A CENTURY OF INNOVATION

CELEBRATING 100 YEARS
OF NANJING UNIVERSITY'S SCHOOL OF LIFE SCIENCES

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A century of life sciences breakthroughs

Nanjing University's School of Life Sciences has a HISTORY OF CHALLENGING TRADITION.

TEN MILESTONES AT THE SCHOOL OF LIFE SCIENCES, NANJING UNIVERSITY

1921 Bing Zhi, a member of the Chinese Academy of Sciences, launches the country's first Department of Biology at Nanjing Higher Normal School.

1946 Zheng Ji launches the Institute of Biochemistry at the National Central University, China's first formal institute to offer postgraduate programmes in biochemistry.

1955 The Department of Biology relocates to the Xinan Building.

1965 Studies such as 'the comprehensive survey of the Inner Mongolia Grassland' and 'the introduction and utilization of common cordgrass' are produced.

1978 Zhong Chongxin is assigned by the State Scientific and Technological Commission to launch the Institute of Common Cordgrass and Beach Development and is appointed its founding director.

1992 The School of Life Sciences (SLiS) at Nanjing University is established.

1995 The State Key Laboratory of Pharmaceutical Biotechnology is formally approved and launched, with Zhu Dexu as its founding director.

2001 Nanjing University's Model Animal Research Center is launched.

2014 SLiS relocates to the SLiS Building on the Xianlin Campus.

2021 SLiS celebrates its 100th anniversary.

The motto at Nanjing University's School of Life Sciences (SLiS) is: don't follow the crowd.

Since its 1921 founding, SLiS has been working at the cutting-edge of life sciences research, publishing results that have revolutionized fields such as nucleic acid biology, biotechnology, and ecology.

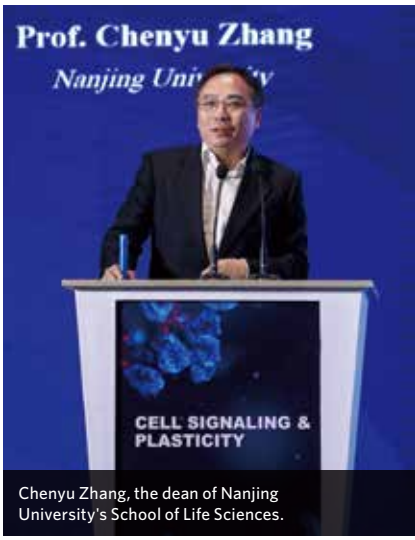
As SLiS celebrates its centenary this year, its dean, Chenyu Zhang, attributed its innovative spirit and willingness to break with tradition as key to its achievements over the past 100 years.

The school features five disciplines: biology, biochemistry, biotechnology and pharmacology, physiology, and ecology. Researchers at the SLiS have made a range of significant findings including the discovery of stable extracellular miRNAs, and identifying the dominant role of human activity in reducing biodiversity.

Since 2000, SLiS has been granted 226 patents, four of them internationally, and has led research projects on nucleic acid biology in collaboration with institutions such as Harvard University and the University of Cambridge.

This success is partly due to its collaborative and supportive research environment, according to Zhang. In 2006, he introduced a system that allowed senior scientists to work on their research interests in different labs, but all under the same direction. The system also created more opportunities for junior researchers to join the labs and develop their career pathways.

Zhang is also proud of the great achievements of SLiS undergraduate students. In the last five years, they have contributed to 226 papers, 188 of them Science Citation Index papers. In particular, 21 papers were first-authored or co-authored by undergraduate students.



Chenyu Zhang, the dean of Nanjing University's School of Life Sciences.

WE HOPE TO DEVELOP SUBJECTS SUCH AS AI BIOLOGY AND EVOLUTIONARY BIOMEDICINE

"Most students stay in the frontline of research after their graduation," said Zhang.

