CAS Achievements in Lens of 2011 "Top 10" Scientific Advances of China

By SONG Jianlan (Staff Reporter)

As a routine since 2005, at the end of the year 2011, leading scientists in China including Members of the CAS and the Chinese Academy of Engineering, voted to elect the top 10 scientific advances of China in their mind. Remarkably six projects led and completed by CAS scientists ranked into the top 10; and the very top one also received contributions from CAS as a cooperator.

Naturally the accurate docking of the unmanned spaceship *Shenzhou* 8 and the space lab *Tiangong* 1 tops the list. Their kissing in orbit over the territories of China caught the eye of the world and won a lot of acclaims. Organized and mainly accomplished by the China Aerospace, Science and Industry Corporation, this grand project also had support from CAS scientists. It is well anticipated that the summer sky of 2012 will embrace another unmanned docking of the *Shenzhou* 9, *Shenzhou* 8's younger sister, and the *Tiangong* 1.

Coming second is the successful modeling of loop-top X-ray source and reconnection of outflows in solar flares with intense lasers (highlighted in P130), accomplished by a joint team consisting of scientists from Shanghai Jiao Tong University, the National Astronomical Observatories, CAS and the Institute of Physics, CAS.

Ranked third on the list is the successful induction of functional hepatocyte-like cells from mouse fibroblasts, a study led by Prof. HUI Lijian at the Institute of Biochemistry and Cell Biology (IBCB), the Shanghai Institutes for Biological Sciences, CAS. (For details please see Page 133.) Remarkably IBCB also contributed the seventh of the top 10 projects, in which Prof. XU Guoliang's group successfully revealed the role of Tet (ten-eleven translocation) family of dioxygenases in epigenetic regulation of mammalian animals. (For details please see Page 134.)

The fourth and the fifth places of the top 10 are won by scientists with the Huazhong University of Science and Technology and Tsinghua University, respectively. The former succeeded in high-resolution visualization of the mouse brain with aid of micro-optical sectioning tomography, and the latter made a smart design of silicon-based magnetic resistance devices with enhanced sensitivities to both high and low magnetic fields.

Another institute under CAS, the Institute of Metal Research (IMR) based in Shenyang City, northeastern China also dwarfed other institutions in the election, with two feats elected respectively as the sixth and the eighth. CAS Member Prof. LU Ke's group at IMR won the sixth for successfully revealing the mechanism underlying the extraordinary intrinsic tensile plasticity in gradient nano-grained copper. Demonstrating marvelous strength and plasticity, this new type of materials might herald a new solution for the dilemma between strength and plasticity in metal materials.

Prof. CHENG Huiming's group at the same institute successfully grew three-dimensional interconnected graphene networks in lab with high flexibility and conductivity via chemical vapor deposition. Their invention, with extremely low density and high ratio of surface area, demonstrates excellent electric, thermal and chemical performance, thus are expected to greatly expand the potential of grapheme.

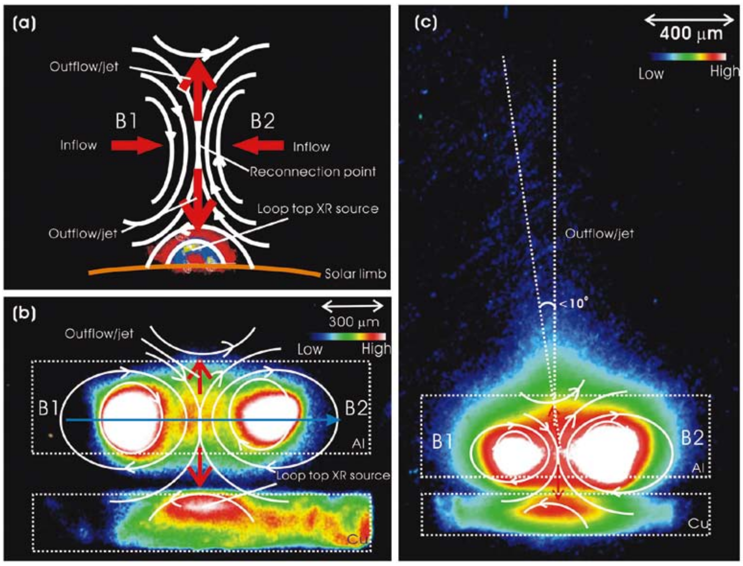
The discovery of glacial-interglacial Indian summer monsoon dynamics (see P131) by scientists led by CAS Member Prof. AN Zhisheng at the CAS Institute of Earth Environment was voted as the ninth, and an achievement by Perking University, the realization of high-efficiency PV multiplier effect in carbon nanotubes, the tenth in the top 10 list.

