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WONDERS OF SCIENCE

CAS HIGHLIGHTS IN 2023



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Lead Article

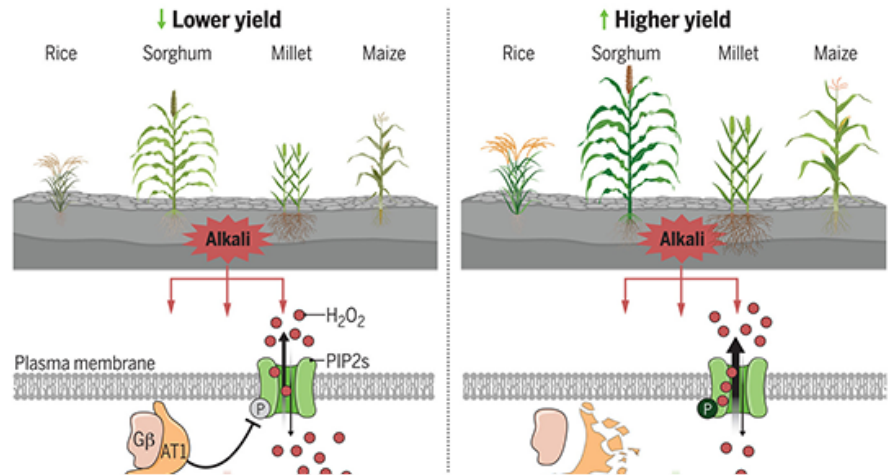


CHINA'S SCIENTIFIC ACHIEVEMENTS IN 2023

Chinese scientists achieved a lot of breakthroughs in various fields in 2023, such as quantum computing, astronomical observation, and brain-computer interfacing. Let's review some of the highlights obtained by Chinese Academy of Sciences (CAS) researchers over the year.

1. New gene discovery points way to better alkaline tolerance in crops

Scientists identified a key gene involved in crop alkaline tolerance that may improve crop yield in sodic environments. In addition to illustrating an ecologically important molecular mechanism, this study has great potential for guiding the planting











Lead Article



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CHINA LAUNCHES NEW SATELLITE FOR VIOLENT COSMIC PHENOMENA OBSERVATION

China on January 9, 2024 sent a new astronomical satellite into space to observe mysterious transient phenomena in the universe which flicker like fireworks, trying to reveal more about this violent and little-known side of the cosmos.



A Long March-2C carrier rocket carrying a new astronomical satellite named Einstein Probe (EP) blasts off from the Xichang Satellite Launch Center in Southwest China's Sichuan Province, January 9, 2024. [IMAGE: ZHANG JING/XINHUA]



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Sichuan Province.

Weighing about 1.45 tonnes and as large as a full-size SUV, the satellite is








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**OBSERVE THE
MYSTERIOUS
UNIVERSE
UNVEIL THE
UNKNOWN
WORLD**



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Hot Issue

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Giants once roamed the karst plains of southern China, three-meter tall apes weighing in at 250 kilograms. These very distant human ancestors — *Gigantopithecus blacki* — went extinct before humans arrived in the region, with few clues to why and leaving around 2,000 fossilized teeth and four jawbones as the only signs of their existence.

New evidence from this region published in *Nature*, uncovered by a team of Chinese, Australian and US researchers, demonstrates beyond doubt that the largest primate to walk the earth went extinct between 295,000 and 215,000 years ago, unable to adapt its food preferences and behaviors and vulnerable to the changing climates that sealed its fate.