As SLiS celebrates its 100th anniversary, Zhang is setting ambitious goals for its future. "We hope to develop prosperous cross-disciplinary subjects such as AI biology and evolutionary biomedicine while continuing to explore our traditional research strengths," said Zhang. "We welcome international scholars and talents to join us." ■

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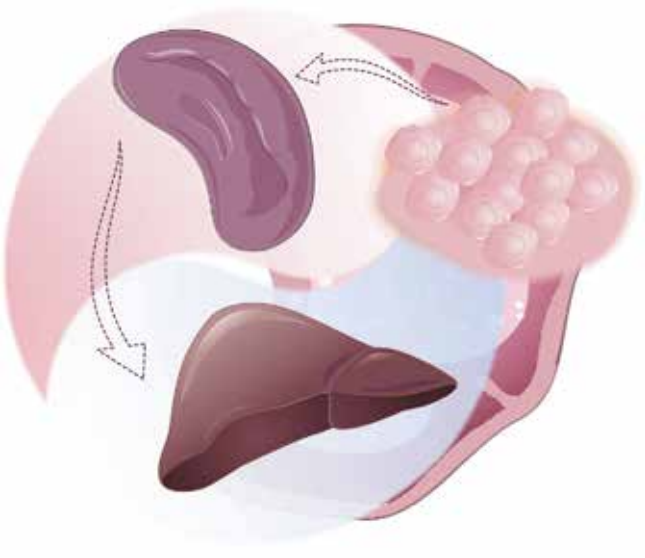
Leading a revolution in biochemistry

Scaling up the production of UROKINASE FOR CLINICAL USE.



School of Life Sciences, Nanjing University

By injecting a tumour extract into a mouse spleen, Lei Dong and colleagues were able to remodel the microenvironment such that liver cells were able to function in the spleen.

Today, the enzyme urokinase is mass-produced for treatment of thrombosis, atherosclerosis, and other cardiovascular diseases. This was made possible by the work of Dexu Zhu, and his ground-breaking research in 1996 on renaturing human pro-urokinase, expressed in *Escherichia coli*. But when Zhu, who is now regarded as one of China's pioneers in biochemistry and molecular biology, began his research, he encountered many challenges. Lei Dong, a biochemistry professor at Nanjing University, and Zhu's student, recalled that at that time, many biochemists tended to use mammalian cells and yeast cells for recombinant pro-urokinase expression, which could not satisfy mass production needs.

Rather than continuing to optimize these processes in yeast cells, Zhu turned to procaryotic organisms like *E. coli*. Because these bacteria lack the machinery required for the correct folding of human proteins, the recombinant human pro-urokinase was in a denatured state when expressed in *E. coli*.

Previously, the biochemist Christian Anfinsen, had succeeded in renaturing proteins in vitro, but applying the technique to large, cysteine-rich, and multi-domain proteins for mass production and clinical use was still difficult.

Based on Anfinsen's experiments, Zhu assessed factors that could affect an efficient renaturation of bacterially expressed human pro-urokinase. Based on the assessment, he developed a new technique that could increase its yield. The technique later became the foundation for the mass production of urokinase.

Thinking outside the box is a hallmark of SLiS's biochemistry pioneers, according to Dong. He has been inspired by Zhu's example to take an unconventional approach to his own research, and is now leading research on organ regeneration. In a paper published in *Science Advances* in 2020, the tissue structure of a mouse spleen was remodelled into an immunosuppressive microenvironment through the injection of tumor extract, followed by the implant of liver cells therein. Dong and his team demonstrated that these allograft or xenograft liver cells could still function in the mouse's spleen, and might ultimately provide an alternative to organ transplantation. ■

RESEARCH AT NJU LIFE SCIENCE'S DEPARTMENT OF BIOCHEMISTRY

- Junfeng Zhang and Lei Dong's team focuses on drug delivery systems and bioactive materials. Their research demonstrates the behaviour of drug delivery systems and bioactive materials, as well as their immunological effects and histopathological response mechanisms.
- Genxi Li's lab looks into biosensors and investigates new methods for protein qualification. The team proposes a nucleic acid-based method for protein quantification, and designs a new recognition system and assembling methods for molecules.
- Jin Wang's team develops a series of interdisciplinary bioinformatics methods, tools, and databases for promoters, binding sites of transcription factors, and microRNAs and the prediction of their action targets.
- Xiaoyun Ji and Xianchi Dong's team investigates the science of proteins, including developing protein and peptide drugs and introducing new technologies for their formulation and delivery.

An estuary water purification in Xiong'an New Area, Hebei Province, China.

Revisiting biodiversity and coexistence

Research from Nanjing University has prompted a rethink of how we consider MEGAFAUNA DIVERSITY, MUTATIONS, AND PLANT SPECIES COEXISTENCE.

