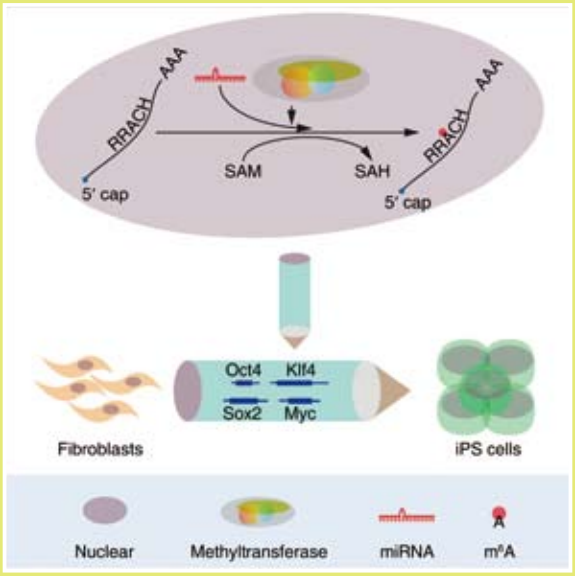
Major Achievements and hallmark advances during the period of the 12th National Five-Year Plan

Cell Programming and Re-programming Mechanisms

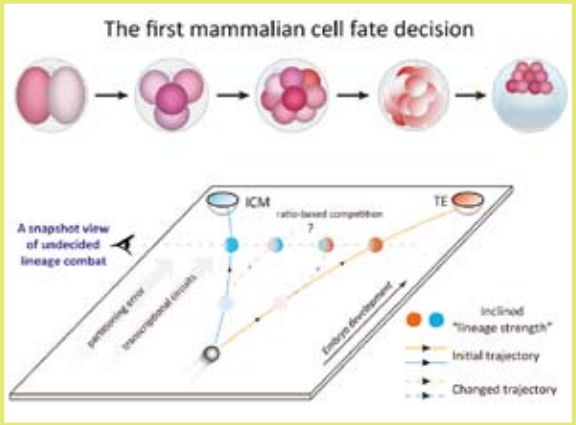
Explorations into mechanisms underlying cell programming and re-programming represent an emerging discipline vital for understanding the inherent nature of life. During the period of China's Twelfth National Five-Year Plan (2011–2015), Prof. ZHOU Qi at the CAS Institute of Zoology (IOZ) took the lead in mapping out a grand program in this field, seeking breakthroughs in areas from basic theories, key techniques, to technology transfer and applications. With support from CAS and national authorities, his team reaped great achievements.

Major Discoveries in Fundamental Theories

In cooperation with two research groups from other institutes of the Academy, IOZ revealed a novel mechanism governing the methylation modification of mRNA by microRNA mediated by complementary sequences and the vital role played by m^6A modification in the reprogramming process of somatic cells towards iPS cells. The joint research successfully unveiled some important episodes in the process, including characterization of the loci selection in m^6A modification, exploring novel functions of microRNA and discovering new factors in regulating cell re-programming. The research was highlighted as a cover paper in 2015 by *Cell Stem Cell*.



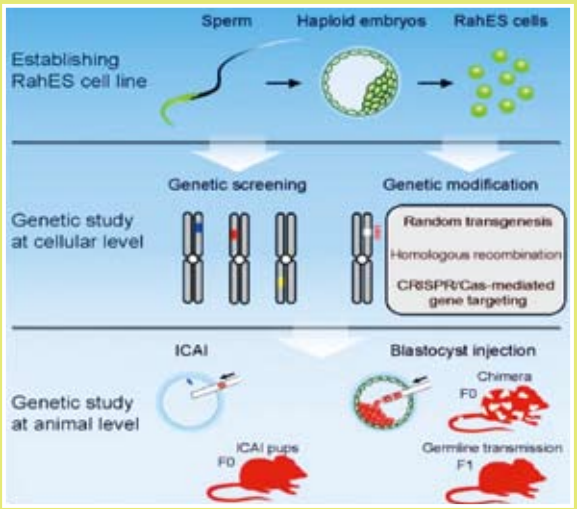
Loci selection mechanism for methylation of RNA m^6A and its important roles in regulation of cell re-programming.
In a research highlighted as a cover paper published in March 2015 in *Cell Stem Cell*, ZHOU and colleagues successfully demonstrated that formation of m^6A on mRNAs is regulated by miRNAs via a sequence pairing mechanism; they found in the same research that m^6A plays a positive role in the reprogramming process to pluripotency, in addition to its differential distribution in pluripotent and differentiated cells.



Shown is a new mechanism underlying the fate decision of early mammalian embryos identified by the team led by Prof. ZHOU Qi at the CAS Institute of Zoology.

