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Profile of Qi Zhou

Dr. Qi Zhou received his Ph.D. degree in Histology and Embryology from Northeast Agricultural University, China, in 1996. He then joined the Institute of Developmental Biology, Chinese Academy of Sciences (CAS), as a postdoctoral fellow, and was qualified as associate professor two years later. In 1999, he joined Prof. Jean-Paul Renard's group at the Developmental Biology and Reproduction Unit of the French National Institute for Agricultural Research (INRA) as a postdoctoral fellow. He soon led several researchers working on an animal cloning project, and, among other animals they cloned, produced the world's first cloned rat. In 2002, with the support of the CAS Hundred Talents Program, Dr. Zhou went back to China to join the Institute of Zoology, CAS, as a professor, and set up his own research laboratory. In 2005, he received the National Science Fund for Distinguished Young Scholars from the National Natural Science Foundation of China. Dr. Zhou is currently a professor and deputy director of the Institute of Zoology, CAS, and is the director of the State Key Laboratory of Stem Cell and Reproductive Biology (formerly the State Key Laboratory of Reproductive Biology). In 2015, he was elected as a CAS Member.

Since he came back to China, Dr. Zhou has focused on stem cell research and has led a group carrying out a series of projects in the field of stem cell biology, with emphasis on studying the mechanisms of cell reprogramming and pluripotency of embryonic stem cells. He has also promoted the translation of stem cells to clinical applications. During the past years, Dr. Zhou has made many outstanding achievements.

Developing novel methods for somatic cell reprogramming

In the 1990's and the early 21st century, when cloning technology was in its early stages, Dr. Zhou was the first to develop a one-step somatic cell nuclear transfer (SCNT) method (Zhou et al., 2000), and used a protease inhibitor to prevent rat oocytes from spontaneous but incomplete activation. This allowed him to generate the world's first fertile cloned rats. The work was published in *Science* (Zhou et al., 2003) and received comments stating that it was "a significant step toward" producing genetically modified rats, and that it would help study many human diseases. For this work, Dr. Zhou won the 3rd genOway Prize for transgenic technologies.

The advent of iPSC (induced pluripotent stem cell) technology greatly advanced the development of stem cell and cell reprogramming research. However, whether iPSCs have developmental pluripotency was one of the most challenging questions in the field. By optimizing induction protocols and establishing new induction and culture methods for iPSCs, research groups led by Dr. Qi Zhou and Dr. Fanyi Zeng efficiently obtained stable iPSC lines. After injecting iPSCs into tetraploid blastocysts, they obtained healthy iPSC-generated mice and offspring through tetraploid complementation (Zhao et al., 2009). The work demonstrated that iPSCs are capable of producing healthy organisms independently, and therefore hold the same developmental

potential as embryonic stem cells (ESCs). This work made outstanding contributions to the improvement of iPSC theory and to future applications of iPSCs in regenerative medicine, and was reported on by hundreds of media outlets worldwide, including Nature, Science, Times, and Reuters, among others. The paper published in *Nature* reporting this work has been cited more than 480 times to date. The first iPSC-produced mouse, "Xiao Xiao", was considered to have "received the torch lit by Dolly". The work was selected as one of TIME's Top 10 Medical Breakthroughs of 2009, and one of the Top 10 Breakthroughs in Science and Technology of 2009, in China.

Dr. Zhou and his team also successfully reprogrammed Sertoli cells of the mesoderm layer into neural stem cells of the ectoderm layer (Sheng et al., 2012). A series of marker expression and functional analyses demonstrated that adult cells of different germ layers might achieve transdifferentiation. This finding has an enlightening significance in studying the mechanisms of organ formation. It also suggests that neural stem cells, derived through such induction, might become a resource for cells used in the treatment of neurodegenerative diseases and for screening new drugs.

Investigating the mechanisms of cell reprogramming and cell fate control

Dr. Zhou and his team discovered that a histone deacetylase inhibitor, CBHA, could increase the efficiency of cell reprogramming by nuclear transfer, suggesting that histone deacetylation may play an important role in regulating cell reprogramming (Dai et al., 2010). They also conducted long-term investigations and found that tumor prevalence in adult iPSC-generated mice was much higher than that of control mice, suggesting that the endogenous oncogenic risk of iPSCs is associated with the re-activation of their induction factors (Tong et al., 2011).