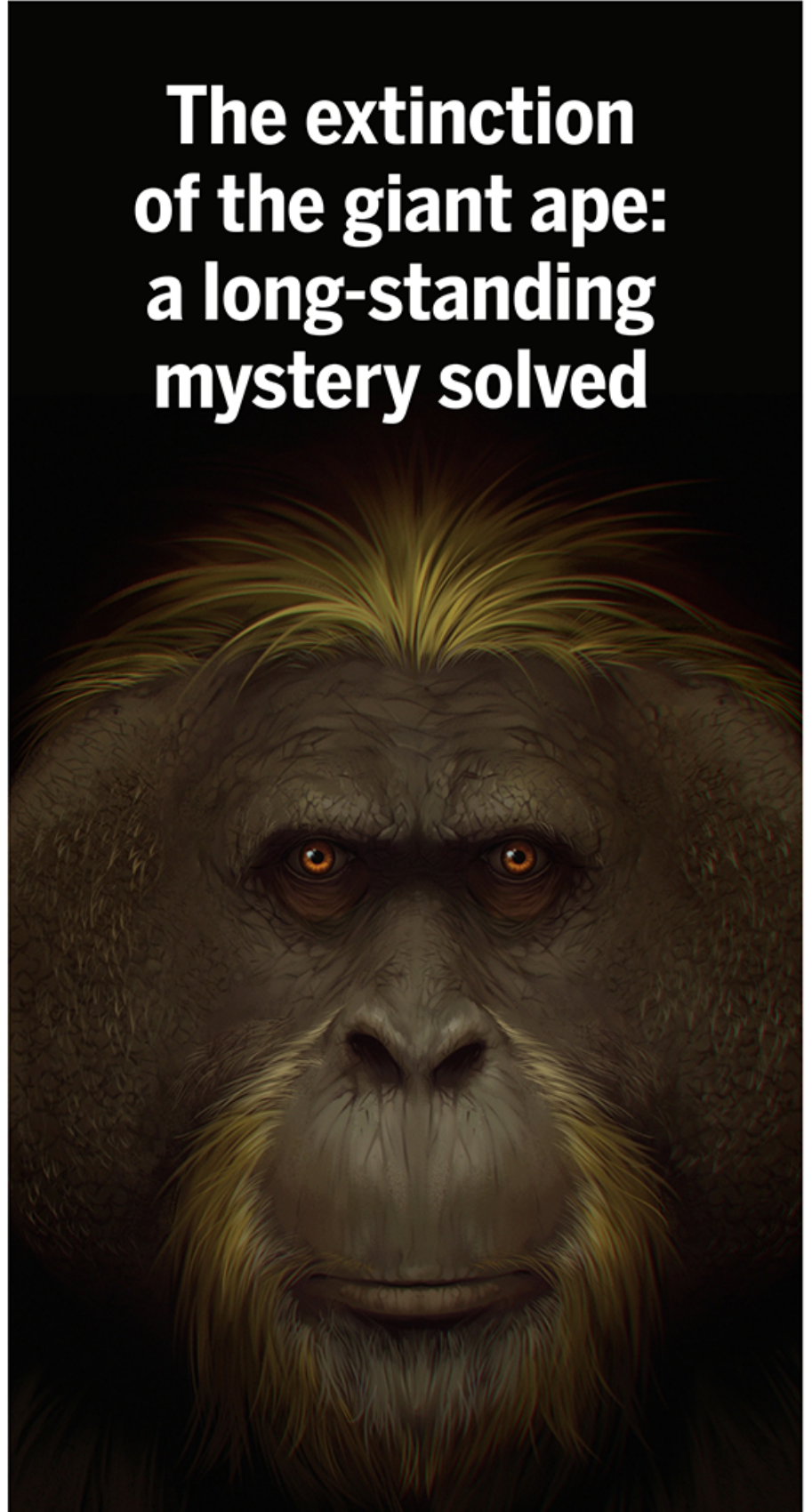
“The story of *G. blacki* is an enigma in palaeontology — how could such a mighty creature go extinct at a time when other primates were adapting and surviving? The unresolved cause of its disappearance has become the Holy Grail in this discipline,” said palaeontologist and co-lead author Professor Zhang Yingqi from the Institute of Vertebrate Palaeontology and Palaeoanthropology (IVPP) of the Chinese Academy of Sciences (CAS).

“The IVPP has been excavating for *G. blacki* evidence in this region for over 10 years but without solid dating and a consistent environmental analysis, the cause of its extinction had eluded us.”

Definitive evidence revealing the story of the giant ape’s extinction has come from a large-scale project collecting evidence from 22 cave sites spread across a wide region of Guangxi Zhuang Autonomous Region in southern China. The foundation of this study was the dating.

“It’s a major feat to present a defined cause for the extinction of a species, but establishing the exact time when a species disappears from the fossil record gives us a target timeframe for an environmental reconstruction and behavior assessment,” said co-lead author, Macquarie University geochronologist Associate Professor Kira Westaway.

The extinction of the giant ape: a long-standing mystery solved



An artist's impression of the giant ape from southern China. SOURCE: CAS/IVPP/JOHANNES BOVILL



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An artist impression of a group of *G. blacki* within a forest in southern China [IMAGE: GARCIA/JOANNES-BOYAU]

“Without robust dating, you are simply looking for clues in the wrong places.”

Six Australian universities contributed to the project. Macquarie University, Southern Cross University, Wollongong University and the University of Queensland used multiple techniques to date samples. Southern Cross also mapped *G. blacki* teeth to extract information on the apes' behaviors. ANU and Flinders University studied the pollen and fossil bearing sediments in the cave respectively, to reconstruct the environments in which *G. blacki* thrived and then disappeared.

Six different dating techniques were applied to the cave sediments and fossils, producing 157 radiometric ages. These were combined with eight sources of environmental and behavioral evidence, and applied to 11 caves containing evidence of *G. blacki*, and also to 11 caves of a similar age range where no *G. blacki* evidence was found.

Luminescence dating, which measures a light-sensitive signal found in the burial sediments that encased the *G. blacki* fossils, was the primary technique, supported by uranium series (US) and electron-spin resonance (US-ESR) dating of the *G.*

blacki teeth themselves.

“By direct-dating the fossil remains, we confirmed their age aligns with the luminescence sequence in the sediments where they were found, giving us a comprehensive and reliable chronology for the extinction of *G. blacki*,” said Southern Cross University geochronologist Associate Professor Renaud Joannes-Boyau.

Using detailed pollen analysis, fauna reconstructions, stable isotope analysis of the teeth and a detailed analysis of the cave sediments at a micro level, the team established the environmental conditions leading up to when *G. blacki* went extinct. Then, using trace element and dental microwear textural analysis (DMTA) of the apes' teeth, the team modelled *G. blacki*'s behavior while it was flourishing, compared to during the species' demise.