Researchers from Nanjing University's Department of Ecology are working to unravel the mechanisms behind biodiversity, from demonstrating that human activities have had a greater impact on China's megafauna biodiversity than climate change, to casting doubt on the 'rare plant advantage' hypothesized to foster plant species coexistence.

Data collated by Shuqing Teng and Chi Xu suggests the importance of cultural filtering in shaping China's biodiversity over the past 2,000 years. The team analysed data gleaned from administrative and historical prefectural records about the presence of megafauna, such as Asiatic elephants, rhinoceroses, tigers, Asiatic black bears, and brown bears. They found that human activities, including the spread of farming, agricultural intensification, and the expansion of the Han culture, were key contributors to the extensive range contractions of the megafauna taxa, and that climate change had little or no direct impact on the contractions over the period.

"Biodiversity is the key to evolution, though it is generally thought of as just a consequence of mutation and natural selection," says Sihai Yang. Focusing on spontaneous mutations at the genomic level, a team led by Dacheng Tian and Yang used parent-progeny sequencing of Arabidopsis, rice, and the honey bee to prove that mutation rates were higher in heterozygotes and in close proximity to crossover events. "We demonstrated that genomic diversity and heterozygosity can promote mutation rate, and thus evolution, through a positive-feedback loop," says Yang.

Shu Cun Sun and his colleagues are interested in species coexistence in local communities.

The 'rare-species advantage' hypothesis provides a stabilizing mechanism for species coexistence based on antagonistic interactions like herbivore and pathogen damage disproportionally affecting common species. "But this hypothesis overlooks the fact that the fitness of plants species is determined collectively by both antagonistic and mutualistic interactions," explains Sun.

Sun's team studied networks of 24 plant species in an alpine meadow on the eastern Tibetan plateau, including their seed predators and pollinators, representative of antagonistic and mutualistic interactions. They found that common plant species interacted with more pollinator species compared to rare plant species, which led to higher seed set rates, even when factoring in their greater losses due to consumption by animals."This demonstrates that both mutualistic and antagonistic interactions should be considered to understand species coexistence and suggests that species interactions are not necessarily the key mechanisms underlying the survival of rare species in plant communities," says Sun. ■

OTHER PROJECTS AT NJU LIFE SCIENCES DEPARTMENT OF ECOLOGY

- Shuqing An's team investigates coastal wetlands and inland wetland restoration in China using nature-based solutions and intelligent monitoring.
- Jianlong Li's team disentangles the effects of climate change and human activity on carbon sequestration and storage in global grassland.
- Dacheng Tian and Sihai Yang's team mainly studies the molecular ecology mechanisms of mutation and maintenance of biodiversity.
- Xingjun Tian's team aims to elucidate the role of soil animals and microbes in leaf litter decomposition and nutrient cycling.
- The Lab of Animal Behaviour and Conservation, led by Zhongqiu Li, explores the behavioural ecology and conservation biology of endangered endemic species in China.

Boosting nutrition through plants

Plant biology research could change approaches to CROP IMPROVEMENTS AND THERAPEUTICS.

Plant biology has been at the heart of Nanjing University's Department of Biology since its beginning in 1914. Its scientists have achieved significant results in plant classification, algae research, plant ecology, plant cell physiology and biochemistry, and plant molecular structure and function. The department's current focus is on plant evolution and development, molecular mechanisms, and adaptive growth.

Of particular interest are the interactions between plants and diverse microorganisms and the role they play in adaptive evolution.

A team led by Jian-Qun Chen, has studied the origins of plant disease resistance genes, and shown that the adaptive evolution of these genes is driven by pathogenic microorganisms at the molecular level. The researchers are now focused on exploring the role of pathogenic and symbiotic microbes in plant adaptive evolution.

Another team, led by Bin Wang, is working to understand arbuscular mycorrhiza, a symbiosis between plants and members of an ancient phylum of fungi, and how it could improve crop growth and yield.

Researchers led by Dijun Chen develop and apply statistical machine learning approaches to investigate basic molecular principles and complex gene regulation in diverse plants, providing new potential targets and strategies for crop improvement and breeding.