BCAS Vol.26 No.2 2012

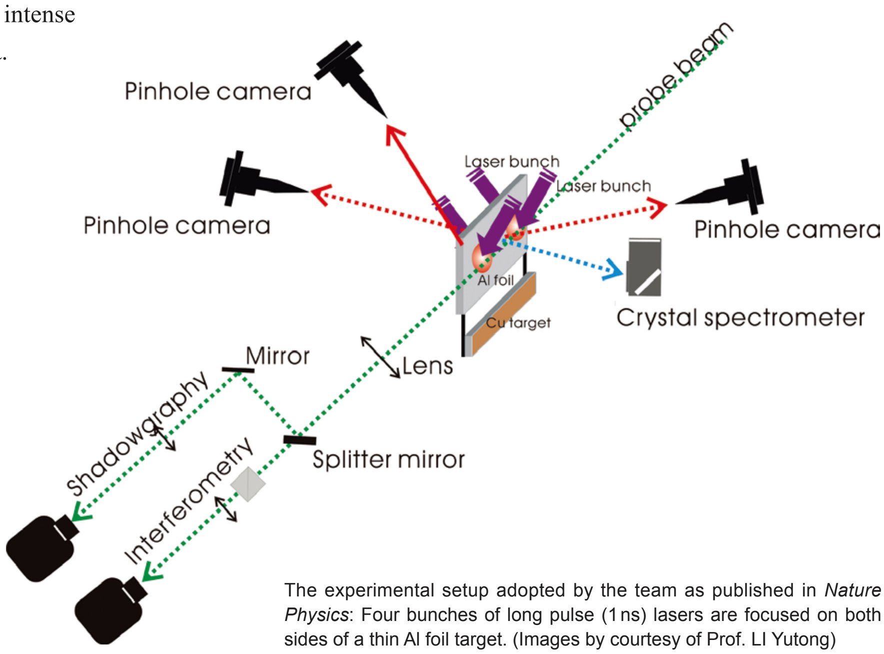
Modelling loop-top X-ray source and reconnection outflows in solar flares with intense lasers

Magnetic reconnection (MR) refers to the breaking and reconnecting of oppositely directed magnetic field lines in a plasma, and it is a process of energy conversion in plasma physics. The model of MR is widely applied in astrophysics including investigations on solar flares, star formation, the coupling of solar wind with earth's magnetosphere, accretion disks, and Gamma-ray bursts.

Scientists from CAS Member Prof. ZHANG Jie's group with Shanghai Jiao Tong University, Prof. ZHAO Gang's group with the National Astronomical Observatories, CAS and Prof. LI Yutong's group with the Institute of Physics, CAS succeeded in reproducing a magnetic reconnection topology similar to what occurs in solar flares, using the mega-gauss-scale magnetic field generated by highly intense laser beams interacting with a plasma.



Magnetic reconnection model simulated by the groups for the loop-top X-ray source in a compact solar flare.