“Teeth provide a staggering insight into the behavior of the species indicating stress, diversity of food sources, and repeated behaviors,” said Associate Professor Joannes-Boyau.

The findings show *G. blacki* went extinct between 295,000 and 215,000 years ago, much earlier than previously assumed. Before this time, *G. blacki* flourished in a rich and diverse forest.

By 700,000 to 600,000 years ago, the

environment became more variable due to the increase in the strength of the seasons, causing a change in the structure of the forest communities.

Orangutans (*genus Pongo*) — a close relative of *G. blacki* — adapted their size, behavior and habitat preferences as conditions changed. In comparison, *G. blacki* relied on a less nutritious back up food source when its preferences were unavailable, decreasing the diversity of its food. The ape became less mobile, had a reduced geographic range for foraging, and faced chronic stress and dwindling numbers.

“*G. blacki* was the ultimate specialist, compared to the more agile adapters like orangutans, and this ultimately led to its demise,” said Professor Zhang.

“With the threat of a sixth mass extinction event looming over us, there is an urgent need to understand why species go extinct. Exploring the reasons for past unresolved extinctions gives us a good starting point to understand primate resilience and the fate of other large animals, in the past and future,” said Associate Professor Westaway.

Source: Institute of Vertebrate Palaeontology and Palaeoanthropology, Chinese Academy of Sciences

Hot Issue



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Homo sapiens dispersed from deteriorating environments in Southeast Africa to more optimal environments in Asia [IMAGE: AO HONG]

Orbitally-induced strong monsoons facilitated early human dispersal to east Asia

In a study published in *PNAS*, researchers have shown that orbitally induced strengthening of the Asian summer monsoon played a key role in the dispersal of *Homo sapiens* from Africa to East Asia during the last interglacial period 125,000 to 70,000 years ago.

Led by Professor Ao Hong from the Institute of Earth Environment of the Chinese Academy of Sciences (CAS), the researchers integrated a comprehensive compilation of paleoanthropological site data with new high-resolution reconstructions of the Asian

summer monsoon based on Chinese loess data, continuous modeling of the East Asian hydroclimate, and a novel human habitat simulation — all covering the past 280,000 years.

How human ancestors responded to past climate change remains a key question in research on human evolution. Climate variability was a key driver of human evolution and dispersal within Africa during the Pleistocene. However, our understanding of the orbital hydroclimatic influence on the early dispersal of our species, *Homo sapiens*,

from Africa to East Asia, is hampered by the lack of integrated paleoclimatic and paleoanthropological studies from Asia.

To reconstruct orbitally resolved Asian summer monsoon variability over the past 280,000 years, the researchers collected 2,066 samples in the field from the rapidly accumulating Huanxian loess-paleosol section on the central Chinese Loess Plateau for measurements in the laboratory.



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Field photograph of the Huanxian loess-paleosol sequence on the central Chinese Loess Plateau [IMAGE: AO HONG]

The resulting unprecedented centennial-resolution reconstructions suggest that the orbital-scale variability of the Asian summer monsoon responds to the combined action of changes in insolation (a so-called external forcing, i.e., one coming from outside Earth), and ice volume and greenhouse gas concentration (examples of what we call internal forcings, i.e., those coming from the Earth system), rather than to their individual actions. This argument is strongly supported by the Ao team's model-based reconstructions of the East Asian hydroclimate over the past 280,000 years.

“When we integrated proxy- and model-based spatiotemporal paleoclimatic reconstructions with paleoanthropological data compilations from

Asia across time and space, we found, to our surprise, that *H. sapiens* dispersed to East Asia at the same time as the Asian summer monsoon was intensified. This suggests an important influence of the paleo-monsoon on the early dispersal of *H. sapiens* from Africa to East Asia,” said Professor Ao, lead author of the study.

“In contrast to the strengthening of the Asian summer monsoon, the climate in much of southeast Africa worsened during the last interglacial. It is possible that these Asian and Southeast African hydroclimate changes acting together spurred the early dispersal of *H. sapiens* from Africa to East Asia,” said Dr. Thibaut Caley, an author of the study and a paleoclimatologist from the Université de Bordeaux, France. In contrast, the lush vegetation in East Asia at the time would have attracted