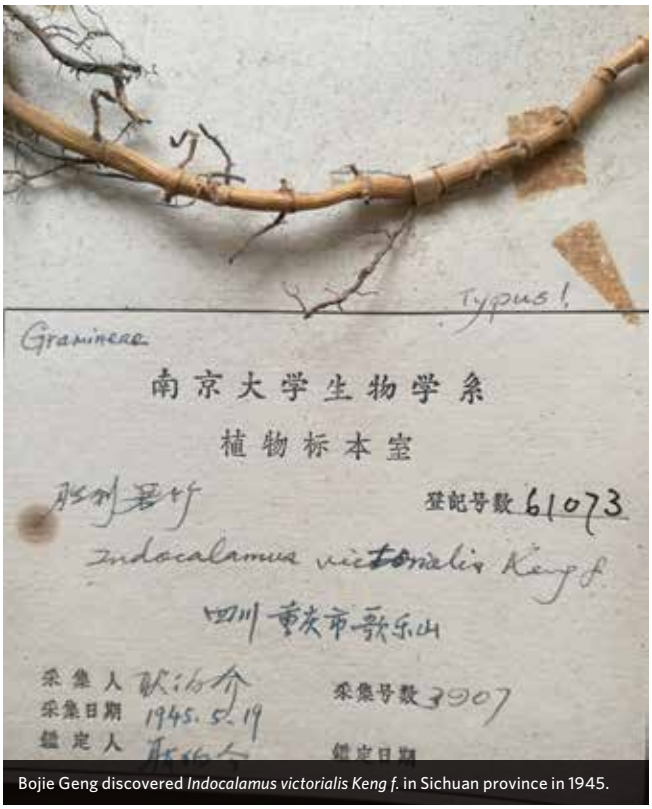
The link between plants and medicine is central to traditional Chinese medicine. The team led by Yonghua Yang, has been studying shikonins derived from the roots of traditional Chinese medicinal plants from the *Boraginaceae* family for at least 30 years, focusing on biosynthesis, genetic regulation, structural modification and pharmaceutical function. They searched for potential anti-tumour, anti-inflammatory, and antibacterial effects of shikonins mainly by inhibiting NF-κB/STAT3 and other signalling pathways.

Plastids, organelles that are the main sites of photosynthesis and other essential metabolic processes in plants, are another area of active research for the department. The lab of Shan Lu uses rice and *Arabidopsis thaliana* as model plants to uncover the molecular mechanisms that coordinate the metabolic and developmental scenarios during plastid biogenesis. The lab works to apply their knowledge to improve the nutritional value of crops.

Considerable breakthroughs have been achieved in plant growth and development, specifically in the areas of plant organ development, protein modification and nutrient allocation.

A team led by Zhi Hong examines the biological functions of protein glycosylation in plants. They found that protein-carrying N-glycan chains (a chain of sugar molecules connected to a nitrogen atom) play multiple roles during protein folding and secretion, and regulate plant resistance to external stress by controlling the abundance of functional proteins that influence the development of organs such as root systems and stomata.

Bo Sun's team considered the regulation of plant floral stem cells and revealed the termination mechanism of floral stem cells, which ensures the flower's reproductive organs, such as the carpel, are properly differentiated, and that seeds for the next generation may be set. A better understanding of this stem cell termination process during flower development could ultimately help increase fruit yield and size.



Bojie Geng discovered *Indocalamus victorialis Keng f.* in Sichuan province in 1945.

Wenzhi Lan's team looks at membrane transport processes during plant adaptation, with a focus on molecular identification and functional characterization of plant transport proteins. They identified transporter proteins that supply nutrients for plant growth and development, including the vacuolar phosphate transporter VPTs and the chloroplast manganese transporter CMT1.

