences
Honorary Fellow of the Royal College of Obstetricians and Gynaecologists, UK
Academician of the Academy of Developing World Sciences
Member of the Chinese Academy of Medical Sciences

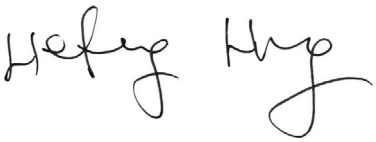
Distinguished readers,

Spring is in its prime, with nature flourishing. On the occasion of the new edition of ZJU Medicine, I feel proud to represent the faculty and students of Zhejiang University School of Medicine (ZUSM) and extend our heartfelt gratitude and profound respect to our friends, who have shown interest in and supported the development of ZJU Medicine.

Standing at the new starting point of 2024, I feel the significance of our responsibility and the brilliance of our missions. Looking back, we have remained true to the original aspiration to provide medical care, pursue excellence, and actively contribute to national healthcare and people's well-being. Looking ahead, following the development idea centered on people's health, we will continue to deepen educational reform and innovation, enhance the construction of first-class disciplines, improve the quality of talent cultivation, and bolster scientific achievement transfer, contributing more wisdom and strength to ***ZJU Medicine*** in order to build a global community of health for all.

In 2024, many topics concerning "Healthy China" sparked heated debates. From reinforcing the construction of a community-level medical service system and promoting the inheritance and innovative development of traditional Chinese medicine to deepening the medical and health system reform, all of these topics demonstrate our country's high regard and firm determination to promote people's health. As the Dean of ZUSM, I will work closely with ZUSM's faculty and students to fully leverage our strengths in line with the requirements of the national strategies. With a more open mind, we will strengthen our cooperation and exchanges with universities, colleges, research institutes, and enterprises across the world, embracing changes while seeking innovation. Meanwhile, we will continue to elevate the comprehensive capabilities and influence of ZJU Medicine, jointly boosting its high-quality development.

Finally, I sincerely hope that ZJU Medicine will continue to thrive as an important window for showcasing our educational, scientific, and research achievements, as well as the development of ZUSM. Let us join hands and make an even greater contribution to advancing China's education, science and technology, and talent cultivation while promoting a healthy China!



Reconstructing the Digital Tree of Life

ZHANG Guojie

Qiushi Chair Professor at Zhejiang University
Director of Center for Evolutionary & Organismal Biology
Zhejiang University School of Medicine
Principal Investigator of Liangzhu Laboratory

Genetic variation, the root cause of many diseases, serves as the fundamental driving force for the evolution of life. Advancements in this cutting-edge field, which explores the evolution of life, necessitate collaboration among experts from diverse disciplines, encouraging them to expand their thinking and transcend traditional boundaries.

Brief us on your research. What has been the most interesting discovery in your field recently?

Our research focuses on biodiversity genomics and evolutionary biology. We use a comparative genomics approach to study the evolutionary history and adaptation mechanism of modern species including humans. Our group has organized several biodiversity genomic consortiums to resolve the long-lasting tree of life challenges in vertebrate taxa, such as birds. Our recent comparative genomics across primates have revealed key genomic changes underlying the evolution of traits like brains, limbs, and social systems that are crucial for the adaptive diversification of primates.

You joined ZJU in 2022 and set up the Center for Evolutionary & Organismal Biology. How did the Center come out?

Darwinian evolutionary theory is the fundamental theory for all disciplines in life science. Evolutionary thinking is important for biologists to understand how and why the traits evolved. However, this has often been ignored in the biomedical research field which emphasizes more on the study of mechanisms. We hope our new center can promote the communication between evolutionary biologists and molecular biologists and train the students the ability to drive the interdisciplinary programs.

What impact do you hope your work will have on science/society?

A key goal of our center is to introduce evolutionary thinking to researchers from broader backgrounds by developing interdisciplinary programs. Particularly, through these programs, we hope more biomedical researchers and doctors can embrace the evolutionary theory and start thinking about why humans are vulnerable to infectious and degenerative disorders from an evolutionary perspective.

Why did you choose Zhejiang University when you decided to come back to China?

Zhejiang University is one of the top universities in China and has been very successful in developing cross-disciplinary research programs in the past decades. It is a renowned university attracting the most talented students in China.

As a professor, what advice do you have for undergraduate and graduate students?

Keep tracking the most up-to-date research progress, and think deeply about the topics that you are interested in.

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Cultivating for Over Three Decades: Innovative Approaches to the Treatment of Cardiovascular Disease

XU Qingbo

Member of Academia Europaea
Tenured Professor at the Cardiovascular Division, King's College London
Committee Chair of the Chinese Life Scientists Society in the UK
Qiushi Chair Professor at Zhejiang University
Director of the Cardiovascular Disease Research Center at the First Affiliated Hospital of Zhejiang University School of Medicine (FAHZU)

Could you briefly introduce your research?

I have been engaged in vascular biology, stem cell, and regenerative medicine research. Among these, the theory of "vascular stem cells participating in vascular injury repair and vascular transplantation regeneration" is the most representative. This theory, which is characterized by attracting autologous stem cells, promotes vascular healing and has led researchers to develop a new generation of vascular scaffolds, based on attracting autologous stem cells. Its application for vascular regeneration transplantation has led researchers to develop further chemotactic factor-type artificial blood vessels, which offer clinical benefits that are significantly higher than those of traditional cell mixture-type transplantation vessels. Currently, the research process has advanced to Phase I clinical trials.

After joining the FAHZU, what new explorations have you and your team undertaken?

Since joining FAHZU six years ago, our focus has been on mechanistic research and clinical translational exploration into "in-stent restenosis in vascular drug stents". We established the Cardiovascular Disease Research Center and collaborated with multidisciplinary labs located in renowned domestic research institutions in materials science, surgery, internal medicine, and tissue engineering, to develop new vascular bio-scaffolds/ artificial blood vessels. We aim to advance treatment for cardiovascular disease patients.

After being elected as a Member of the Academia Europaea, what are your future outlooks?

Being elected to the Academia Europaea is an honor and motivates me to continue my work in translating research into clinical applications and nurturing young researchers. I aim to use my experience to contribute to the development, academic innovation, and talent cultivation in cardiovascular research in China, enhancing its international standing.

Your research has taken you to many countries around the world. What insights have you gained from these experiences?

Scientific research requires persistence, similar to climbing a mountain. I have conducted scientific research in many countries and found that the most outstanding scholars possess the excellent quality of "persistence", along with experience and lessons learned along the road of scientific research. These accumulated experiences have become a valuable asset for me on my scientific research journey. I firmly believe that to make breakthroughs and succeed in scientific research, one must not give up continuous exploration and learning. At the same time, one should not limit one's research path but instead, always maintain confidence and curiosity to explore more possibilities.

As an educator, what are your insights into cultivating students' research interests and abilities?

As a mentor, I firmly believe that to cultivate talent, one must provide the space and stage to enable individuals to develop their abilities and inspire them to achieve their dreams. I treat every student equally and am willing to discuss any matters related to research with them. I believe that if students genuinely feel that their teachers are doing their utmost to help and empower them, they will be more motivated to engage in learning and research.

If we can first break through this 'bottleneck' technology, it will be a great help not only to the patients but also to the country.

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The MOE Frontier Science Center for Brain Science and Brain-Machine Integration at Zhejiang University

Brain science aims to explore the essence and laws of brain cognition and consciousness, while artificial intelligence (AI) contributes to achieving human intelligence through machines. Brain science and AI are both employed to fathom the ultimate secrets of human intelligence from different perspectives, and are showing a trend of convergence in their development. To promote the advancement and cross-disciplinary innovation of brain science and AI, the MOE Frontier Science Center for Brain Science and Brain-Machine Integration at Zhejiang University (BBMI), one of the first national-level frontier science centers launched by the Ministry of Education, was officially established in October 2018.

BBMI fully leverages the advantages of the relevant disciplines at Zhejiang University to explore and promote the integration of brain science and AI, striving to make significant breakthroughs in fundamental theories, frontier technologies, and the transfer of research achievements.

Zhejiang University is a leader in the field of invasive brain-machine interfaces in China, making remarkable achievements related to foundational hardware technology for brain-machine interfaces, the audiovisual enhancement of robotic rats through brain-machine integration, the fine gesture control of robotic hands by cortical signals issued by clinical patients, and closed-loop neural modulation to mitigate brain disorders. Over the past five years, BBMI has published a total of 823 academic papers the first author or corresponding author of which is Zhejiang University, with 18 in top-tier journals such as ***Nature***, ***Cell***, and ***Science***, one in ***Nature Medicine***, six in ***Nature Neuroscience***, and 19 in ***Neuron***. Currently, 282 BBMI research projects have been approved, including 65 projects on key programs, enterprises, and areas, with a total grant funding of over 750 million yuan.

BBMI is operated under the leadership of top scientists. Academician DUAN Shumin, the Director of ZJU Faculty of Medicine and Pharmaceutical Sciences, has been appointed the chief scientist; Professor HU Hailan, the Dean of ZJU School of Brain Science and Brain Medicine, has been appointed the Director of BBMI; and academician DU Jiangfeng serves as the Director of the BBMI Management Committee.

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Exploring the Cutting Edge of Infectious Disease at State Key Laboratory of Diagnosis and Treatment of Infectious Diseases

Infectious diseases continue to be a significant risk to global public health and safety, threatening human welfare. The First Affiliated Hospital, Zhejiang University School of Medicine (FAHZU) has confronted this challenge by taking proactive measures in disease prevention and control. Founded in 2007, the State Key Laboratory of Diagnosis and Treatment of Infectious Diseases quickly became a pivotal entity in combating the diseases, and successfully passed its inaugural inspection in 2009 and the latest reshuffle in 2022. The laboratory has been led by Prof. LI Lanjuan, Academician of the Chinese Academy of Engineering and a preeminent Chinese expert in infectious diseases.

The laboratory distinguishes itself through its comprehensive research methodology, seamlessly merging basic and clinical sciences across 18 cutting-edge technological platforms, including Artificial Liver, Infection Microecology, and Multi-omics, as well as nine specialized wards such as the Artificial Liver Center, Intensive Care Unit, Infectious Diseases, Viral Hepatitis, Tuberculosis, AIDS, etc. Its powerhouse team includes four academicians and numerous top-tier national researchers, totaling 242 dedicated personnel. Their pioneering work not only achieves a domestic leading position but also makes a significant international impact.