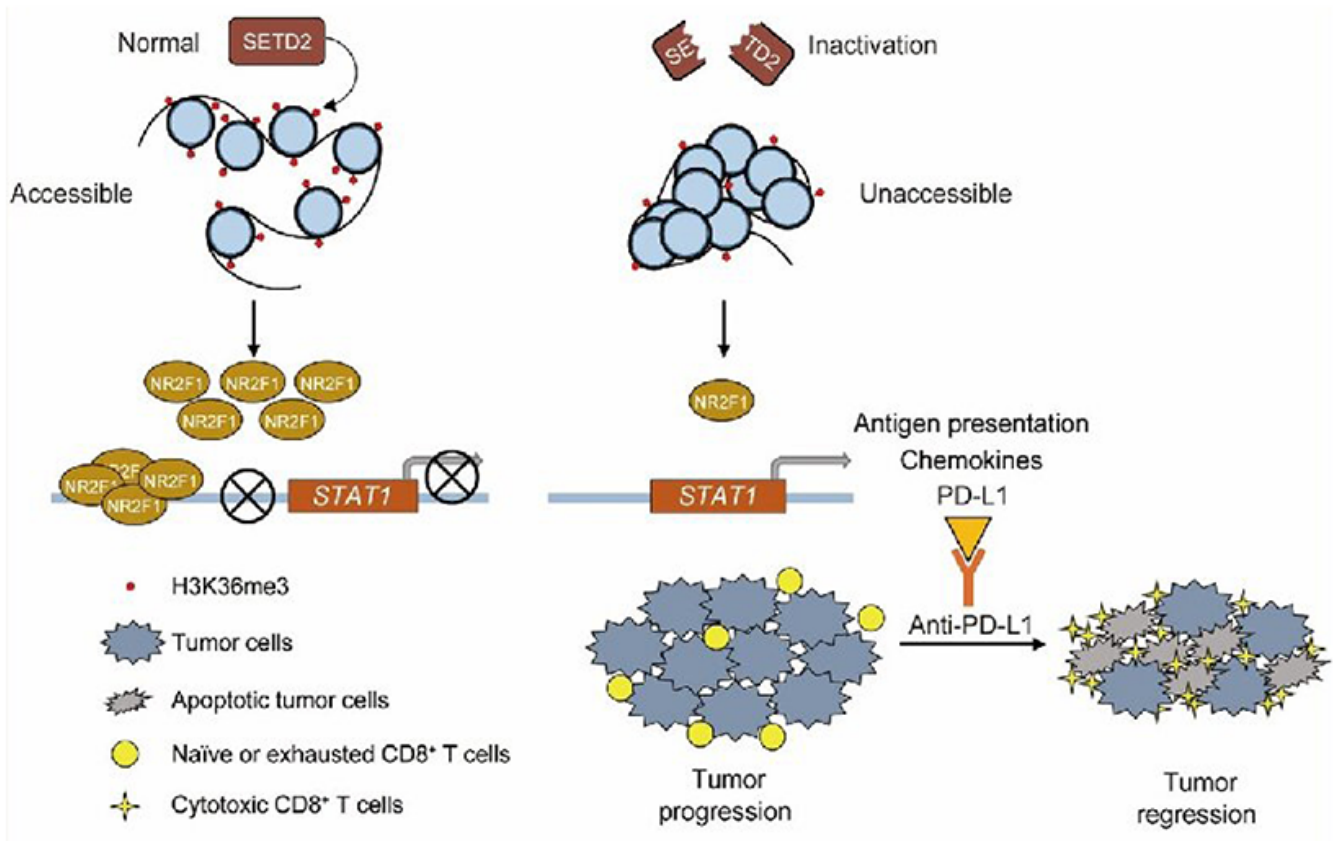
H. sapiens habitation.

To provide further quantitative evidence of climate effects on *H. sapiens* dispersal, Dr. Ruan Jiaoyang, corresponding author of the study and assistant researcher at the IBS Center for Climate Physics, South Korea, performed computer simulations of *H. sapiens* habitats and found that the *H. sapiens* occupation of East Asia was consistent with a transcontinental increase in simulated habitat suitability.

This study was funded by the Strategic Priority Research Program of CAS, the Second Tibetan Plateau Scientific Expedition and Research Program, and the National Natural Science Foundation of China.

Source: Institute of Earth Environment,
Chinese Academy of Sciences

Research Progress



Novel biomarker for immune checkpoint inhibitors in human lethal cancers discovered

A research article describing a novel biomarker for immune checkpoint inhibitors in human cancer, entitled “Tumor cell-intrinsic SETD2 inactivation sensitizes cancer cells to immune checkpoint blockade through the NR2F1-STAT1 pathway” was published online ahead of printing in the scientific journal *J Immunother Cancer* on December 6, 2023.

Immune checkpoint inhibitors (ICIs) mainly include antibodies that target programmed cell death protein-1 (PD-1), programmed cell death ligand 1

(PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). ICIs immunotherapies have revolutionized the treatment of patients with a wide range of advanced cancers, including malignant melanoma, renal cell carcinoma, non-small cell lung cancer, breast cancer, and gastric carcinoma. Although only a minority (approximately 20 percent) of cancer patients benefit from ICIs immunotherapy, it is of vital significance to identify those who are more likely to benefit from ICIs.

SETD2 is the sole histone methyltransferase responsible for the tri-

methylation of histone H3 at lysine 36 (H3K36me3) and plays a critical role through H3K36me3. Genomic mutations of SETD2 are prevalent in ~5% of human cancers and promote tumor progression and metastasis, including clear cell renal cell carcinoma, pancreatic cancer, colorectal cancer, prostate cancer and breast cancer. However, no small molecules or antibodies that specifically target SETD2-deficient tumors and show therapeutic potential have been developed.