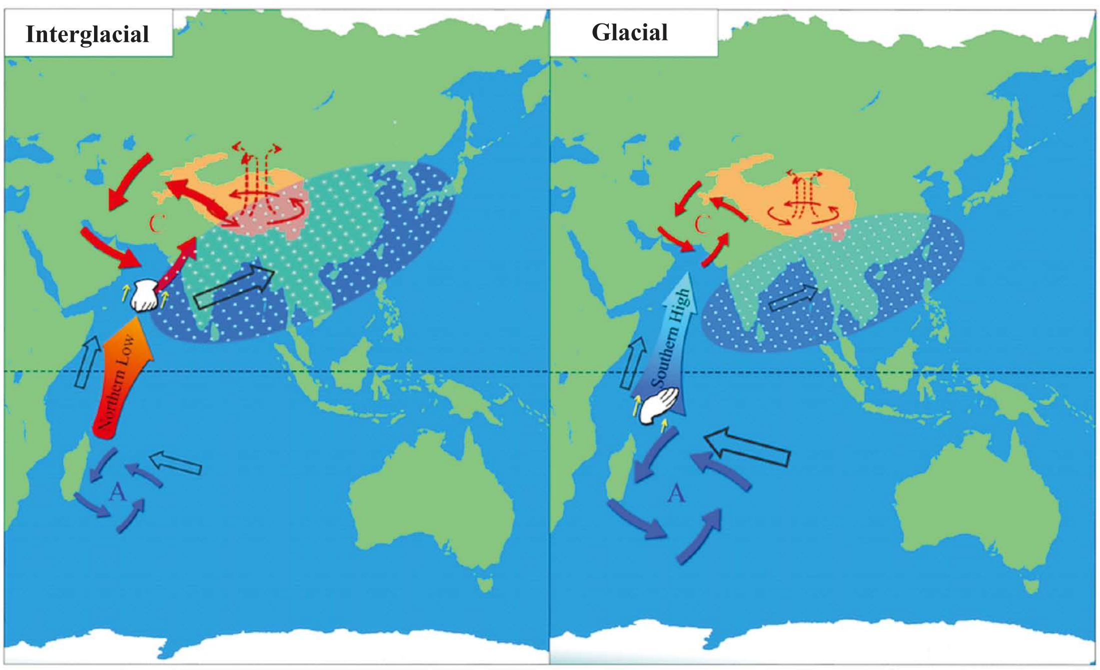
The experimental setup adopted by the team as published in *Nature Physics*: Four bunches of long pulse (1 ns) lasers are focused on both sides of a thin Al foil target. (Images by courtesy of Prof. LI Yutong)

Discovery of Indian summer monsoon dynamics at the glacial-interglacial timescale

Based on a multi-disciplinary analysis of a 666-m long lacustrine sediment core drilled from the Heqing Basin on the southeastern fringe of the Tibetan Plateau, CAS Member Prof. AN Zhisheng's group at the CAS Institute of Earth Environment successfully reconstructed the changing history of the Indian summer monsoon (ISM) during the Pleistocene (2.6 Ma) and demonstrated the importance of global ice volume and Antarctic temperature in driving ISM variability at the glacial-interglacial timescale.

Their study, which was published in the August 5, 2011 issue of *Science*, indicated the importance of interhemispheric forcing in driving ISM variability at the glacial-interglacial timescale as well. The team identified a stronger ISM variability during Middle Pleistocene in comparison with Early and Late Pleistocene, which is attributed to the dominated influence of northern hemisphere climate. The most important is that they found an early strengthening of the ISM prior to full glacial conditions, and they attributed this early strengthening to an increased cross-equatorial pressure gradient (XEPG) derived from southern hemisphere high-latitude cooling.

As stated in a commentary in the same issue of *Science*, the analysis of the limnological record from the Heqing Basin posed a challenge to the traditional dynamics theories about ISM. AN *et al.*'s study is welcome for having provided a solution to the dynamics of glacial-interglacial ISM, a long-standing puzzle among geophysicists, from a novel perspective. This new insight into ISM is also believed to be helpful for understanding the potential impacts of global warming on ISM variability and climatic conditions in the southwestern China under the background of global warming.