Viral Hepatitis and Severe Liver Diseases: The laboratory has achieved global leadership in addressing viral hepatitis, particularly severe liver conditions. The LI's Artificial Liver system has revolutionized treatment outcomes for liver failure, increasing survival rates dramatically and promoting the 'Hangzhou Standard' for liver transplants—a now globally recognized protocol.

Infection Microecology: The laboratory has taken the lead internationally with its research into infection microecology, promoting microbial interventions to protect human health. It has made groundbreaking contributions to understanding gut microbiota changes in liver cirrhosis, with significant findings published in ***Nature***. In 2013, Academician LI Lanjuan was elected as the President of the International Human Microbiome Consortium (IHMC), demonstrating China's international leadership in this field.

Emerging Infectious Diseases: The laboratory stands as a vanguard in shaping national strategies for emerging infectious diseases, exemplified by its pivotal role in combating threats such as the H7N9 avian influenza. Setting global standards in disease prevention, its methodologies have garnered international adoption. In recognition of its groundbreaking contributions, the laboratory was honored with the National Grand Prize for Progress in Science and Technology, signifying a "0-1" moment in China's educational and healthcare sectors.

Epidemic Response and COVID-19 Management: The laboratory was pivotal during the COVID-19 crisis,

achieving major breakthroughs in understanding the virus and developing the 'Zhejiang Experience' to improve patient outcomes significantly, reducing the fatality rate of severe cases from 50.98% to 4.17% in the early stage of the epidemic and promoting nationwide application. These efforts have been recognized globally, enhancing China's reputation in international scientific communities, by providing support to European, American, and Belt and Road countries, contributing to global efforts. The achievements received numerous awards including the UNESCO International Life Science Research Award.

Dedicated to pushing the boundaries of research on severe infectious diseases, the laboratory prioritizes elucidating disease mechanisms and refining precision in diagnostics and treatment. Rooted in a robust culture of innovation and propelled by a forward-looking vision, it strives to uphold its leadership role in global scientific endeavors aimed at managing infectious diseases.

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Why Can Tumor "Bite" Hard Bones? Researchers at Zhejiang University Have Made a New Discovery

Bone is one of the most common sites of early metastasis of cancer and is also a "hotbed" for tumor cells. Why do tumor cells go after hard bones first? The latest study by teams from FAN Shunwu & Lin Xianfeng's Lab from Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, found that they are directed at osteoclasts, the only cells in the human body that can secrete acid and dissolve bone. By "feeding" them closely, tumor cells "ripen" osteoclast-precursor cells and fuse them into larger and more destructive osteoclast named "tumasteoclast", which acts like a crazy "ice-breaker" to carve out habitable zones on hard bone.

Based on this finding, the research team proposes a novel "circuit breaker" strategy for bone metastasis: nano-scale "anti-osteoclast landmines" are placed on the bone surface. Once tumor cells are coupled with tumasteoclasts, the "landmines" will be triggered immediately, physically killing the tumor cells and tumasteoclasts, thus stifling bone metastasis in the "cradle". On March 18, 2024, "Targeting initial tumour-osteoclast spatiotemporal interaction to prevent bone metastasis" was published in ***Nature Nanotechnology***.

Why do stones become "hotbeds"?

Metastasis is the most dangerous part of cancer development. Some tumor cells will enter the blood, circulate throughout the body, and then "settle down" away from the primary site. Clinical statistics show that bone is one of the earliest sites of metastasis. Tumor cells often use bone as a "springboard" to spread to other organs such as the liver, lungs and brain.

Puzzlingly, hard bones do not seem to be "habitable". The large amount of calcium salt in bone tissue constitutes a strong "iron bastion", which will greatly hinder the proliferation and growth of tumor cells. But in fact, bone metastases develop faster than metastases in other sites due to the abundance of cell growth factors in the bone marrow. This makes Prof. FAN very confused: since "softening" the bone matrix is a prerequisite for metastasis, how do tumor cells "bite" the hard bone? "To spread cancer to the bone is like planting flowers on a stone." Fan believes that if we find the answer, it is possible to find a way to prevent bone metastasis early.

While observing histological sections of the bone metastasis, PhD student GU Chenhui noticed that the metastasis was surrounded by many osteoclasts. While this is a classic phenomenon that has been observed before, the team believes that previous studies have not fully explained the reason for such close proximity and high density. "What are the tumor cells and osteoclasts doing when they are so close?" This key question led them to a new discovery.

Tumor cells "feed" tumasteoclasts closely

Osteoclasts are the only cells in the human body with the function of acid secretion and bone lysis. They usually stay in the bone tissue in the "reserve" state. Under certain conditions, they can be stimulated and "integrated" into giant mature osteoclasts. A small number of mature osteoclasts are responsible for absorbing bone, and then osteoblasts secrete calcium salts to regenerate bone, thereby maintaining a certain level of bone renewal. "This process is similar to repairing a broken pavement, where osteoclasts are responsible for removing the broken pavement and osteoblasts are responsible for repaving the pavement," Gu said. Clinically, the overactivity of osteoclasts is one of the direct causes of osteoporosis.

The research team first discovered the "crime tool" of tumor cells. Under the scanning electron microscope, Gu found that the edges of the osteoclasts were very rough, which turned out to be many micron-scale vesicles with "peduncles". The research team determined that this was the new organelle, the migrasome, recently discovered by Professor LI Yu of Tsinghua University. "The vesicles we observed are very similar to the migrasomes in terms of formation, shape, and size," Gu said.

It turns out that as soon as tumor cells "land" on the surface of bone, they make up to osteoclasts. Tumor

cells transfer RNA, protein and other cytoplasmic components to osteoclast-precursor cells through the migrasomes, and "ripen" them in large quantities. Opening this "recipe" presented by tumor cells, the researchers found mRNA associated with a non-classical osteoclast differentiation transcription complex. "Tumor cell-derived mRNA allows osteoclast precursor cells to differentiate into osteoclasts under abnormal conditions," said TIAN Hongsen, a doctoral student. "Tumor cells are metabolically active, and their special RNAs and proteins can speed up the metabolism of normal cells," Dr. CHEN Pengfei explained," and it makes the osteoclast precursor cells fuse into a bruiser."

The research team believes that this tumor-coupled osteoclast in tumor metastasis is different from the previous osteoclasts in terms of induction mode, mediator and transcription pattern, and thus represents a new subtype of osteoclast. "We named it tumasteoclast (TAOC)," said LIN Xianfeng. After "ripening" and fusion, tumasteoclasts, a frenzied acidic machine, help the tumor cells absorb bone and remove obstacles.

Set up "landmines" to stop the metastasis

In clinical practice, bone metastases of tumor cells are very common. FAN Shunwu, who has been a doctor for more than 40 years, has contacted many patients who suffer from joint pain and mobility difficulties, which may be related to bone metastasis. According to reports, there are still limitations in the current diagnosis and treatment of bone metastases: the lesions generally have to reach the millimeter-scale before they can be detected by imaging methods such as X-ray and CT. "We have to find a way to 'kill' tumor cells when they induce tumasteoclasts at an early stage." Fan said that only by achieving cell-level tumor killing would it be possible to stifle bone metastases in the "cradle" and achieve the effect of prevention.

Based on the new findings, the research team proposed that the "coupling" behavior of tumor cells and tumasteoclasts should be targeted. "Tumor cells are very cunning. In conventional tumor cell targets, specific molecules are often used as targets, but tumor cells may take 'disguise' and other means to evade recognition." Lin introduced that the team proposed the idea of "behavior targeting" to tumor cells by recognition of tumasteoclasts.

The team has previously developed liposomes that specifically release sodium bicarbonate in the acidic sealing zone of osteoclasts for preventing osteoporosis, and the related research has been published in the ***Journal of the American Chemical Society***. Inspired by this strategy, they developed a new type of "anti-osteoclast landmine". Chen introduced that there are two substances in this nano-scale liposome "landmine": one is sodium bicarbonate, which can react with acid secreted by osteoclasts to produce gas, thus detonating the "landmine"; and the other is sodium hydrogen phosphate. After the "mine" is detonated, hydrogen phosphate ions will form "sharp" calcium-phosphorus crystals with calcium ions in situ, which will "stab" into the cell membrane of tumor cells and cause physical damage.

The team also embedded tetracycline molecules on the surface of the anti-osteoclast landmines, which allowed them to be directed to the bone surface. Once tumor cells and tumasteoclasts are "coupled", acidic substances from tumasteolasts will immediately detonate "landmine". "This is when the tumor cells step on the 'land mine'," Lin introduced, "and then the formation of a large number of calcium-phosphorus crystals can effectively kill tumor cells." Because sodium bicarbonate and sodium hydrogen phosphate are existing substances in the body, they have biological safety. This protocol has been validated in a mouse model of bone metastases. The team said that the effect with the nanoliposomes was surprising. Animal experiments have shown that the combination of the "landmine" and anti-PD-1 antibody can inhibit bone metastases by about 90%.

At present, the team has completed the effect verification of a variety of animal bone metastasis models, and simultaneously submitted the invention patent and started to carry out translation to clinical practice. The research team believes that the success of this study is due to the interdisciplinary advantages of Zhejiang University and the free exploration atmosphere of Sir Run Run Shaw Hospital. The orthopaedic team at Sir Run Run Shaw Hospital has long been engaged in the mechanism of musculoskeletal diseases and the treatment strategy of biomaterials, and actively explored the possibility of clinical translation. The innovation of the study was unanimously recognized by the reviewers, and was invited by the editor to share "Behind the Paper": Tumor-Osteoclast Spatiotemporal Coupling: A Cell Behavior Target for Bone Metastasis Prevention.

Doctor LIN Xianfeng and Professor FAN Shunwu of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, are the co-corresponding authors of this paper. Doctoral student GU Chenhui, Dr. ChEN Pengfei, and doctoral student TIAN Hongsen from Sir Run Run Shaw Hospital, Zhejiang University School of Medicine are the co-first authors of this paper. This work was supported by the National Natural Science Foundation of China (82322043, 92268113, 82072414, 82372454) and other projects.

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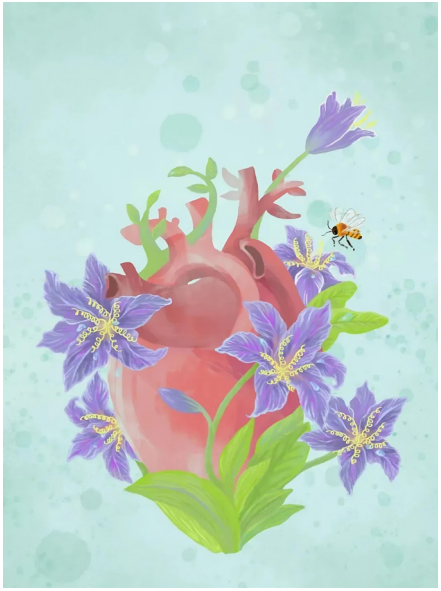
"Trim" the Heart and "Strengthen" It!