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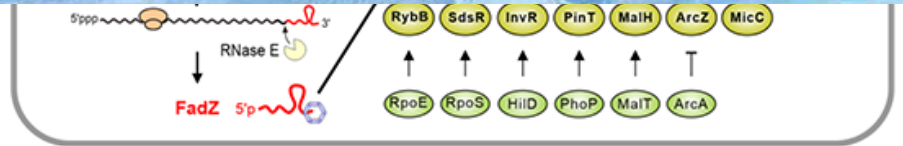


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nology for analyzing the RNA-RNA interactions in microorganisms, and also proposes a new way to study RNA-RNA interactions in eukaryotic cells.

The researchers further mapped for the first time the dynamic RNA-RNA interactomes of bacterial pathogen *Salmonella enterica* at multiple growth stages, identified more than 2,000 RNA-RNA interactions, and discovered many key mRNA regulatory hubs. The largest mRNA regulatory hub in bacteria to date was shown to be the mRNA encoding the outer membrane porin OmpD, which is regulated by at least 12 different non-coding small RNAs.

Experimental characterization of these small RNAs led to the identification of a novel small RNA FadZ that is cleaved from an mRNA 3'UTR by ribo-



iRIL-seq identifies the mRNA encoding outer-membrane major porin OmpD as the largest mRNA hub in *Salmonella*. The *ompD* mRNA is regulated by 12 different small noncoding RNAs, including a novel 3'UTR-derived sRNA FadZ. [IMAGE: SIII]

nuclease. The expression of FadZ and its parental *fadBA* mRNA is regulated by the upstream transcription factors FadR, CRP, and long-chain fatty acid signals. Under long-chain fatty acid conditions, both FadZ sRNA and its target gene *ompD* are activated by the transcription factor CRP, and together constitute a type I incoherent feed-forward loop (I1-FFL). The discovery reveals the post-transcriptional regulatory mechanism of bacteria in response to long-

chain fatty acid metabolism in hosts.

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Shanghai Institute of Immunity and Infection,

Chinese Academy of Sciences

Source: *Shanghai Institute of Immunity and Infection, Chinese Academy of Sciences*

Research Progress

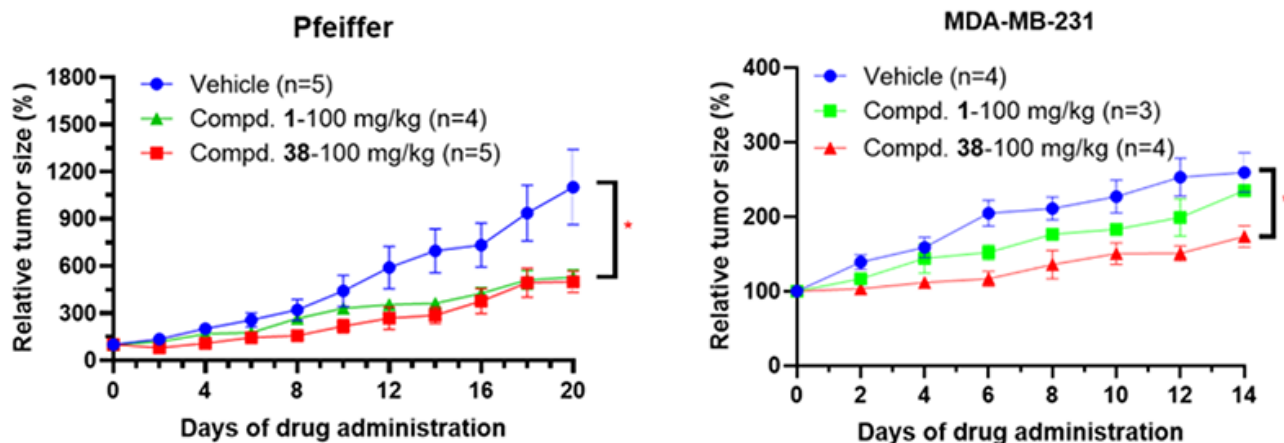


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Anti-tumor efficacy evaluation of IHMT-EZH2-426 (Compd. 38) in xenograft mouse models [IMAGE: ZHOU BIN]

Novel covalent EZH2 degrader discovered

Recently, a research team led by Professor Liu Qingsong from the Hefei Institutes of Physical Science (HFIPS) of the Chinese Academy of Sciences discovered a novel covalent EZH2 degrader, IHMT-EZH2-426.

Their findings, published in *European Journal of Medicinal Chemistry*, hold promise for combating triple-negative breast cancer (TNBC) and other types of cancer.

EZH2 is a protein that is often over-expressed in various cancers, including TNBC, and its high levels are associated with poor prognosis. However, solely inhibiting the enzymatic activity of EZH2 without decreasing its expression has proven insufficient in curbing the growth of breast cancer cells. The EZH2 degrader, inhibiting the enzymatic activities of EZH2 as well as degrading

EZH2, is a novel strategy for the treatment of TNBC.

In this study, the researchers discovered a novel EZH2 down regulator IHMT-EZH2-426 using the covalent drug design and medicinal chemistry approaches based on EPZ6438. This degrader forms a covalent bond with the residue Cys663 of EZH2.