A schematic diagram illustrating the proposed dynamical mechanism driving Indian summer monsoon variability on glacial-interglacial time scales.
Left: During interglacials, decreasing NH ice volume intensifies the Indian low, while the Mascarene high is weakened by high Antarctic temperature and decreasing southern ice volume; the Northern low effect dominates the large XEPG, resulting in a strong ISM circulation.
Right: During glacials, low temperature and increasing ice volume in Antarctica intensify the Mascarene high, while the Indian low is weakened by increasing NH ice volume; the Southern high effect dominates the increased XEPG from the minimum of the ISM, resulting in early ISM intensification in the full glacial times. (Images by courtesy of Prof. AN Zhisheng)

CAS Strategic Priority Research Project on Stem Cell and Regenerative Medicine Research in Progress

Lots of diseases, like congenital defects, aging, chronic diseases, metabolic disorders, and severe infectious diseases are among the major challenges to human health and modern medicine. With a large population, China faces the most serious situation in the world in terms of occurrences of tissue/organ disfigurement, failure or dysfunction. Traditional medical approaches, which are based on medication and surgery treatments, are far from enough to fulfill the large demand in the clinical setting. On the frontiers of current life sciences, stem cell and regenerative medicine spark new hopes for curing such diseases, through providing new regenerative sources for repairing damaged or injured tissues and therapies for diseases in the terminal stage. Regenerative medicine, based on the regeneration and replacement therapy abilities of stem cells, marks a new round of medical revolution following traditional medicines and surgery treatments, and will become one of the most promising frontiers to produce new landmark breakthroughs of current biology.

China is a latecomer in research of stem cells and regenerative medicine. Increasing clinical needs and relatively inadequate scientific studies call for collaboration and concentration on stem cell research and regenerative medicine around the whole country. To build up domestic innovation forces and finally establish a platform of excellence for stem cell and regenerative medicine research, a strategic priority research project was launched by CAS to address major scientific issues and break through critical technical hurdles in related fields, including stem cell regulation, mechanisms for stem cell therapies, and clinical translation.

By revealing the fundamental mechanisms underlying stem cell origination, development and regeneration of organs, as well as developing new techniques to control stem cell behavior for repairing pathological damages, this project is to promote clinical applications of stem cell therapies. It aims to understand basic biological mechanisms including derivation, maintenance, differentiation and functioning of stem cells in both normal developmental and pathological processes of liver, nervous system and other important organs, integrating the establishment of stem cell resources, techniques of directed differentiation and acquirement of functional cells, generation of artificial organs, and strategies for stem cell applications. Led by Prof. ZHOU Qi with the CAS Institute of Zoology (IOZ), the team is striving to discover important mechanisms and methods of stem cell derivation and regulation, develop critical techniques to acquire functional cells, generate new drugs based on stem cells, and to establish a scientific, ethical and legal standard for future application of stem cells and regenerative medicine.

The project is based on the CAS network for stem cell and regenerative medicine research, which consists of four research centers respectively located in Beijing, Shanghai, Guangzhou and Kunming. Radiating from this network, the project also involves and integrates the main research forces from 17 CAS institutes majoring in life science, materials science, chemistry and biomechanics. Through optimized overall deployment of distributed R&D forces, the project aims to establish a systematic research network for this strategically important discipline, building a complete research value chain connecting different scientific phases from fundamental research to application and translation.

So far the team has made progress in fundamental studies, such as reprogramming of somatic cells, tissue repairing products and standardization of clinical applications of stem cells. Highlighted in this issue is two advances achieved by researchers based in Shanghai, both of which were elected into the top 10 scientific advances of China in 2011.

(Reported by SONG Jianlan based on materials from IOZ)

Successful induction of functional hepatocyte-like cells from mouse fibroblasts

Functional liver cells independent of donor organs, if available, would be of great therapeutic value for liver diseases. Such cells generated from the patient's own body cells would be an even better solution, as it will free the patient from suffering immunological rejection, which is a big challenge to fight following an organ transplant and has led to many failure cases.

Towards this end biologists around the world are pressing to break through hard-nut issues concerning induced pluripotent stem (iPS) cells. Though generated from somatic cells, iPS cells function in many ways as stem cells do, capable of regenerating and differentiating into different kinds of tissues, an ability formerly thought exclusive to stem cells. Such cells hence bear earnest expectation from experts as an easier-to-get substitute for real stem cells.