Key Techniques

ZHOU's team also made important breakthroughs in key biotechnologies during the same period. His team successfully established a mouse androgenetic haploid embryonic stem cell line (ahES cells) by transferring sperms into an enucleated oocyte, and verified that such stem cell lines can replace sperms to inseminate oocytes and generate viable, fertile adults. Given that the genetic modification marks on such ahES cells are inheritable to their progenies, this invention greatly improved the efficiency for genetic modifications and promised expanded application potential. This work has hence provided a new approach to fast producing transgenic model animals carrying inheritable modification marks, offering an important platform for research in genetic functions, and a new pathway to establish models of animal diseases for research in relevant occurring mechanisms. On the other hand, it provides scientists with a model for fundamental research including pluripotency regulation and genetic imprinting. This work has led to publications appearing in *Nature* (2012) and *Cell Stem Cell* (2014), and was voted by Members of the Chinese Academy of Sciences and the Chinese Academy of Engineering into the top 10 science achievements of the year 2012.



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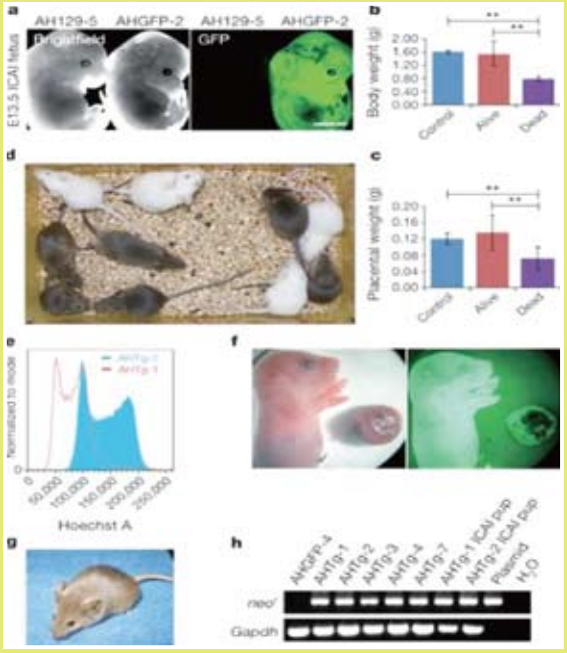


The team succeeded in generating GM animals via ahES cells derived from a mouse androgenetic haploid embryonic stem cell line developed by the team themselves.

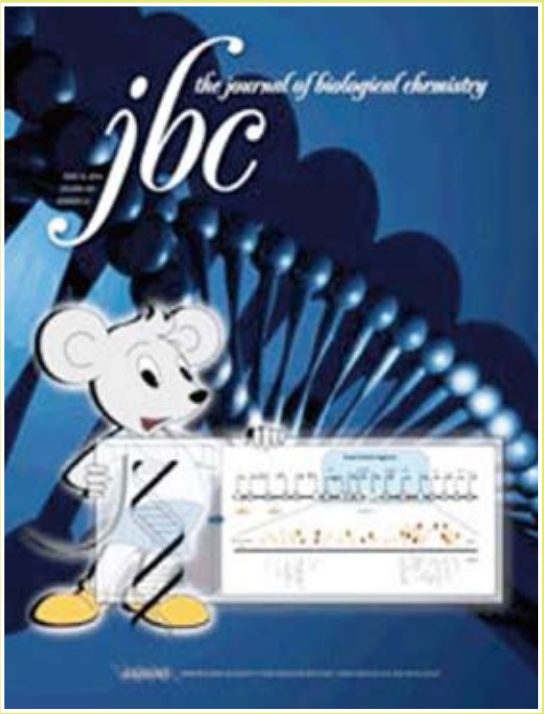
S&T Transfer & Applications

Via CRISPR-Cas system, the IOZ team successfully induced Tet1/Tet2/Tet3 knockout in the rat; on the other hand, they not only achieved the knockout of one specific biallelic gene at an efficiency of 100%, but also the simultaneous knockout of three genes in the rat at an efficiency of 60%. Further more, they successfully demonstrated that the genetic modification introduced via the CRISPR-Cas system can be passed onto the next generation through germ cells. Based on this efficient genetic modification technology, the team established a model of *vWF*-knockout piglet in one step via direct cytoplasmic injection of CRISPR/Cas into zygotes, and a series of models of other animals including p53-biallelic mutant monkey, providing important models for research in triggering mechanisms and drug screening targeting at important human diseases.

Prof. ZHOU's team also took charge of building the stem cell bank of Beijing. As a result from years of continuous efforts, the construction has been completed up to the GMP criteria. So far, the bank has developed a confluence of various stem cell resources, including human and mouse embryonic stem cells. Particularly, it has obtained the first human embryonic stem cell lines and somatic stem cell lines of clinical class that are certified by national authorities and without heterologous elements. Such stem cell lines hold great promise in fundamental research and clinical applications. The team has also established a clinical system of induced differentiation for human embryonic stem cells, which makes it possible for researchers to obtain various functional cells sourced from clinical cells, including nervous cells, myocardinal cells and retinal pigment epithelia. Using stem cells of clinical class, the team also conducted research on a series of primate diseases, including Parkinson, infertility, and pulmonary fibrosis caused by radiation.

During the period of the 12th National Five-Year Plan, the team won multiple awards/prizes including a CAS Award for Outstanding S&T Achievements (Team Award) and a Second Prize from the National S&T Awards for Natural Sciences.

Based on CRISPR genetic modification system, the team established a miniature piglet model for angiohemophilia research.



The team discovered/established a molecular standard to verify the pluripotency of stem cells.