In laboratory experiments, it displayed strong activities against both EZH2 WT and EZH2 mutants, potentially reducing the levels of EZH2 and H3K27me3 in B cell lymphoma and TNBC cell lines. Moreover, IHMT-EZH2-426 successfully inhibited the proliferation of these cancer cells.

To validate the mechanism of action, the researchers conducted washout and competitive experiments, along with mass spectrometry analysis, which confirmed the formation of a covalent

bond between IHMT-EZH2-426 and EZH2. In vivo, IHMT-EZH2-426 exhibited better efficacy than EPZ-6438 in MDA-MB-231 cell-mediated xenograft mouse models. Meanwhile, it displayed effective tumor suppression activity in Pfeiffer cell-mediated xenograft mouse models.

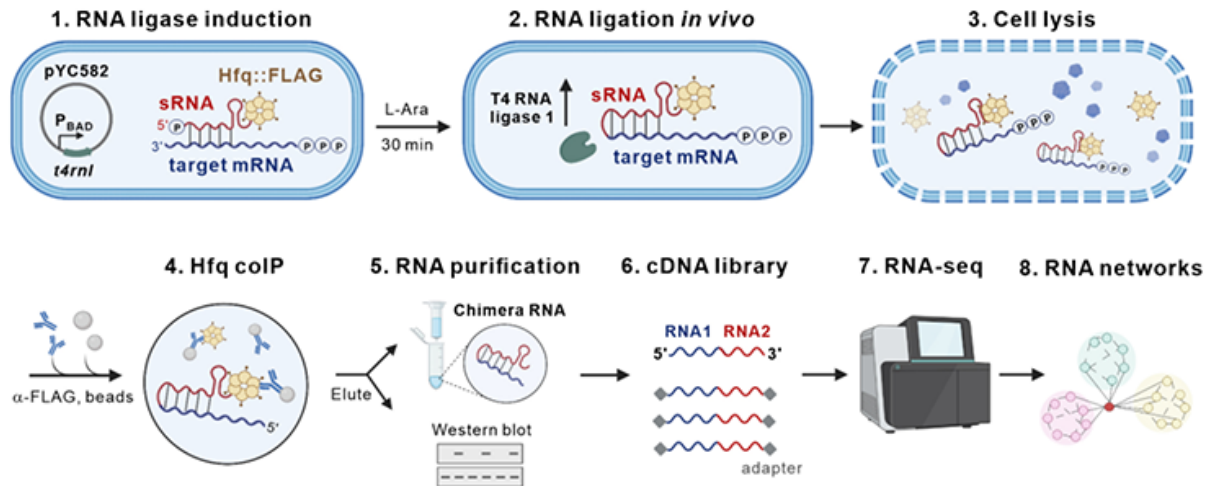
These results demonstrate that the covalent EZH2 inhibitor can offer a new opportunity for the development of promising new-generation drug candidates.

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Source: *Hefei Institutes of Physical Science,
Chinese Academy of Sciences*



Research Progress



Experimental workflow of iRIL-seq, a novel RNA-RNA interactome profiling technology for live microbial cells [IMAGE: SIII]

New technique iRIL-seq to analyze RNA-RNA interactions in live microbial cells developed

In a study published in the journal *Nature Communications* on December 7, 2023, entitled “In vivo RNA interactome profiling reveals 3’UTR-processed small RNA targeting a central regulatory hub”, Professor Chao Yanjie’s group at the Shanghai Institute of Immunity and Infection (SIII) of the Chinese Academy of Sciences reported a novel RNA interactome profiling technology (iRIL-seq), which identifies RNA-RNA molecular interactions in live microbial cells. Using iRIL-seq, the researchers for the first time mapped the RNA-RNA interactome networks of *Salmonella enterica* at different growth stages, and discovered many novel non-coding RNAs and important mRNA regulatory hubs.

Direct RNA-RNA interaction is a main mechanism by which noncoding RNAs exert their functions. In prokaryotic cells, non-coding small RNAs

recognize target mRNAs through very short and imperfect basepairing interactions, which are difficult to predict and identify using conventional methods. Bacterial non-coding RNAs have important regulatory functions, such as controlling the expression of many target genes at the post-transcriptional level, and playing crucial regulatory roles in many biological processes, including bacterial infection, antibiotic resistance, central metabolism, stress response, quorum sensing, and biofilm formation. The analysis of the RNA-RNA interaction network is of great significance in the study of microbial physiology and the functions of non-coding RNAs.

However, the existing RNA-RNA interactome profiling techniques are complicated, and require fixed cells and numerous in vitro steps such as RNA digestion, repair and ligation, and may yield insufficient RNA interactions with

low resolution and accuracy.

In this study, the researchers developed a novel in vivo RNA proximity-ligation approach, namely iRIL-seq (intracellular RNA interaction by ligation and sequencing). In this technology, the researchers induced the expression of T4 RNA ligase in living microbial cells, which leads to the proximity-ligation between interacting RNA molecules in vivo; then enriched the non-coding small RNAs and their interacting transcripts by immunoprecipitation of the major small RNA chaperone Hfq; and finally determined the identity and sequence of the interacting RNA molecules using high-throughput RNA sequencing. The main experimental process can be completed within a single day, thanks to rapid ligation in vivo and streamlined workflow.