Previous efforts have succeeded in achieving hepatic differentiation using induced pluripotent stem cells. However, the technique is so complicated that scientists are endeavoring to find an alternative way out. Now a group of biologists led by Prof. HUI Lijian at the Institute of Biochemistry and Cell Biology, the Shanghai Institutes for Biological Sciences, CAS demonstrated in *Nature* [475(7356):386–89] a smart strategy to generate hepatocyte-like (iHep) cells directly from mouse tail-tip fibroblasts.

The resulted iHep cells resembled normal liver cells in terms of appearance and functions: they showed epithelial morphology, expressed hepatic genes and acquired hepatocyte functions. Notably, when transplanted into mice that were genetically engineered to simulate the human liver disease of tyrosine metabolism deficiency, the iHep cells repopulated the livers and restored liver functions, saving the lives of almost half of the recipients.

Their work is thought to have far-reaching implications to fundamental research on stem cells and applied studies in regenerative medicine. It is also anticipated to inspire further progress in liver engineering.

(Reported by SONG Jianlan)

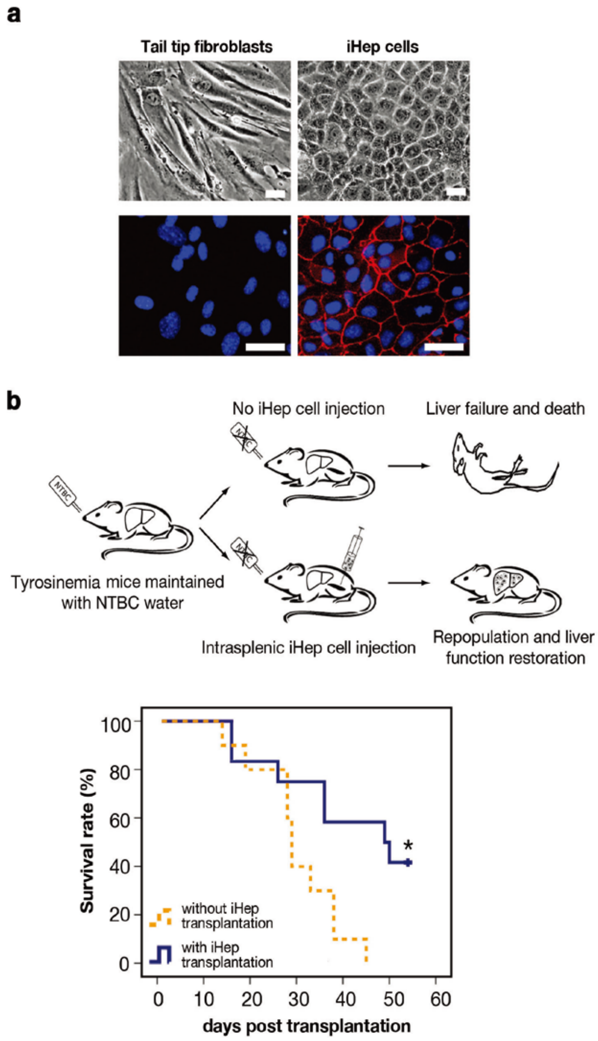


Figure 1. The generation of functional hepatocytes independent of donor liver organs is of great therapeutic interest with regard to regenerative medicine and possible cures for liver disease. By transduction of Gata4, Hnf1a and Foxa3, and inactivation of p19Arf, Prof. HUI's group demonstrated the direct induction of functional hepatocyte-like (iHep) cells from mouse tail-tip fibroblasts. iHep cells showed typical epithelial morphology, expressed hepatic genes and acquire hepatocyte functions. Notably, transplanted iHep cells repopulated the livers of fumarylacetoacetate-hydrolase-deficient mice and rescued almost half of recipient mice from death by restoring liver functions. This study provides a novel strategy to generate functional hepatocyte-like cells for the purpose of regenerative medicine as well as *in vitro* disease models. (*Nature* [475 (7356): 386–389])
(Picture story by Dr. LI Qing, picture by courtesy of Prof. HUI Lijian)

Role of Tet family dioxygenase in mammalian epigenetic regulation

The development and growth of organisms, as well as the occurrence of diseases are widely subject to epigenetic regulation. Active DNA demethylation occurring in the epigenetic reprogramming process plays an important role in the development of early embryos and the generation of germ cells, hence attracting keen attention from scientists. However, the biological significance and mechanisms of this epigenome remodelling have remained unclear.