Myocardial hypertrophy, characterized by an increase in cardiac muscle mass, is an adaptive response to pathological stimuli such as hypertension and valve disease. While initially beneficial, sustained hypertrophy may lead to further disease progression and exacerbate heart failure, which is one of the most common and deadly medical conditions worldwide and remains incurable. Inhibition or reversal of cardiac hypertrophy and subsequent maladaptive myocardial remodeling are the main treatments for heart failure.

Cardiomyocyte hypertrophy can be triggered by diverse intrinsic and extrinsic stimuli including mechanical stress and hormones that are recognized by cardiomyocytes via a range of cell membrane receptors. A broad spectrum of GPCR antagonists have been used to treat heart failure, including those targeting β-adrenergic receptors, angiotensin II receptors, and aldosterone receptors. Owing to inadequate efficacy and adverse effects, only a few drugs for cardiovascular diseases, especially for heart failure, have indications for improving quality of life, physical function, or symptoms. Therefore, it is imperative to identify new therapeutic targets and strategies to fight against heart failure.

Professor ZHANG Yan's research team from the School of Medicine at Zhejiang University, partnered with Professor ZHANG Yan's research group from the School of Basic Medical Sciences at Peking University to conduct groundbreaking research. Together, they developed an effective apelin receptor modulator that, when compared to the established APLNR agonists, exhibits superior therapeutic effects against cardiac hypertrophy and reduced adverse effects, opening up a new avenue for the targeted development of cardiovascular disease drugs.

Their findings were published in the journal ***Cell*** on March 1.

G protein-coupled receptors (GPCRs) are the largest family of membrane receptors that serve as primary targets of ~1/3 of currently marketed drugs. The apelin receptor (APLNR, also known as APJ), a prototypical Class A GPCR, activates both G protein and β-arrestin signaling pathways through the endogenous ligand apelin. This dual activation modulates various physiological and pathological processes. Especially in the cardiovascular system, APLNR activation facilitates vasodilation, positive inotropy, angiogenesis diuresis, and lower blood pressure. Moreover, it regulates cardiovascular disease by inhibiting myocardial fibrosis, reducing pathological myocardial hypertrophy, and offering resistance against heart failure and pulmonary arterial hypertension. APLNR is therefore regarded as a promising therapeutic target for cardiovascular disease. However, adverse effects through the β-arrestin pathway limit its pharmacological use.

It is this "duality" that has baffled scientists, as it entails both positive effects and negative side effects, significantly impacting the efficacy and safety of drugs. Many world-renowned pharmaceutical companies and research institutions are striving to develop safe and effective APLNR agonists, but so far, no precisely targeted drug molecules have received approval for the market.

Professor ZHANG Yan's team at Zhejiang University has long been committed to delving into transmembrane signal transduction mechanisms and devising precise control strategies. Their work centers on the development and implementation of innovative methods utilizing cryo-electron microscopy for GPCR pharmacology research. This approach empowers them to intervene in diseases with precision through structure-based design, finely tuning GPCR functions for therapeutic purposes.

Simultaneously, Professor ZHANG Yan's team at Peking University has steadfastly focused on the mechanisms of myocardial injury and its implications for cardiovascular disease. Their research endeavors have led to the identification of targeted disease prevention and treatment strategies, opening the door for the prevention and treatment of cardiovascular disease.

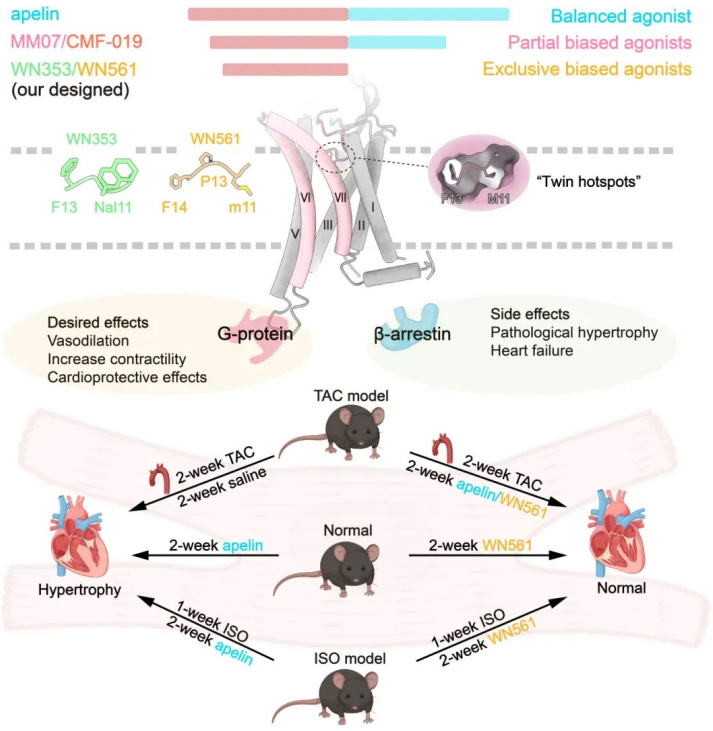
The first step in this study involved unraveling the enigma of how different signal spectrum agonists activate receptors to mediate downstream signaling pathways.

The research team has successfully resolved the high-resolution cryo-EM structure of the APLNR-Gi1 complex, activated by the endogenous balance agonist apelin and two biased G protein agonists, MM07 and CMF-019. They found that the APLNR-Gi1 complexes bound to these three agonists appeared remarkably similar, resembling "triplets," with seemingly no discernible difference.

However, the research team persisted and, after multiple experiments, finally identified subtle differences among them. If the ligand was likened to a key and the receptor to a lock, the top end of apelin, or the key handle, would be relatively extended, while MM07's key handle would be bent into a ring. This resulted in differences in the depth and specific position of their key main parts inserted into the receptor lock, with the critical sites inserted into two pockets defined as "twin hotspots," M11 and F13, affecting biased signal transduction.

Furthermore, they have also revealed the signal transduction mechanism from the ligand binding pocket to the downstream effector protein binding pocket—wherein D752.50, located at the hub of a polar network, acted as a switch for biased signaling, causing a 0.1 nanometer structural displacement. It is this minuscule difference in the spatial position, equivalent to one millionth the diameter of a hair strand, that triggered distinct conformational changes in downstream effector protein-binding pockets and ultimately determined whether G protein signaling or β-arrestin signaling would be initiated.

According to Professor ZHANG Yan at Zhejiang University, "By uncovering the molecular mechanism through which different biased signaling molecules



recognize and activate APLNR, we have designed two exclusive G protein-biased agonists WN353 and WN561. These agonists effectively suppress β-arrestin activity while preserving G protein signaling capability."

To minimize interference, the team blended the newly designed agonists with existing ones on the market, scrambled their numbering, and utilized both in vitro cultured cardiomyocytes and in vivo animal models of heart disease for "double-blind" functional screening and validation. Dr. WANG Weiwei said, "I was extremely nervous when 'the mystery box' was opened. However, the results were reassuring, demonstrating that our G protein-biased agonists WN353 and WN561 did not incur any myocardial hypertrophy. Our experiments also reaffirmed the β-arrestin signaling pathway of APLNR as the primary pathway leading to myocardial hypertrophy."

Subsequently, the researchers simulated the therapeutic effects of APLNR agonists in the context of myocardial hypertrophy, excluding pathological stimuli, such as valve disease or hypertension. The results revealed that Apelin exacerbated myocardial hypertrophy, while MM07 and CMF-019 had no effect. Encouragingly, the newly developed agonist WN561 demonstrated efficacy in alleviating myocardial hypertrophy in mice, regardless of pathological or non-pathological conditions, further showing the promising prospects of this novel G protein-biased APLNR agonist for the treatment of myocardial hypertrophy and heart failure.

This work revealed the distinctive recognition properties of APLNR complexes when bound to various biased ligands. It also led to the rational design of APLNR agonists with absolute G protein signal selectivity. Through experimentation on three different animal models, the safety and efficacy of these newly devised active molecules were demonstrated for the development of cardiovascular medications targeting APLNR.

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LI Xiao-Ming's Group Published in *Nature Neuroscience* for Neuromechanism of Fear and Anxiety

Excessive or repetitive fear plays a significant role in the development of anxiety disorders, with the amygdala serving as the central locus for fear processing. Clinical research has demonstrated that individuals with bilateral amygdala damage are still capable of experiencing fear, indicating the amygdala may not be absolutely required for fear. To date, the neural mechanisms underlying fear that are independent of the amygdala are still poorly understood.

On February 12th, Prof. LI Xiao-Ming and his team from Zhejiang University School of Medicine published an article entitled "A molecularly defined amygdala-independent tetra-synaptic forebrain-to-hindbrain pathway for odor-driven innate fear and anxiety" on ***Nature Neuroscience***. The study revealed the significant role of the main olfactory bulb → dorsal peduncular cortex → lateral parabrachial nucleus → parasubthalamic nucleus pathway in fear and anxiety.

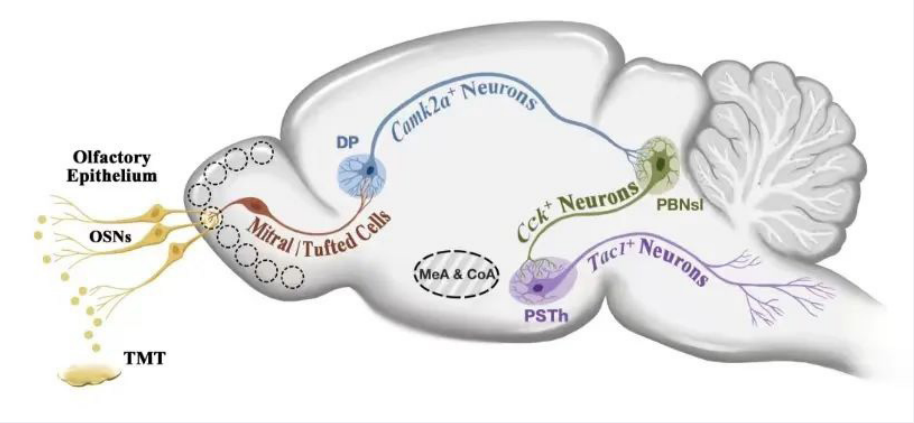
Olfaction serves as a common sensory modality that elicits innate fear in animals. Through the use of 2,4,5-trimethyl-3-thiazoline (TMT), a compound present in fox feces, which is a stimulus with fear-eliciting properties for rodents, the research team observed a notable decrease in aversive and freezing behaviors triggered by TMT in mice, accompanied by the apoptosis of neurons in the cortical amygdala and medial amygdala. However, this kind

of apoptosis did not have a significant impact on TMT-induced escape behavior. Therefore the team focused on finding the specific brain region that mediates the olfaction-evoked escape behavior.