This is just a selection of the research being conducted by NJU's Department of Biology. Now one of China's 7 key national biology programmes, the department comprises 19 faculty members, including 7 professors, 9 associate professors, and 3 full-time research and postdoctoral fellows. The department will continue to build on its long history and is keen to both further develop its existing research strengths and to invite new talents to join. ■

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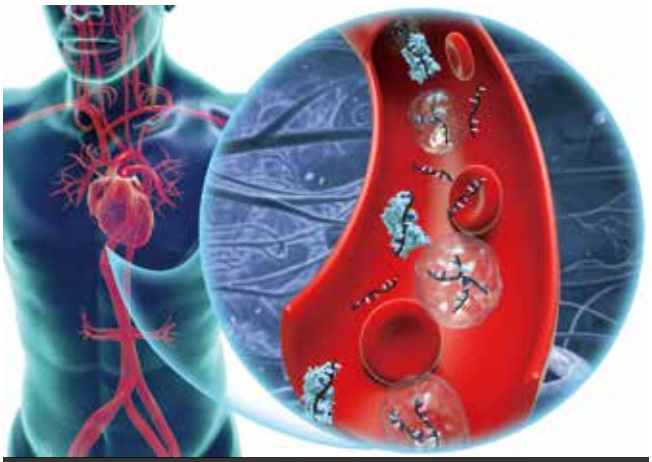
Deep miRNA discovery that challenges tradition

Research led by Nanjing University's School of Life Sciences opened new avenues FOR PHYSIOLOGICAL ASSESSMENT AND DISEASE DIAGNOSIS.



microRNAs circulate in the blood in a stable, cell-free form.

As a graduate student at Nanjing University, Xi Chen was familiar with the theory that RNA could not exist outside cells due to its instability. Therefore, when he joined a project led by Chen-Yu Zhang at SLiS's Jiangsu Diabetes Centre that was attempting to challenge that theory, he doubted the venture would succeed.

However, Zhang's team made the ground-breaking discovery in 2008 that a large amount of stable and reproducible micro RNAs (miRNAs) does exist outside cells. The researchers identified these miRNAs, derived from various tissues or organs, in the serum and plasma of humans and other animals, such as mice and horses.

They also found that these miRNAs can serve as non-invasive biomarkers for the diagnosis of many diseases, including cancer, diabetes, and immune diseases. "Based on these discoveries, we further studied their formation, biological functions, and potential applications in pharmacology and biotechnology," says Chen, who is now a professor at SLiS.

The discovery of these extracellular mRNAs opened up the potential of using non-invasive biomarkers for cancer classification, prognosis estimation, therapeutic efficacy, post-surgery surveillance, and the invention of new medications for cancer, viral infection, and neurological disorders. So far, the research has been cited in 16 physiology textbooks around the world.

"Since the research programme was launched, we, along with other researchers, have found that this form of extracellular RNA can exert a wide range of physiological functions, from maintaining metabolic homeostasis in individuals, transmitting stress susceptibility between generations, to even regulating development and differentiation across different kingdoms," says Chen.

"Research like this in our department has revealed a series of very important signalling molecules that can regulate and maintain the physiological state in which life is best adapted to a certain environment or a specific spatiotemporal condition," said Chao Yan, head of the Department of Physiology.

Chen says it is the strong research expertise and supportive environment at SLiS's physiology department that encouraged the researchers to challenge the traditions with such a rigorous scientific approach.

"As SLiS celebrates its 100th anniversary this year, I hope when our students talk about our physiology discipline, they are very proud of the groundbreaking research led by our school," Chen says. ■

NJU LIFE SCIENCE'S DEPARTMENT OF PHYSIOLOGY

- Jian-Jun Wang and Jing-Ning Zhu's team investigates motor neurobiology, with a focus on the functional neuronal circuitry between the hypothalamus and the somatic motor system and the mechanisms underlying somatic-nonsomatic integration.
- Jian Jing's team considers neuroscientific theories by researching the neural circuits of sea slugs, studying the neural basis of behaviour using animal model systems, and examining the neural circuits underlying motivated behaviours and neuromodulation.
- Chao Yan's lab focuses on the pathology and pharmacology of KRAS-driven cancers, especially pancreatic cancers and non-small-cell lung cancers.
- Jiayu Chen's lab focuses on developing cutting-edge genomics and bioinformatics approaches to understand the RNA-DNA/RNA/protein interactions, RNA modifications, as well as their evolution.
- The Institute of Artificial Intelligence Biomedicine, founded by Chen-Yu Zhang and Chao Yan, uses artificial intelligence to explore integrative physiology and precision medicine, as well as to develop new drugs.

Using nature as inspiration

Increasing understanding of INNATE IMMUNITY MECHANISMS and THE BIOSYNTHESIS OF NATURAL PRODUCTS could lead to new treatment pathways.