Recent research revealed that the Tet (ten-eleven translocation) family of dioxygenases is responsible for the oxidation of 5-methylcytosine (5mC), changing 5mC into 5-hydroxymethylcytosine (5hmC). The Tet family dioxygenase has since been better characterized, and the involvement of 5hmC in epigenetic regulation of embryonic development and disease has started to be elucidated.

Lately a group of biologists led by Prof. XU Guoliang at the Institute of Biochemistry and Cell Biology under the Shanghai Institutes for Biological Sciences, CAS successfully revealed a molecular-level episode in

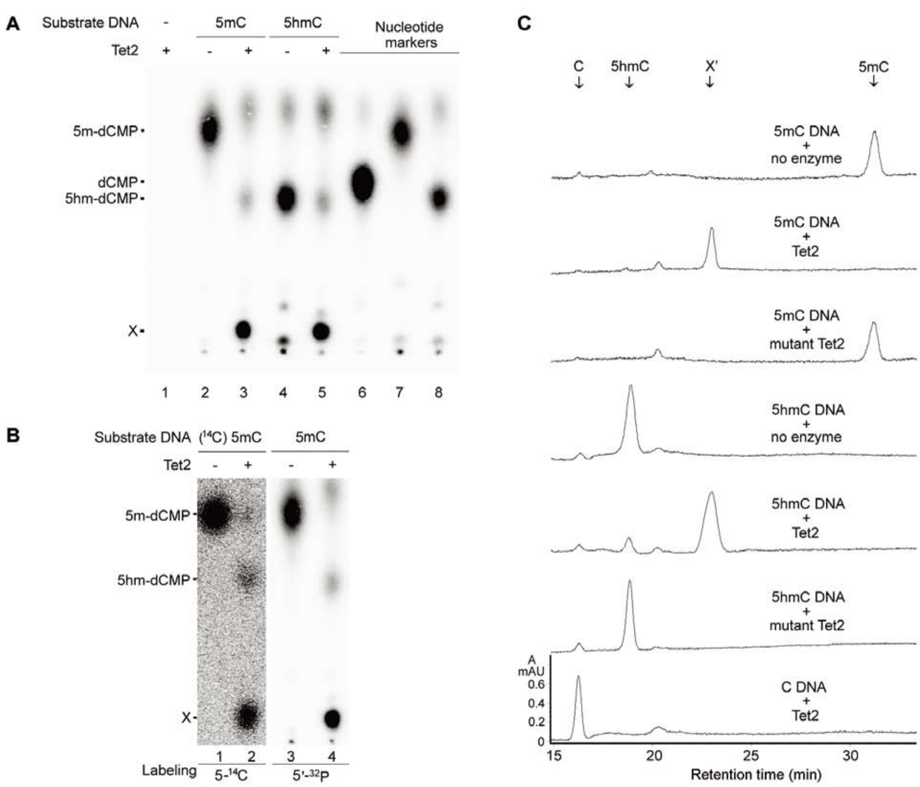


Figure 1: Prof. XU Guoliang's group provides direct evidence that 5mC (the 5th base) and 5hmC (the 6th base) in DNA are oxidized to 5-carboxylcytosine (5caC, the 7th base) by Tet dioxygenases. 5caC is specifically recognized and excised by thymine-DNA glycosylase (TDG). These data suggest that oxidation of 5mC by Tet proteins followed by TDG-mediated base excision of 5caC constitutes a pathway for active DNA demethylation. (*Science* [333 (6047): 1303–1307])

(Picture story by Dr. GUO Fan, Picture by courtesy of Prof. XU Guoliang) linking Tet-mediated oxidation of 5mC with active DNA demethylation.

In their experiments, the team demonstrated that Tet dioxygenases are able to oxidize 5mC and 5hmC in DNA to 5-carboxylcytosine (5caC) both *in vitro* and in cultured cells. Later on, the 5caC is specifically recognized and excised by thymine-DNA glycosylase (TDG), as depletion of the latter in mouse embryonic stem cells causes the 5caC to accumulate to a readily detectable level.