In the subsequent experiments, Dr. WANG Hao, the first author of the study, characterized neuronal activity as reflected in Fos expression in response to TMT. He observed a notable elevation in Fos expression in the dorsal peduncular cortex (DP), which receives distinct inputs from the main olfactory bulb (MOB). In addition, the MOB-DP neural circuit exhibits markedly heightened activity following TMT stimulation.

"The role of DP in olfaction-evoked innate fear was investigated by inhibiting DP neurons in mice using an apoptosis virus, which resulted in the absence of obvious escape behavior in response to TMT stimulation and a significant reduction in aversive and freezing behaviors. Conversely, activating DP neurons using optogenetics induced escape behavior in mice, along with observable fear-like reactions such as dilated pupils and decreased heart rate," explained Dr. WANG Hao.

Concurrently, the team integrated optogenetic inhibition of DP neuron function with localized amygdala damage in mice. They observed that the combination of localized amygdala damage and DP inhibition resulted in a significant reduction of escape behavior induced by TMT in mice, as well as a further decrease in aversive and freezing behaviors. "Notably, the mitral/tufted cells projecting to DP and the cortical amygdala are two distinct groups of neurons. The aforementioned functional and structural observations suggest that DP is capable of autonomously mediating olfaction-evoked innate fear that bypasses the amygdala," stated Dr. WANG Qinng, co-first author of the study. Consequently, following input



from the main olfactory bulb, how does DP convey the fear response elicited by predator odor?

Combining virus tracing and patch-clamp electrophysiology, the team has discovered that DP forms excitatory synaptic connections with cholecystokinin (Cck) positive neurons in the superficial lateral parabrachial nucleus (PBNsl), which then project to tachykinin 1 (Tac1) positive neurons in the parasubthalamic nucleus (PSTh). This results in the formation of a molecularly defined tetra-synaptic pathway: $MOB^{Slc17a7+} \rightarrow DP^{Camk2a+} \rightarrow$ anterior $PBNsl^{Cck+} \rightarrow PSTh^{Tac1+}$.

In order to investigate whether the tetra-synaptic pathway participates in olfaction-evoked innate fear, PhD candidates CUI Liuzhe and FENG Xiaoyang delved deeper into the functional properties of the neural circuit. Their investigations revealed that this neural circuit exhibits significant activation during TMT-induced escape behavior. Furthermore, optogenetic inhibition of this pathway markedly diminishes mouse escape behavior and ameliorates fear-related responses. Even in mice with concurrent damage to the cortex and medial amygdala, activation of this pathway remains capable of inducing mouse escape behavior and replicating autonomic nervous response of innate fear. These findings suggest that the identified forebrain-to-hindbrain neural circuit can autonomously regulate TMT-induced innate fear independent of the amygdala. As a consequence of excessive or repetitive fear contributing to fear-related disorders, such as anxiety, the research team conducted a more in-depth examination of the pathway's function in anxiety. Dr. WANG Hao stated, "We observed that continuous optogenetic activation of this pathway (1h per day for three days) resulted in markedly observable anxiety-like behaviors in mice. Furthermore, the inhibition of this pathway led to a significant reversal of the anxiety-like behavior after 2h of acute restrain stress."

This study revealed a tetra-synaptic neural circuit of the main olfactory bulb → dorsal peduncular cortex → lateral parabrachial nucleus → parasubthalamic nucleus, and demonstrated that this pathway can regulate olfaction-evoked innate fear and anxiety that bypasses the amygdala. Prof. LI Xiao-Ming, the corresponding author of the article, believes that this research not only expands our understanding of the neural mechanisms underlying fear and anxiety but also provides new insights into the pathogenesis of mental disorders.

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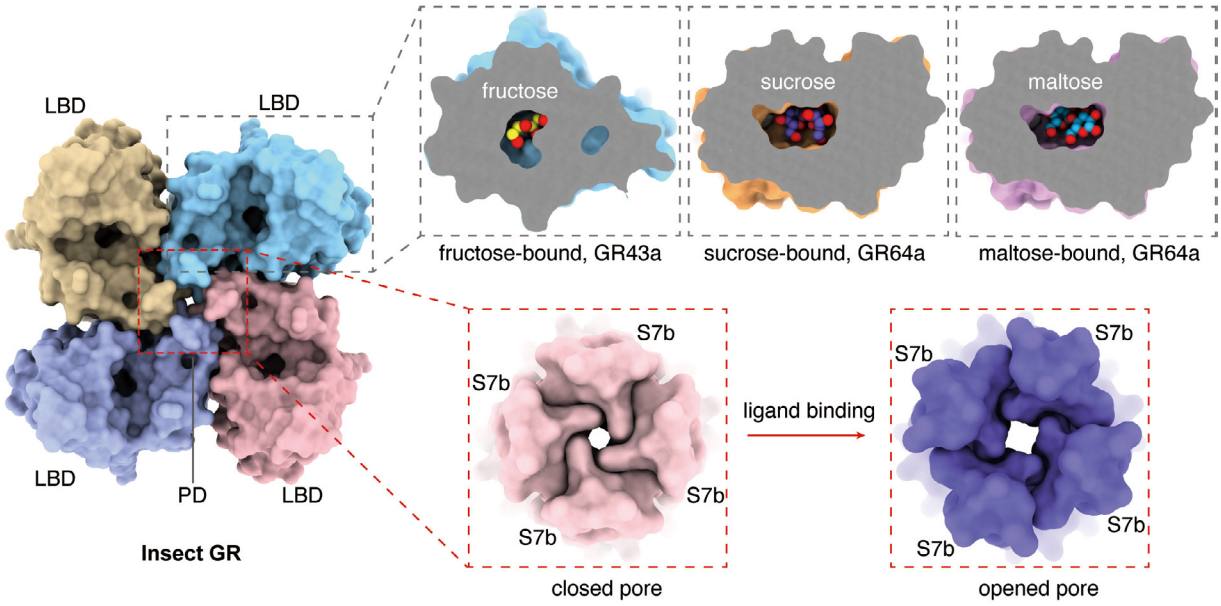
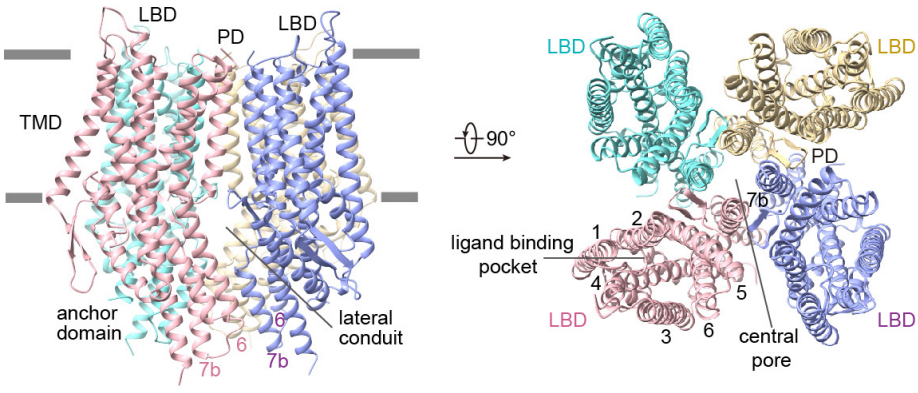
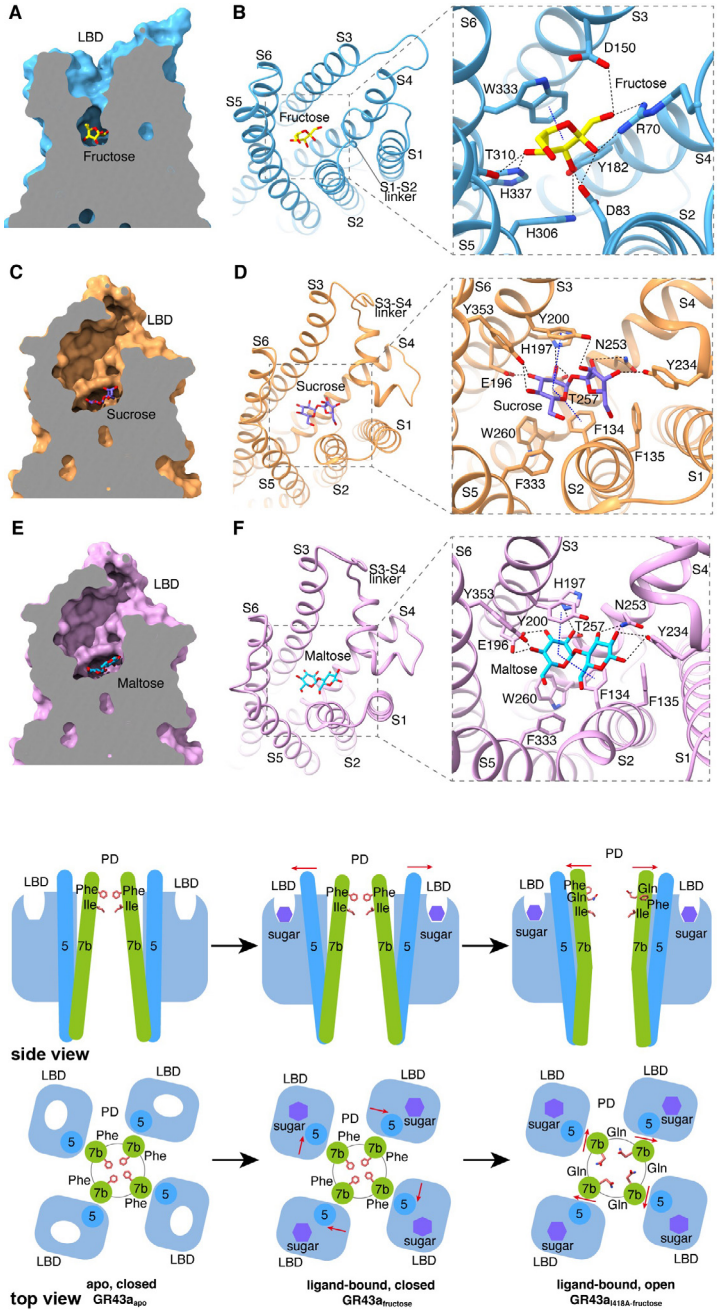
Scientists Reveal Molecular Basis for Sugar Detection by Drosophila Taste Receptors



Taste perception plays an essential role for animals to seek nutritious foods but avoid harmful compounds. Unlike mammals that detect sweet, umami, and bitter tastants via G-protein-coupled receptors, insects harness a large group of ligand-gated ion channels called gustatory receptors (GRs) for the perception of sweet, bitter, and other tastes. Among these, sweet sensation is particularly important due to its crucial role in detecting sugars and regulating carbohydrate intake. It remains unclear how GRs recognize tastant molecules and transit from a closed state to an open conformation due to the lack of three-dimensional structural information.