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cer patients. By analyzing patient prognosis and omics datasets, 127 genes showed correlations with beneficial effects of immunotherapy. The top genes included known predictive biomarkers for ICIs therapy, including TP53, PAK7, TET1, PTPRD/PTPRT and STK1. SETD2 ranked among the top three hits of the 127 genes. Patients with inactivating mutations in SETD2 had more favor-

an integrated multiomics analysis using ATAC-seq, ChIP-seq and RNA-seq, the research team demonstrated that SETD2 inactivation reduces NR2F1 transcription by impairing H3K36me3 deposition and chromatin accessibility, which activates the STAT1 signaling pathway to promote chemokines and PD-L1 expression and enhance antigen presentation.

These findings provide novel insights

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Shanghai Institute of Nutrition and Health,

Chinese Academy of Sciences

*Source: Shanghai Institute
of Nutrition and Health,
Chinese Academy of Sciences*



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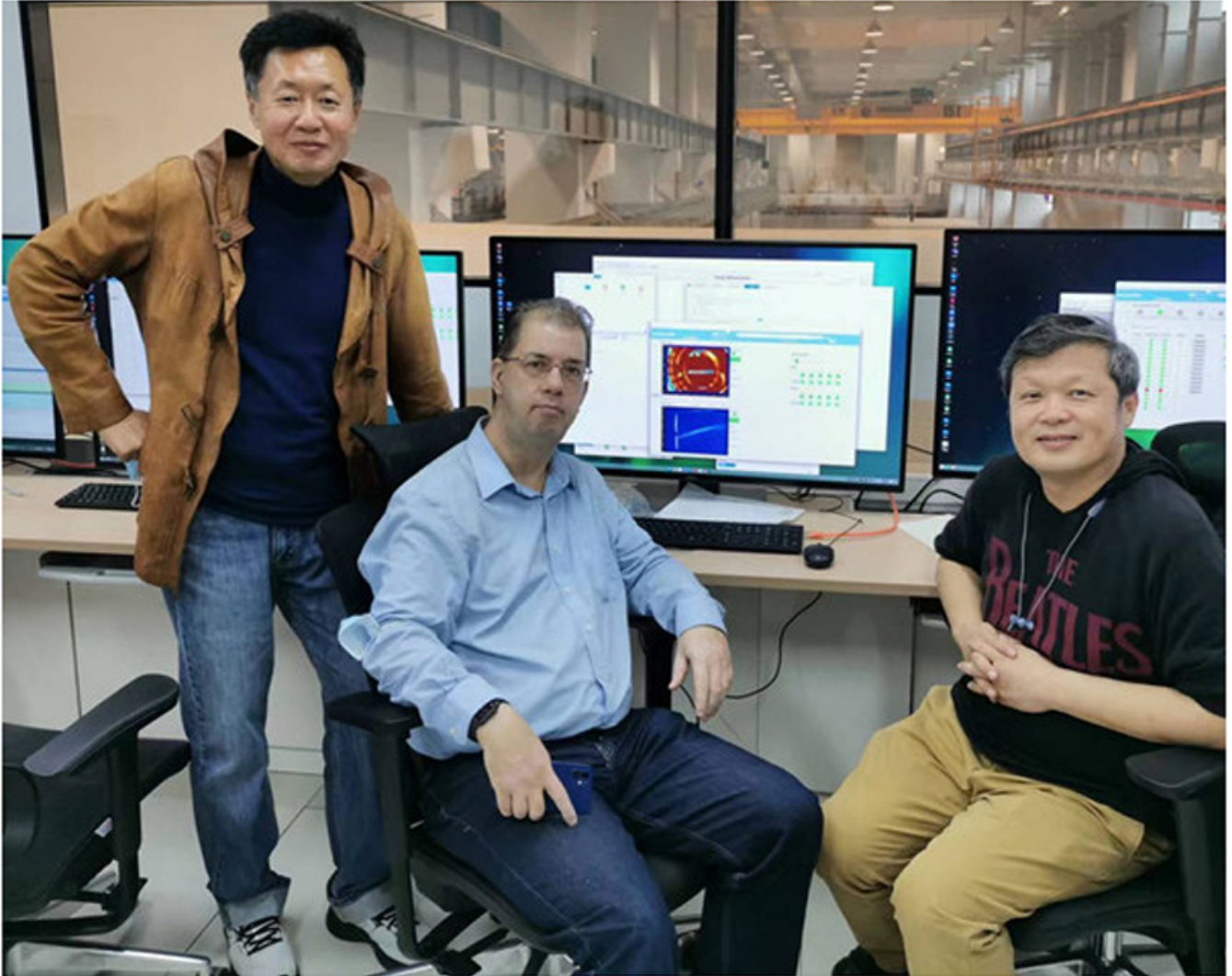


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International Cooperation

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Combining a relaxed private life with a competitive working environment in Shanghai