In a parallel study, they found that DNA oxidation mediated by a Tet family dioxygenase, the Tet3, plays an important role in DNA demethylation and gene activation in the paternal DNA of the male pronucleus following natural fertilization. Cooperating with Prof. LI Jinsong's group, they revealed that Tet3 may also contribute to somatic cell nuclear reprogramming during animal cloning.

Their studies shed light on a possible pathway for active DNA demethylation, in which 5mC is first oxidized by Tet proteins and the production 5caC is specifically recognized and excised by TDG.

(Reported by SONG Jianlan)

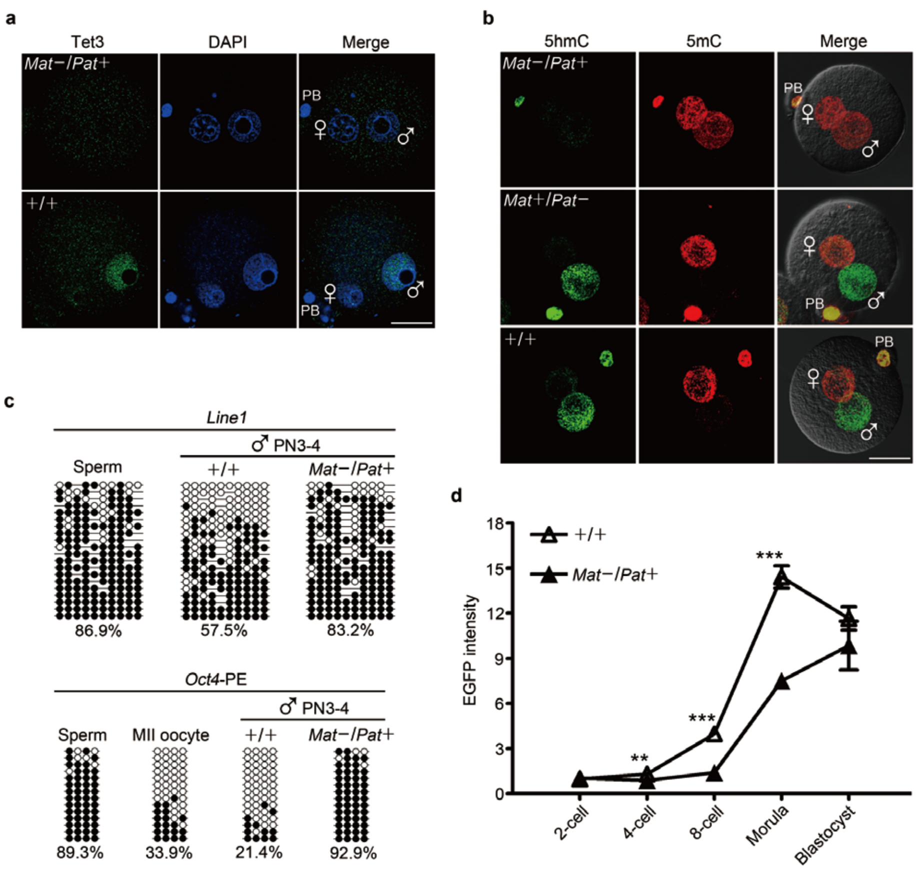


Figure 2: Sperm and eggs carry distinctive epigenetic modifications that are adjusted by reprogramming after fertilization. The paternal genome in a zygote undergoes active DNA demethylation before the first mitosis. The biological significance and mechanisms of this paternal epigenome remodelling have remained unclear. Prof. XU Guoliang's group, in cooperation with Prof. LI Jinsong's group, has demonstrated that Tet3-mediated DNA hydroxylation is involved in epigenetic reprogramming of the zygotic paternal DNA following natural fertilization and may also contribute to somatic cell nuclear reprogramming during animal cloning. (*Nature* [477 (7366):606–611])

(Picture story by Dr. LI Qing; picture by courtesy of Prof. XU Guoliang)