Researchers at the Department of Biotechnology and Pharmaceutical Sciences at Nanjing University's School of Life Sciences have looked to nature as inspiration to develop new synthesis approaches and potentially improve the design of combined immunotherapy.

A team led by Renxiang Tan and Huiming Ge showed that enzyme-catalyzed pericyclic [6+4] cycloadditions, a class of reactions in organic synthesis first proposed in 1965, are present during biosynthesis.

Their identification of a group of enzymes that catalyze these cycloadditions can be traced back to their discovery of Streptoseomycin published in *Organic Letters* in 2018. Streptoseomycin is an antibiotic derived from *Streptomyces seoulensis* A01, a marine microbe.

In a recent paper published in *Nature,* the team then demonstrated that a group of enzymes called [6+4]/[4+2] bispericyclases, could catalyze pericyclic [6+4] cycloadditions - a crucial step in the biosynthesis of Streptoseomycin, as well as [4+2] cycloadditions, also called Diels–Alder reactions.

Another group at SLiS, led by Qiang Xu and Yang Sun, dissects the molecular mechanisms of cancer and inflammatory diseases.

The NLRP3 inflammasome, is an innate immune system receptor that is extensively studied due to its activation by infection, tissue damage and metabolic stress. Using a mouse model, Xu and Sun's team demonstrated that the protein, tyrosine phosphatase SHP2, negatively regulated NLRP3 inflammasome activation via ANT1-dependent mitochondrial homeostasis. This finding will help scientists better understand how the body controls dysregulation of inflammation.

The team is also interested in increasing the efficiency of checkpoint-blocking therapy in treating cancer. In another study, they demonstrated that the antitumour effect of cytotoxic T lymphocytes requires the presence of CXCR6, a chemokine receptor. "This finding will contribute to the rational design of combined immunotherapy," says Sun.

Both Ge and Sun attribute SLiS's cross-disciplinary research tradition as a key component of their teams' successes.

"Besides the efforts from our lab, we were also supported by a structural biologist and a physiologist from the school," explains Ge. "SLiS provides a wonderful cross integration platform," adds Sun. ■

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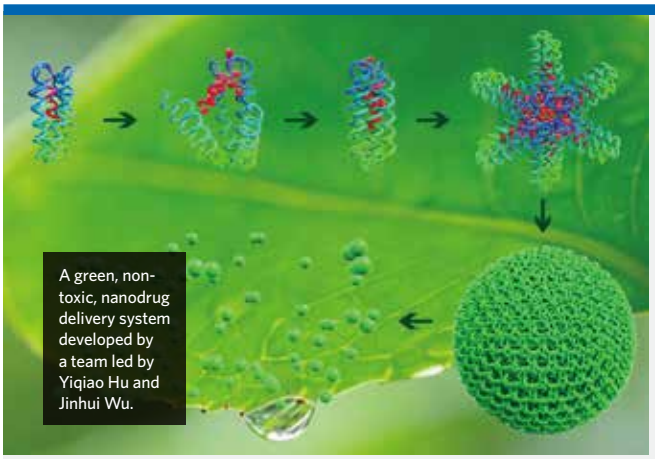

A green, non-toxic, nanodrug delivery system developed by a team led by Yiqiao Hu and Jinhui Wu.

RESEARCH AT NJU LIFE SCIENCE'S DEPARTMENT OF BIOTECHNOLOGY AND PHARMACEUTICAL SCIENCES

- Renxiang Tan and Huiming Ge's team focuses on discovering new drugs from nature as well as analysing the complex structures and features of natural products.
- Qiang Xu and Yang Sun's group is focused on inflammation-related diseases, specifically, their pathological mechanisms and pharmacological intervention.
- Lingdong Kong and Dongmei Zhang's team explores the pathological mechanisms of metabolic and psychiatric diseases while experimenting with the use of traditional Chinese medicines.
- Yiqiao Hu and Jinhui Wu's group is developing efficient and economical nanodrugs.
- Zichun Hua is focused on the development and transformation of biological drugs, and exploring the relationship between protein structure and function.
- Hailiang Zhu conducts methodological research on drug synthesis.
- Jiangning Chen explores the molecular mechanism of inflammation-related diseases and tumours, drug delivery systems, and gene/cell therapy of major diseases.
- Wu Yin explores the new biological functions of Na-K-ATPase.

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