On February 2, 2024, Prof. GUO Jiangtao's group from Zhejiang University School of Medicine in collaboration with XU Haoxing's group from Zhejiang University School of Medicine/Liangzhu Laboratory, FAN Minrui's group from CAS Center for Excellence in Molecular Plant Sciences, and SU Nannan's group from the Fourth Affiliated Hospital published a research article in ***Science***, entitled "Structural basis for sugar perception by Drosophila gustatory receptors". This study has revealed how sugar molecules bind to activate insect sweet taste receptors, provided a prototypical platform for understanding how different tastants are perceived by diverse members





of the insect GR family, and offered accurate structural models for the rational design of attractant or repellent modulators for pest control.

Using electrophysiology and Ca^{2+} imaging, the researchers revealed that GR43a and GR64a are ionotropic sugar receptors with distinct sugar selectivity. GR43a is activated by monosaccharide fructose, while GR64a is activated by maltose and sucrose, two disaccharides found in the fly food.

To uncover the sugar activation mechanisms of insect GRs, the researchers determined cryo-EM structures of wild-type (WT) GR43a and GR64a in the apo (GR43a$_{apo}$ and GR64a$_{apo}$) and sugar-bound states (GR43a$_{fructose}$, GR64a$_{sucrose}$, and GR64a$_{maltose}$). GR43a and GR64a channels are both homotetramers composed of four symmetric subunits. Each GR subunit contains seven transmembrane helices (S1-S7) with S1-S6 forming the ligand-binding domain (LBD) and S7 contributing to the formation of the central pore domain (PD). At the cytosolic side of the GR channel, four lateral conduits between adjacent subunits act as potential ion exit routes.

In the sugar-bound GR structures, sugars bind to the extracellular-facing pockets of LBDs via hydrogen bonds and CH-ϖ interactions. GR43a recognizes fructose with a narrow pocket that can neither accommodate disaccharides nor optimally fit other monosaccharides such as glucose. GR64a binds disaccharides with a larger and flatter pocket that possesses structural plasticity to accommodate both sucrose and maltose, but not monosaccharides. In the apo state and sugar-bound structures of GR, the channel pores remain closed.

To understand how sugar binding triggers the opening of the channel pore, the researchers identified a constitutively activated mutant GR43a-I418A and determined the structure of GR43a-I418A in an open conformation in the presence of fructose. By comparing structures of GR43a in the apo closed, fructose-bound closed, and fructose-bound open conformations, the fructose activation mechanism of GR43a was uncovered. The binding of fructose to the LBDs induces motions of S5-S6 toward the ligand binding pocket center, which then causes a bending of pore-lining S7 to open the channel pore through hydrogen bonds and hydrophobic interactions between S5 and S7.

"This study elucidated the sugar binding and activation mechanisms of different GRs, and may guide the development of new strategies to tune the physiology and behavior of insects, as well as to control pests," said Prof. GUO Jiangtao.

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Zhejiang University Team Publishes a Paper Revealing the Presence of a "Clean-up Crew" in the Urinary Tract

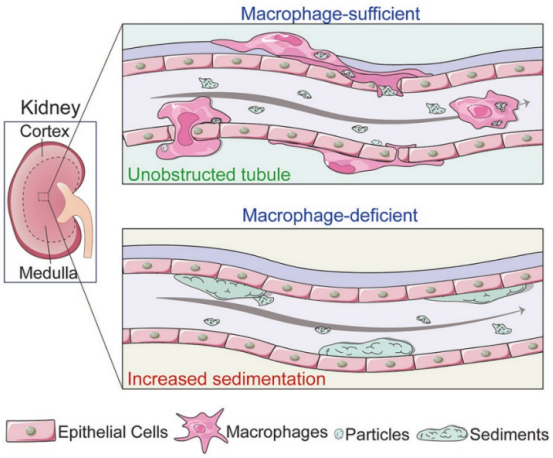
The kidneys are vital organs responsible for filtering blood, removing waste, and balancing body fluids. The kidney tubular system, which extends from the glomerular corpuscle through various tubular segments to the renal pelvis, is the site where the filtrate is processed into urine. During this process, the filtrate becomes concentrated, leading to the formation of microscopic sediments that, if not properly managed, can develop into kidney stones.

On December 29th of 2023, the research teams led by SHEN Xiao and SHI Peng at the School of Medicine, Zhejiang University, published a paper online in the journal ***Immunity***, entitled "Renal macrophages monitor and remove particles from urine to prevent tubule obstruction". This study has uncovered and verified that, beyond the flushing action of urine, a cellular mechanism exists within the kidneys, i.e., renal macrophages actively monitor and clear particulate matter from the urine to prevent blockages in the tubules. This discovery not only revises our conventional understanding but also offers new perspectives for the clinical prevention and treatment of kidney stones and other intratubular cast diseases.

Key Findings of the Research

Using high-resolution microscopy, Shen and colleagues observed that macrophages in the renal medulla exhibit unique transepithelial protrusions that reach into the tubular lumen. These protrusions allow the macrophages to "sample" the urine content and efficiently capture and digest the sediment particles. This proactive approach by the macrophages is crucial in preventing the obstruction of the tubular system. Furthermore, experiments involving the introduction of fluorescent markers and inert particles into the kidneys illustrated that these macrophages could not only capture but also transport sediment particles out of the tubules, actively participating in their removal from the kidneys.

The study also demonstrated that the density of these protrusions increases in response to certain conditions like hyperoxaluria, suggesting a dynamic adjustment to heightened risk factors for sediment formation. In genetically altered mice with reduced numbers of these macrophages, there was a marked increase in sediment formation of various natures, including proteins, lipids and minerals, highlighting their protective role. The interaction between the macrophages and the tubular epithelium is mediated by integrin β1—a molecule that facilitates the attachment of macrophages to the epithelial layer. This attachment is essential for the macrophages to perform their barrier function effectively.



Conclusion

This groundbreaking research sheds light on a previously unknown internal defense mechanism within the kidneys, emphasizing the role of immune cells in not just fighting infections but also in preventing common and painful conditions like kidney stones. By understanding how these macrophages function, new therapeutic strategies could be developed to enhance their activity or mimic their actions, potentially leading to new treatments for preventing kidney stones.

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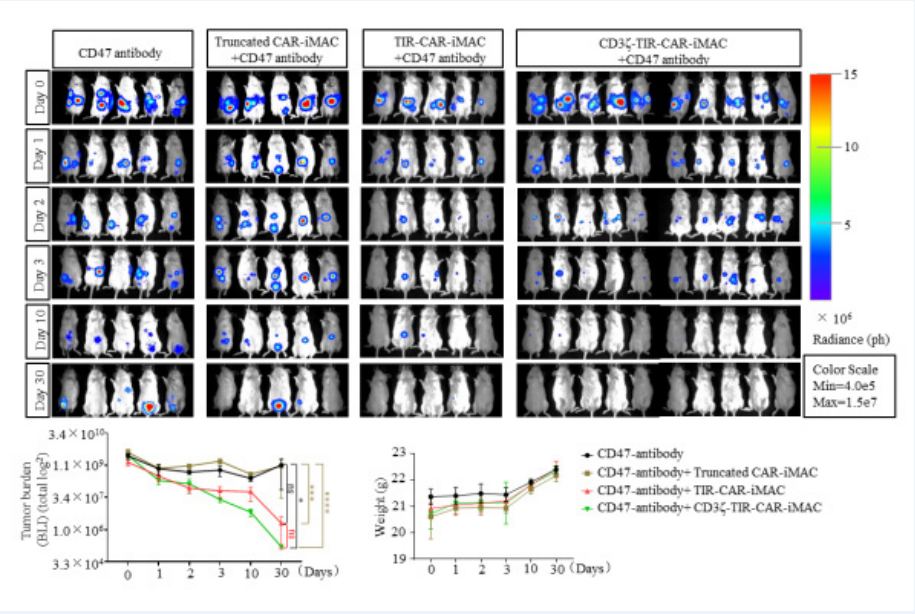
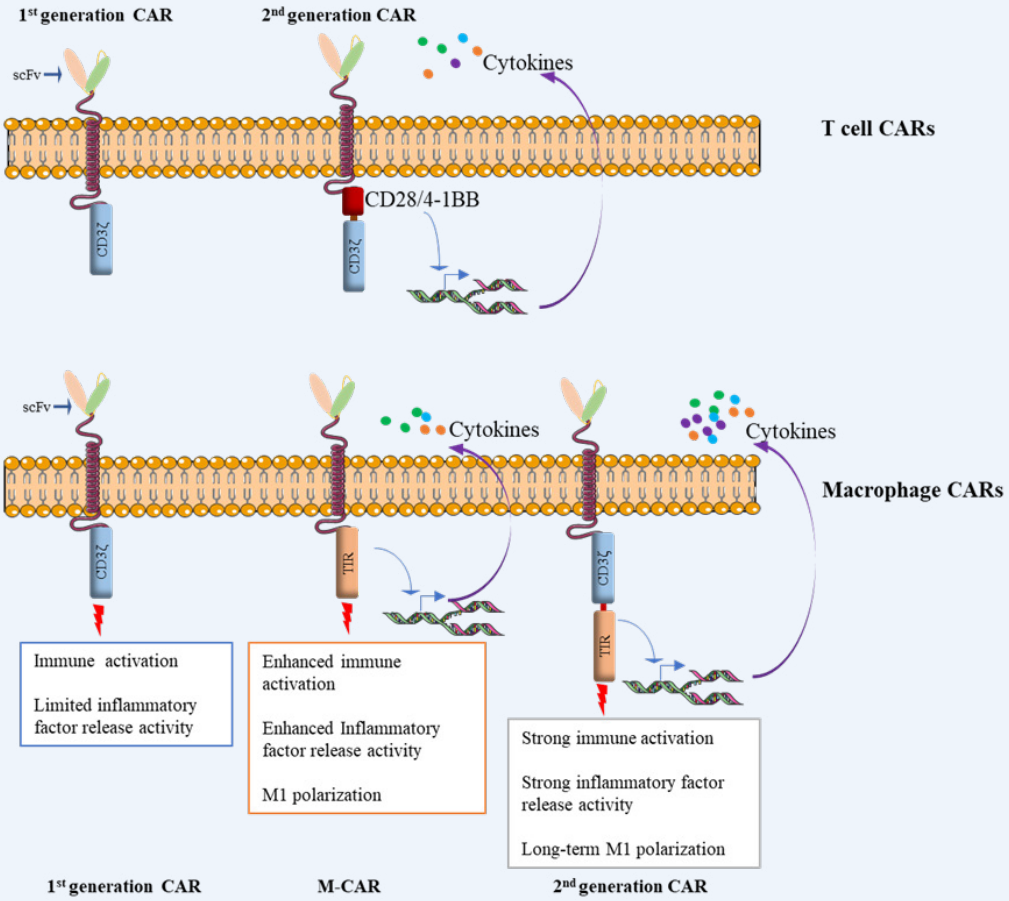
Second-generation CAR Macrophages with "efferocytosis" Function Against Tumor Cells