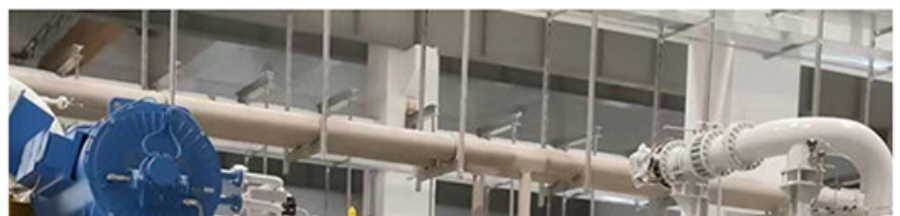
My interest in China and Chinese culture dates back almost 40 years, when I tried to learn more about this fascinating country. Back then, the language had already proved too difficult for me, but

my passion and interest in the culture has endured.

I have collaborated with scientists of the Shanghai Institute of Applied Physics (SIAP) of the Chinese Academy of Sciences (CAS) for over 10 years. While

I was employed in Germany, several of them visited my old institute as guest scientists or as employees, where they already left a very positive impression on

me. During my frequent visits to Shanghai, the speed at which scientists here could produce new results has always been extraordinary. When I had the op-





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more incredibly grateful that CAS made it possible for me to work in such a great environment at SARI.

Being involved in the SXFEL and the SHINE project, I have been impressed by how much progress both were able to make. Maybe the best way to characterize work here is the flexible and dynamic way in which people handle the scientific and technical challenges. Scientifically, the work is of a high standard. Experts here can compete internationally without issue. You have to get used to a different way of working, one with less planning, which allows for faster progress than I am used to. Because of the speed with which progress is made, it is difficult to keep track. My task to propose changes to procedures and designs either now or in future upgrades was therefore a challenging and ever changing one. I nevertheless hoped to contribute to the success of both machines.

Now that my contract has ended, I will continue to collaborate with my colleagues here in the future. I am sure that I will continue to visit Shanghai and further discuss the SHINE project and the SXFEL facility. It will be interesting to follow how these machines evolve over time to become world-leading and a driving force for scientific advancement across many disciplines.

Interesting enough, my private life



here in Shanghai did not change much compared to my time in Germany or Italy. Even without speaking Chinese at all, in most cases, I could manage, and enough people here speak English to make communication possible. In the exceptional cases that I could not manage alone, there was always somebody around who was willing to help me with practical issues. Shanghai is a very modern and open city with everything available that I am used to in Europe. Once you get used to modern tools (telephone apps like WeChat and AliPay), most things work perfectly. Public transportation is frequent, modern and easy to

use. You can find almost everything if you know your way around (which took me some time, I have to admit), even the most unlikely (Dutch) food, which was difficult to find in Italy and Germany. And with a wide variety of great Chinese food in restaurants within walking distance, who cares anyway? I will really miss the combination of a relaxed private life with a competitive working environment that I have been able to enjoy here for the past three years.

*Source: Bart Faatz,
Shanghai Advanced Research Institute,
Chinese Academy of Sciences*

News in Brief



A skeleton fossil of the world's only *Sinosaurus dongi* is displayed at Baoding Natural History Museum, or the Paleozoological Museum of China, in North China's Hebei Province, January 3, 2024. [IMAGE: CHINA NEWS SERVICE/SUN ZIFA]

World-class natural history museum under construction in North China city

A world-class natural history museum is under construction in Baoding, North China's Hebei Province, expected to bring thousands of paleontological fossil specimens on exhibit.

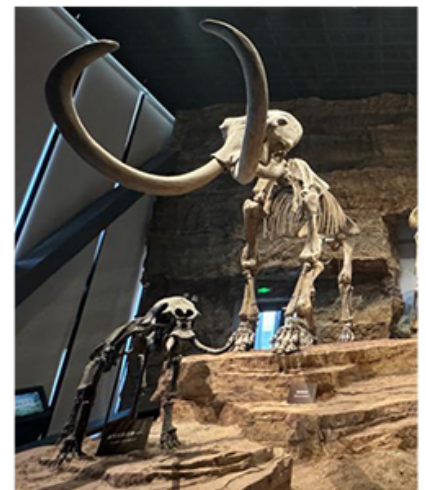
The museum project is jointly carried out by the Baoding Municipal Government and the Institute of Vertebrate Paleontology and Paleoanthropology of the Chinese Academy of Sciences (CAS).

With paleontological fossils as the theme, the museum with a total investment of 1.7 billion yuan (about 273.5 million U.S. dollars) is designed to have floor space of about 73,100 square meters with six halls for fixed exhibitions and two rooms for temporary exhibitions.

The new Baoding museum will provide more exhibition space to the institute's 400,000 paleontological fossil specimens in stock.



A Megalodon giant shark tooth fossil is displayed at Baoding Natural History Museum, or the Paleozoological Museum of China, in North China's Hebei Province, January 3, 2024.



Skeleton fossils of mammoth are displayed at Baoding Natural History Museum, or the Paleozoological Museum of China, in North China's Hebei Province, January 3, 2024.