Through systematically examining and analyzing pluripotent stem cell lines of different developmental potencies, Dr. Zhou and his team discovered a key generegulation region, the expression of which is positively correlated to the stem cell pluripotency level. Therefore, this region may serve as a molecular marker for evaluating the pluripotency of stem cells (Liu et al., 2010). The work was published as the cover image and "Paper of the Week" in the *Journal of Biological Chemistry* in 2010, and garnered great attention from international peers. The American Society for Biochemistry and Molecular Biology (ASBMB) pointed out that the "Finding is expected to steer future work on therapies down the most efficient and promising paths". The team also discovered that miR-323-3p, of the above imprinting region, could influence the pluripotency level of stem cells by regulating the PRC2 complex (Zhang et al., 2013).

In collaboration with the teams of Drs. Xiujie Wang and Yungui Yang, Dr. Zhou discovered a new function for microRNAs in regulating the formation of N6-methyladenosine (m^6A) RNA modification and a positive role for m^6A in promoting cell reprogramming to pluripotency (Chen et al., 2015).

Generating important animal and cell models for stem cell research and regenerative medicine

Haploid cells exist in many plant species and are an important tool used extensively for studying recessive traits and breeding. However, in mammalians, only gametes or tumor cells with gene mutations are haploid. Dr. Zhou and his team derived mammalian androgenetic and parthenogenetic haploid embryonic stem cells (ahESCs and phESCs, respectively), and showed that ahESCs can replace gametes to produce offspring. The work not only demonstrated the developmental pluripotency of ahESCs, but also provided new tools for the rapid generation of genetic models for recessive traits; it also shed new light on assisted reproduction. This series of work was published in *Nature* and *Cell Stem Cell*, among others. (Li et al., 2012; Wan et al., 2013; Li et al., 2014), was co-selected (with work from another team) as one of China's top 10 Scientific Advances in 2012.

Recently, Dr. Zhou's group showed that after proper imprinting modifications, mouse phESCs can efficiently produce viable fertile offspring upon intracytoplasmic injection into MII oocytes (Li et al., 2016), thus establishing a novel strategy for generating bimaternal mammals. This is valuable to uncover the function of genomic imprinting, and to improve assisted reproduction in diverse mammalian species.

In addition, Zhou and his team generated mouse-rat allodiploid embryonic stem cells (AdESCs) by fusing haploid ESCs of two species. This was the world's first mammalian diploid hybrid ESC of phylogenetically distal species. This will be a valuable tool for studying X chromosome inactivation and genes with functional differences between species. The work was published in *Cell* in January 2016 (Li et al., 2016).

Transgenic animal models may establish new phenotypes through gain or loss of function of genes, and are necessary tools for studying gene functions and the pathogenesis of diseases. With the platform of the CRISPR-Cas9 system, Dr. Zhou and his team achieved simultaneous mutations of multiple genes in rats (Li et al., 2013), generated live vWF-knockout pig models using a one-step method (Hai et al., 2014), and produced the first live p53 homozygous mutant monkey (Wan et al., 2015). These studies provide a new approach for rapid generation of genetically modified animal models of human diseases, and will promote research on pathogenesis and treatment of diseases.

Obtaining standardized and scalable seed cells for therapeutic use, and carrying out evaluations of pre-clinical safety and efficacy

Safety and efficacy remain two primary concerns when applying cell therapy to clinical use. How to combine basic research with clinical application, how to evaluate the efficacy and safety of cells used for therapy, and how to comply with clinical standards, are major research focuses. During recent years, Dr. Zhou has been working on establishing Beijing Stem Cell Bank that is in accordance with clinical standards, has performed rigorous cell safety tests, and has formulated an entire set of relevant rules and regulations. He has also promoted the formulation of international guidelines for the clinical application of stem cells and promoted the implementation of international action schemes related to stem cells.

Dr. Zhou's distinguished work has resulted in over 100 publications, many of which were published in top-ranked scientific journals, including *Cell*, *Nature*, *Science*, *Nature Biotechnology*, *Cell Stem Cell*, and *PNAS*. He has been awarded many prizes, including the Second Class Award of the National Natural Science Award of China (2014), the Outstanding Science and Technology Achievement Prize of the CAS (2013), and the Prize for Scientific and Technological Progress from the Ho Leung Ho Lee Foundation (2010).

Apart from his academic achievements, Dr. Qi Zhou also takes great responsibility for, and makes many contributions to, the entire stem cell research society in China. He serves as a consultant for the China Ministry of Science in the Program of Development and Reproduction and Technology. He promoted the setup of the Strategic Priority Research Project of Stem Cell and Regenerative Medicine of the Chinese Academy of Sciences, and serves as the chief scientist to coordinate the research of over 80 stem cell biologists. After being invited to the International Stem Cell Forum, as the representative of China, of which he currently serves as the president, Dr. Zhou took this responsibility and organized four international workshops related to stem cell study and regulation. This not only strengthened the collaboration between China and other countries but also increased the influence of China in the field of stem cell research.

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