The effective treatment of tumors has always been deemed to be one of the major challenges in the medical field. As the first line of defense of innate immunity against antigens, macrophages are increasingly highlighting their unique advantages in the treatment of solid tumors due to their immune clearance function on abnormal cells and pathogenic microorganisms, as well as their functional characteristics of regulating immune response, and infiltrating into and staying in solid tumor tissues for a long time, which has attracted extensive attention and inspired research enthusiasm at home and abroad. At the same time, benefitting from increasingly mature and diversified gene editing technology, macrophages' functional diversity and plasticity make them a promising candidate for anti-solid tumor cell drug development. However, the application of macrophages in the treatment of solid tumors still faces numerous obstacles, such as that the macrophages are easy to be polarized into a cancer-promoting M2 state in the tumor microenvironment; the low editing efficiency of genes, limited cell number, and long preparation cycle of autologous mature macrophages cannot meet clinical requirements. In addition, how to endow macrophages with specific targeting-killing efficacy to enhance their therapeutic efficiency and overcome the On-Target Off-Tumor effect is also a problem that must be solved in the study of macrophages against solid tumors.



Beijing Time on November 27, 2023, Zhang's team published a research study entitled "A second generation M1-polarized CAR macrophage with antitumor efficacy" in the journal ***Nature Immunology***. In this work, the team designed an enhanced second-generation iPSC-derived CAR macrophage (CAR-iMAC) and elucidated its antigen-dependent polarization and immune activation, as well as its mechanism of killing tumors through "efferocytosis", providing a more solid theoretical basis for the application of CAR-iMAC in immune cell therapy of solid tumors.

ZHANG Jin's team attempted to entrust macrophages with the function of target-dependent M1 polarization and immune activation and provide a stable and reliable source to solve the problems macrophages faced. Based on a series of rigorous screening, the team first creatively constructed a macrophage-exclusive CAR (M-CAR) by designing the intracellular TIR signal transduction domain of Toll-like receptor 4 (TLR4), which has the function of polarizing and activating macrophages, to the intracellular location of the CAR. Then the researchers constructed the second-generation CAR with the orthogonal complementary signal of TIR and the CD3ζ signal domain of the first-generation CAR. Resorting to synthetic biology and its mature and reliable iPSC-differentiated Macrophages (iMACs) platform with independent intellectual property rights, the team was able to differentiate the second generation of CAR-iMACs. Experiments



confirmed that the second-generation CAR-iMACs showed significantly enhanced anti-tumor efficacy compared with single-signal CAR-iMACs. Six of the eight hepatocellular carcinoma mice treated with second-generation CAR-iMACs achieved almost complete tumor elimination. The survival of mice bearing extremely malignant glioblastoma (GBM) was also significantly prolonged after treatment with second-generation CAR-iMACs. Further experiments confirmed that the engineered immune cells not only greatly improved the targeted anti-tumor efficacy, but also secreted higher levels of anti-tumor factors such as TNF, and showed considerable antigen presentation ability and stronger ability to resist the immunosuppression of tumor microenvironment. This result also means that the second-generation CAR-iMACs can maintain higher levels of M1 polarization for a longer period during anti-tumor processes. Single-cell sequencing results confirmed that the second-generation CAR-iMACs achieved antigen-dependent M1 polarization and showed a typical M1 macrophage expression profile after co-culturing with tumor cells. In addition, in the anti-tumor treatment of syngeneic tumor-bearing mice with intact immune systems, the researchers found that G2-CAR-BMDMs (the mouse version of the second-generation CAR-iMACs) mobilized T and NK cells in the immune microenvironment while exerting its anti-tumor efficacy and maintaining M1 polarization, indicating that the second-generation CAR-iMACs can promote the transformation of solid tumors from "cold tumors" to "hot tumors". Mechanistically, the team found that nuclear aggregation of NF-κb/P65 mediates target-dependent M1 polarization and activation of TIR-based CAR-iMACs. Blocking the nuclear translocation of NF-κb/P65 significantly inhibited the targeting killing potency of this immune cell, proving the rationality and feasibility of TIR-based macrophage-specific CAR. Simultaneously, the work also revealed the "efferocytosis" approach by which CAR-iMACs eliminate solid tumor cells, that is, by inducing apoptosis of tumor cells and then engulfing the apoptosis bodies.

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CD19 Targeted CAR-T Therapy for Refractory Childhood-onset Systemic Lupus Erythematosus

Chimeric Antigen Receptor T-cell (CAR-T) therapy, a pioneering treatment for B-cell malignancies, has garnered significant attention lately due to its promising potential in tackling severe autoimmune disorders, especially systemic lupus erythematosus (SLE). Nonetheless, there is a notable absence of reported applications of CAR-T therapy in pediatric SLE patients.

In March 2024, the Children's Hospital of Zhejiang University School of Medicine initiated the groundbreaking use of CAR-T therapy in the treatment of refractory childhood-onset SLE, marking a significant milestone as one of the world's earliest applications of this innovative therapy in a pediatric patient.

Chan Chan, a 12-year-old girl from Taizhou city, Zhejiang Province, has been battling with SLE for over three years. Her condition is characterized by a range of symptoms, including a decrease in blood white cell count, recurrent skin rashes, oral ulcerations, and multiple arthralgia accompanied by synovial effusion. Despite receiving sequential treatments, including high-dose glucocorticoids, hydroxychloroquine, cyclosporine, cyclophosphamide, and a year-long B-cell-targeting therapy with belimumab, her health has continued to deteriorate on numerous occasions. Moreover, in February 2024, she developed significant proteinuria, further compounding her already challenging health situation.

After thorough deliberations by both Prof. MAO Jianhua and his nephrology team and Chan Chan's parents, it was decided to proceed with CD19-targeted CAR T therapy for her. Leukapheresis was successfully conducted and CAR-T cells were produced by the technical partner—Chongqing Precision Biotechnology Co., Ltd.

Before the scheduled infusion of CAR-T cells, all treatments, including glucocorticoids and several immunosuppressants, were discontinued. Prior to the infusion (day 0), Chan Chan underwent preparatory lymphodepletion by receiving cyclophosphamide (300mg/m^2/day) and fludarabine (30mg/m^2/day) from -5 to -3 days. Additionally, oral sulfamethoxazole-trimethoprim (SMZ) was prescribed to prevent pneumocystis carinii infection. Subsequently, on March 12th, an infusion of 0.94×10^5 CD19/kg CAR-T cells was administered. The cell infusion, which lasted only about 10 minutes, was similar to a regular intravenous infusion treatment, and Chan Chan did not experience any discomfort during the procedure.

As the CAR T-cells proliferated in vivo, Chan Chan exhibited stable vital signs, absent of severe cytokine release syndrome reactions such as high fever, hypotension, or hypoxemia. Furthermore, there were no notable elevations in cytokine levels observed. However, on the eighth day following infusion, she presented with symptoms of fatigue, limb tremors, and mild expressive and receptive language dysfunction. Promptly after administering glucocorticoid treatment, these symptoms rapidly subsided. Encouragingly, on the 14th day, her proteinuria level had decreased by half compared to its pretreatment baseline.

On March 27th, Chan Chan was discharged from the hospital after successfully completing her treatment and is expected to achieve a complete recovery. This breakthrough is clinically significant, indicating that more children with refractory SLE will benefit from advancements in medical technology and have the potential to fully recover, Prof. MAO Jianhua says.

When compared to adults, children with SLE often experience a higher frequency of the disease, a heightened risk of organ damage (especially kidney damage), a prolonged illness duration, and an overall poorer prognosis. Currently, the available treatment options are limited, and patients often require long-term medication that can come with significant side effects. The successful application of this CAR-T therapy to Chan Chan underscores its feasibility, safety, and efficacy in treating pediatric patients with SLE. In the upcoming period, we will maintain a diligent follow-up on Chan Chan and enroll more pediatric patients with refractory SLE to participate in this clinical study.

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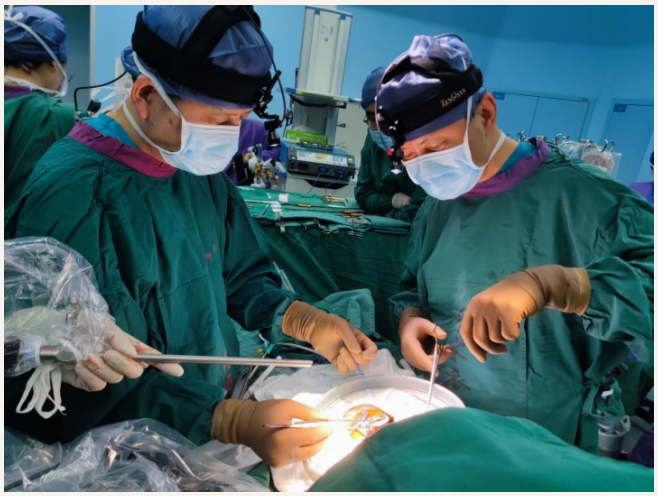
World's Smallest Artificial Heart Gives New Life to 62-year-old Woman

On a typical day in January, 62-year-old Mrs. WANG took a stroll down her hospital ward, leaning on her walker and slinging a black bag over her shoulder. To anyone watching, she looked like any other patient, but hidden beneath her clothes was the world's tiniest artificial heart, quietly pumping life through her arteries. Mrs. WANG's journey to this moment was marked by her battle with dilated cardiomyopathy, a condition that weakened her heart over three years until she sought the expertise of Dr. LI Weidong at the First Affiliated Hospital, Zhejiang University School of Medicine (FAHZU).

Dr. LI remembers when they first met, Mrs. WANG was already in the grips of chronic heart failure. Medication wasn't helping, and the only other chance at life was a heart transplant, a step Mrs. WANG and her family were hesitant to take. By the end of last year, her condition took a nosedive, necessitating her transfer to FAHZU for more specialized care. There, tests painted a grim picture: her heart was operating at less than half its normal capacity, signaling end-stage heart disease, where conservative treatments were minimally effective, leaving surgery as the only viable option.

The situation turned critical on January 4th when Mrs. WANG suddenly collapsed, her heart stuck in a dangerous rhythm. The medical team's swift response saved her life, but it was clear that she needed a more permanent solution—and fast. With no suitable donor hearts available and time running out, Dr. MA Liang, Chief of Cardiovascular Surgery Department of FAHZU, recommended an innovative route: implantation of the world's smallest artificial heart.



This wasn't just any artificial heart. Weighing about 90 grams, the device was a marvel of medical engineering, designed to either assist or completely take over the heart's pumping function. What's more, it was to be implanted via minimally invasive surgery, a technique that promised a quicker recovery than traditional open-chest procedures.

The surgery, led by Dr. MA and Dr. LI, took place on January 10, making Mrs. WANG the first person in Zhejiang Province to receive the world's smallest artificial heart via minimally invasive surgery. Her life post-operation is a testament to the device's success. She's not just surviving; she's thriving, enjoying travels and jogs with her battery pack in tow. Her story offers a glimpse of hope to the over 10 million people in China battling heart failure, especially when donor hearts are scarce.

FAHZU's Cardiovascular Surgery Department has since performed more than ten artificial heart surgeries, each bringing a new lease on life to patients like Mrs. WANG. "The artificial heart can be used long-term in everyday life, with relatively easy replacement if needed," Dr. MA noted, highlighting the device's impact and utility. Through WANG's story, the future of treating end-stage heart failure shines a bit brighter, showcasing the incredible potential of artificial hearts in saving lives.

Mrs. WANG's condition gets better as time proceeds in the following week.

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Excellence in Teaching for Four Consecutive Years! Why are These Medical Courses so Popular?

"Come take a look—this group has found a fascinating dense spot and is here to share their experience!" As their peers gathered around, the group members confidently explained the structures on the screen, frequently engaging in discussions with the teacher in response to questions from other students.

This scene is a common sight in the classroom of ZHONG Jinjie, deputy director of the Department of Human Anatomy and Histology & Embryology, when she is teaching her course titled "Comparative Practical of Human Morphology II." Interactive group discussions greatly motivate the students, enabling them to gradually accumulate visible, tangible, and expressible "mini achievements" throughout their learning journey.

As the director of a nationally recognized, top-tier course, Zhong is dedicated to introducing ongoing innovation into both her educational content and teaching methodologies. Aligned with the OBE principle within the field of medical education, Zhong has devised an integrated histology course that employs both online and offline, mixed teaching. This model combines mobile learning via the MOOC platforms before and after the in-class sessions, transforming smartphones into microscopes to create virtual laboratory experiences. During classes, the focus shifts to face-to-face group discussions that integrate fundamental knowledge with clinical insights, combine active observation and interactive engagement, and include both self-assessment and peer evaluation. This scientifically robust teaching strategy methodically enables students to advance from understanding the basic "what" of their studies to exploring the more complex "why," thereby fostering essential skills for independent learning and promoting a positive mindset toward collaborative education.

"Under the microscope, the human body is unveiled as a sophisticated, magnificent world, meticulously composed of more than 200 distinct cell types. By utilizing digital slide systems, we have shifted the exploration of this microscopic realm from the physical laboratory to the digital domain. This transition allows us and our students to collaboratively to examine the detailed microstructures and functions of basic human tissues and over 40 different organs online. This deepens our understanding of how these vibrant cells are meticulously assembled to safeguard human health," stated ZHONG Jinjie and her team.

The dedication of the faculty is deeply appreciated by the students. As of 2023, "Comparative Human Morphology II" has been consistently rated "excellent" for four consecutive years as part of Zhejiang University's teaching evaluations and has been included on the university's prestigious list of

courses and instructors that are exempt from any further evaluations.

"Professor ZHONG's lectures during the first half of the class are extremely clear and comprehensible. Following her presentations, she provides us with ample time to examine the specimens independently and identify specific structures or cells. When we discover a standard structure, she encourages us to share our findings with the rest of the class, significantly boosting our confidence and motivation," explains ZHAO Jianan, a student from the Clinical Medicine (5+3) program.

In addition to Zhong's course "Comparative Human Morphology II," ZHENG Lianshun, also a deputy director of the Department of Human Anatomy and Histology & Embryology, has had two other courses rated as excellent for four years: "Basic Practical of Human Morphology" and "Anatomy of the Head and Neck." Both courses have been recognized as first-class online undergraduate courses in Zhejiang Province.

"Basic Practical of Human Morphology" is a fundamental course in the medical science field, and is designed to train medical students to understand and master the normal morphological characteristics, microstructures, adjacent positions, developmental patterns, and functional significance of various organs and their systems within the human body. This foundational knowledge is essential for studying other basic medical and clinical courses. During this course, ZHENG Lianshun emphasizes the development of the students' skills regarding self-directed learning, observation, expression, and analytical problem-solving. Her carefully crafted experimental projects not only cover basic morphological observations but also include elements that are

directly relevant to clinical practice. This approach helps to solidify the students' theoretical knowledge and enhance their understanding of medical practice.

"Anatomy of the Head and Neck" is another highly acclaimed course that is taught by ZHENG Lianshun. Serving as a bridge between basic medical science and clinical medicine, this course focuses on the specific regional divisions of the head and neck. It examines the location, morphology, adjacency, and hierarchical relationships between the organs and the other structures that are located within these regions, alongside their clinical applications. Due to the dense, complex layering of the tissues in the neck, this course has always posed challenges for students who are studying regional anatomy. Therefore, based on the theoretical lectures, the teaching team has produced "Regional Anatomy - Practical Dissection Teaching Videos" to help students integrate their theoretical learning with practical operations, thereby deepening their understanding and mastery of human regional anatomy. Additionally, the course embodies the medical ethos of "respecting life, aiding the injured and sick, dedication to service, and boundless love," thus guiding students to prioritize the safety and health of the public, respect patients, and communicate effectively. This approach continually enhances their all-round medical abilities and interpersonal skills.

"Professor ZHENG's courses are renowned for integrating dry academic content with practical and clinical applications, which encourages us to employ multiple senses and actively engage with the topics. For example, on the 'Anatomy of the Head and Neck' course, each week is complemented by practical dissection sessions following the theoretical lectures, in order to solidify our theoretical understanding through hands-on practice," says FANG Meimeng, a student of Dental Medicine. "During these dissection classes, it is common to see us students using our own bodies to locate anatomical sites, guided by Professor ZHENG. We then apply our hands-on knowledge to our dissection practices. Throughout the dissection process, Professor ZHANG provides continuous support and encourages the teams that excel to share their insights, which significantly enhances our grasp of anatomical knowledge and also improves our clinical abilities."

Work Hard to Realize Your Dreams and Devote Your Youth to Social Practices

On March 29, 2024, Zhejiang University announced the outstanding social practice teams for the 2023-2024 academic year's winter vacation. Four teams from ZUSM received the title "Excellent Social Practice Team at the School Level". During the winter holiday, these teams leveraged their professional strengths to engage more deeply at the grassroots level, endure challenges and forge their willpower, thereby showcasing the aspirational spirit of the faculty of ZUSM and reflecting the sentiments and responsibilities of young people in the new era.

The Winter Holiday Social Practice Team titled "Sang Yu Fei Wan (It's Never Too Old to Learn)" visited Hangzhou and other cities in Zhejiang Province.

The team enthusiastically engaged with grassroots communities, investigating sarcopenia among the elderly in various institutions, and conducting eldercare and health promotion activities. They actively implemented interventions involving exercise, diet and mental health to amplify Zhejiang University's impact and contribute to social welfare.

The Winter Holiday Social Practice Team titled "Youth Obesity Research and Prevention" traveled to Taiyuan, Shanxi Province.

The team encouraged youngsters to improve their physical fitness and mental well-being and avoid obesity through conducting professional interviews, interesting presentations, and practical hiking, among other activities, which contributed to the outlook of the "Health China" strategy and demonstrated the dedication and passion of ZUSM students.

The Winter Holiday Social Practice Team titled "75 Years of Service and Leadership in Medicine: Our Commitment to Action", traveled to Hangzhou, Zhejiang Province.

The team engaged in exchange sessions and lab visits with medical students from Tsinghua University. They also engaged in various volunteering activities, including online voluntary teaching for their respective hometowns. Through these efforts, they spread warmth and fostered goodwill, upholding the values of integrity and promoting harmony, thereby showcasing the exemplary spirit of Zhejiang University's medical students.

The Winter Holiday Social Practice Team titled "Elderly Health Promotion" traveled to Shanghai and Zibo in Shandong Province.

The team actively responded to the "Health China" strategy by utilizing surveys, science outreach posts, and offline lectures to conduct extensive, multi-dimensional and widespread activities across several provinces and cities. They investigated in depth the health conditions of the elderly, thereby promoting the awareness of the most common health issues and preventive measures to infuse youthful vigor into the national strategy and demonstrate Zhejiang University's commitment.

Spotlight on the Chu Kochen Scholarship Recipients

Established in 1986 to honor former President CHU Kochen, the CHU Kochen Scholarship represents the top honor of Zhejiang University.

GU Chenhui
Doctoral candidate in Surgical Science, Class of 2022
The 14th Zhejiang University "Top Ten Students"
Recipient of the National Scholarship for Doctoral and Master's Students

Gu focuses his research on the development and clinical application of naturally-derived vesicles technology. He has co-authored a pioneering study on cross-species photosynthesis in ***Nature***. The "Nanoparticle Platelets" that he co-invented with his mentor have entered clinical practice. "I encourage my juniors who are interested in research to pursue their passions relentlessly, gather strength quietly, and face challenges with grace to shine brightly."

KONG Lingzhuo
Master's Student in Psychiatry and Mental Health, Class of 2022
Recipient of the National Scholarship for Master's Students
Excellent Graduate of Zhejiang Province

Her research focuses on the "brain-gut axis" mechanisms in bipolar disorders. She has published 11 high-impact SCI papers and co-authored Zhejiang Province's first mental rehabilitation textbook. As a passionate writer, she has written over three million words and incorporated medical insights into her literary works. "I always believe in the power of words. Words nurture silently, attempting to build a bridge for communication between doctors and patients and so optimize doctor-patient relationships."

JIN Shuyi
Undergraduate Student in Preventive Medicine, Class of 2019
Recipient of the National Scholarship
Top Ten Students of Zhejiang University

Jin focuses on epidemiology related to aging. As the first author, he has published three high-quality papers and holds three utility patents and one design patent. He has also served as an assistant editor at the ***AGMR*** journal. He also won second place in the Zhejiang Provincial Games. "In the future, I hope to contribute significantly to our nation and society through my efforts."

Connecting Globally, Engaging with the World

Zhejiang University School of Medicine (ZUSM) actively constructs a health community of shared future, aiming to enhance innovation and quality development.

A memorandum of cooperation was signed with the Gulf Medical University (GMU) in UAE

On January 18, Hossam Hamdy, Chancellor of the GMU, visited ZUSM. LI Xiao-Ming, Vice President of Zhejiang University, met with the delegates. Both parties agreed on initial cooperation plans regarding talent cultivation, scientific research, and medical services.

ZUSM signed a memorandum of cooperation with the GMU

A cooperation agreement was signed with the National Heart Centre Singapore (NHCS)

On February 12 to 13, Professor WANG Jian'an, a member of the Chinese Academy of Sciences and Secretary of the Party Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (SAHZU), visited Singapore. During the visit, a cooperation agreement was signed with the NHCS. Both parties agreed to strengthen their close cooperation regarding talent cultivation, research collaboration, and technology transfer.

The SAHZU signed a cooperation memorandum with the NHCS

Traveling to Uzbekistan, the team from the SAHZU performed living donor liver and kidney transplant surgeries

On March 11, WANG Weilin, the Dean of the SAHZU, led a multidisciplinary team to Uzbekistan. They successfully completed Uzbekistan's first pediatric living donor liver transplantation, the first adult living donor left lateral liver transplantation, and the first laparoscopic donor nephrectomy for kidney transplantation.

The SAHZU signed a cooperation memorandum with the Republican Specialized Scientific and Practical Medical Center for Surgery, named after Academician V. Vakhidov (RSCS), in Uzbekistan

The ZUSM delegation visited the Dubai Health Authority in UAE

On March 4, a delegation from ZUSM was invited to visit the Dubai Health Authority (DHA). The Director General of the DHA, Awadh Seghayer Al Ketbi, along with officials responsible for medical services and medical licensing, among other departments, held discussions with the delegation.

A group photo of the delegation and the Director-General of the DHA

The ZUSM delegation visited Khalifa University in Abu Dhabi

On March 4, a delegation from ZUSM held discussions with Provost Bayan Sharif, Vice President for Academic Affairs Mohammed Kutari, and relevant officials from the College of Medicine and Health Sciences at Khalifa University in Abu Dhabi, UAE. Both parties reached a preliminary agreement on collaborative teaching and research in the fields of artificial intelligence, big data, and the intersection between medicine and engineering.

Meeting at Khalifa University

The ZUSM delegation renewed the Third Round of Student Exchange Agreement with Mahidol University Faculty of Medicine, Siriraj Hospital

On March 5 and 6, a delegation from ZUSM visited the Mahidol University Faculty of Medicine, Ramathibodi Hospital, and the Faculty of Medicine, Siriraj Hospital (SIRIRAJ), in Thailand. The Deans of these two Medical Schools, Artit Ungkanont and Apichart Asavamongkolkul, respectively, along with their teams who are responsible for international exchange, teaching, and research, welcomed the delegation. Discussions were held to further the cooperation regarding medical education and clinical medicine between the two institutions.

The ZUSM signed a student exchange agreement with the SIRIRAJ

Craftsman's Heart, Clearing Myriads of Dust with Perseverance

Professor XU Yinghan (left) guiding graduate students to conduct experiments

XU Yinghan, born on June 2, 1926, in Xiaoshan, Zhejiang Province, is a professor at Zhejiang University School of Medicine (ZUSM) and a renowned pathologist and forensic scientist. He enrolled in the six-year medical program at ZUSM in 1946. From 1953, he worked in the Pathology Department of the former Zhejiang Medical University until formally retiring in 1998. After 2000, he returned to the Pathology Department of ZUSM to participate in forensic pathology work. In March 2004, the Forensic Science Center of Zhejiang University was established, where he has since served as a senior appraiser and consultant to this day. He has also served as a member of the National Committee of the Chinese People's Political Consultative Conference. In 1987, he was awarded the honorary title of "Zhejiang Province Model Worker" and has received numerous awards for scientific and technological achievements at the provincial level.

Early Years of Study

In 1946, Xu entered the six-year undergraduate program at ZUSM, becoming one of the first students of the medical school, which was established after the Anti-Japanese War ended. Seventy-six years later, recalling his time at ZUSM, he reminisced about how the school had purchased some ordinary residential houses in Haier Lane and transformed them into a hospital, where the equipment was imported from the United States, and the doctors were top-notch. Medical students actively promoted the hospital to the citizens of Hangzhou, recognizing the significance of such publicity and eagerly embracing the task.

Reflecting on his years of study, Professor XU recalled seeing in his teacher BEI Shizhang the demeanor expected of an exemplary mentor. Bei was thoroughly prepared for his classes and never simply recited from textbooks. He could write with a piece of chalk in one hand, draw diagrams with the other, and explain the profound meanings of the knowledge orally. He had a thorough grasp of the course content and effortlessly addressed students' questions, managing the length of classes perfectly so that the bell rang as he completed his final sentence on the topic. Thus, Bei became a role model for Xu. When Xu himself became a medical teacher, he often stayed up late preparing his lessons, refusing to sleep until he felt satisfied. Eventually, he became a teacher who vividly explained the course content and adeptly managed the timing of his lectures, earning the admiration of many

students at that time.

Forensic Affinity

XU Yinghan was selected to study forensic science unexpectedly. At the time, most of his classmates chose specialties like internal medicine, surgery, pathology and anatomy, while Xu wished to pursue clinical medicine. When he was assigned to study forensic science, he hesitated. Later, Dean WANG Jiwu told him that it was a once-in-a-lifetime opportunity to receive guidance from Professor LIN Ji of the renowned National Central University Medical School. Encouraged by this, XU Yinghan journeyed to Nanjing to pursue his studies, marking the beginning of his enduring connection with the field of forensic science.

After graduating, XU Yinghan declined job offers in Beijing and chose instead to return to his alma mater, where he took on roles related to forensic science and pathology education. Previously, the school had not offered a forensic science curriculum, and it was only an elective course. However, during promotional presentations, Xu sparked the students' curiosity by describing practical case studies and vividly explaining the mysteries of forensic exploration. For example, he elucidated how boneless bodies became softened due to acid corrosion, allowing them to curl up, and how flies acted as informants, exposing a murder victim hidden under the kang (a traditional Northeastern Chinese bed, elevated on bricks). These examples of forensic unraveling deeply captivated the students' hearts. Therefore, what was originally an elective course in forensic science turned into a class in which the students competed to enroll and unanimously chose to take, and so was essentially no different from a compulsory course.

In the past, diagnosing patients on the wards relied entirely on the doctors' professionalism. The doctors themselves would take the patients' blood in order to test it, obtain the results, and analyze the condition. Therefore, everyone honed their skills. Xu said that he had no hobbies besides working and teaching; he devoted himself wholeheartedly to his career, working tirelessly from dawn to dusk, day after day. By the time he retired in 1998, he was already over seventy, yet he was rehired as a consultant at the Forensic Science Center to provide professional advice on autopsies and testing. Even now, he continues to offer guidance whenever the center encounters difficult cases.

Many of his classmates have now become scientists and even academicians of the Chinese Academy of Sciences. Although they are scattered across the country, they invented a method called "Chain Letters" to keep in touch. Chain Letters involve a classmate in one city receiving a letter, and then sending a letter to the next person in another city, thus enabling everyone to stay informed about each other's news. These letters have been circulating among these classmates for twenty years, representing their uninterrupted friendship.

Professor XU Yinghan expressed his desires about the future of ZUSM. He hopes that the school will thrive in terms of both education and research and can stand shoulder to shoulder with the top institutions globally. He also conveyed his wishes for the graduates, hoping that they would receive widespread recognition in society and make their own contributions to scientific research. Additionally, he urged students who aspire to become forensic professionals to adhere to the principles, remain objective in their assessments, and remain unmoved by personal feelings, power, or money. He emphasized the importance of constantly pursuing a legal, scientific, objective, and just stance as an appraiser.

Zhejiang University Special Merit Award for Outstanding Doctors and Nurses in 2023

Outstanding Doctors


WANG Jinhu


CHEN Jianghua


ZHOU Jianhong


HUANG Man


GONG Shijin


JIANG Chenyang


FU Baiping

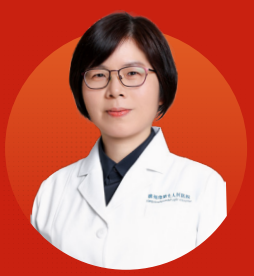

DAI Yiyang

Outstanding Nurses


WANG Lizhu


WANG Xiaoyan


XING Lanfeng


ZHU Xiaoying


ZHOU Yan


FEI Yijun


FU Cangcang


PAN Hongying

ZJUMEDICINE

浙江大学 医学院
SCHOOL OF MEDICINE
ZHEJIANG UNIVERSITY

ZJU MEDICINE
SHOWCASING THE BEST OF ZHEJIANG UNIVERSITY SCHOOL OF MEDICINE

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Benevolence and Humane Proficiency

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