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Special Topic: Stem Cell Research in China

Qi Zhou: the coming of age in China's stem-cell research and regenerative medicine

By Jane Qiu

Between 2011 and 2015, China invested about 3 billion yuan (US$435 million) on stem-cell research and regenerative medicine. This has led to major scientific breakthroughs, solidifying the country's role as a global leader in this field. Last September, China launched another major programm called Stem Cells and Transfer Research — with a similar budget over five years but focusing more on clinical applications. Many see this as a golden opportunity to catalyse significant medical advances, providing relief for patients with conditions such as Parkinson's Disease and macular degeneration. NSR recently talked to Qi Zhou, a leading stem-cell researcher at CAS's Institute of Zoology in Beijing, about recent research progress, China's challenges and opportunities, how the government is trying to tighten the regulation and why we must move forward cautiously when applying new technologies, such as gene editing and mitochondria replacement therapy, in a clinical setting.

NSR: What is the major progress in China's stem-cell research in recent years?
Zhou: During the 12th five-year plan during 2011–2015, there was a concerted effort to establish the differentiation pathways and underlying mechanisms of stem cells and pluripotency. It's important because we need to know where stem cells come from and where they are going, so as to precisely control their fate. Such studies have also led to the identification of novel markers for breast cancers that are negative in all the three previously known tumor markers—cancer antigen 15-3, cancer antigen 27.29 and carcinoembryonic antigen. Those cancer types have been a major challenge in the early diagnosis of breast cancers in some patients.

Another important development is the artificial generation of new cell types that didn't exist before. For example, by fusing the haploid embryonic stem cells from rats and mice, a research group in China succeeded in producing a diploid cell line that contains the genome of both species (Li, X. *et al. Cell* **164**, 279–292, 2016). The hybrid cells are stable, can differentiate into all three germ layers, including early stage germ cells. This could address some of the questions in evolution that could not be addressed before. It provides, for instance, a new approach to assessing the differences in gene regulation that affect phenotypic differences across different species. It's also a power model for studying X-chromosome inactivation—a process by which one copy of the X chromosome in female mammals is inactivated so they don't have twice as many gene products as males. While this process is thought to be random in terms of which X chromosome is silenced, it's interesting that the rat X chromosome is always expressed in the hybrid cells whereas its mouse counterpart is always silenced.

Qi Zhou, stem-cell researcher at the Institute of Zoology, Chinese Academy of Sciences, in Beijing, China. *(Courtesy of Qi Zhou)*

NSR: How about research areas that are geared towards clinical applications?
Zhou: China is very strong in primate research. While undergoing decline in the West because of societal resistance and some regulatory hurdles, it's gathering pace here. Stem cells in

monkeys, especially rhesus or cynomolgus macaques, are very similar to their human counterparts, presenting a powerful tool to understand mechanisms of stem-cell differentiation and human diseases. China now has many primate models of neurological conditions—such as autism, Parkinson's Disease and macular degeneration—which have symptoms more closely related to humans than models of other species.

And we shouldn't focus only on cell therapy, but need to combine with approaches to creating a conducive microenvironment for transplanted stem cells to survive and fulfil their functions. There have been some promising results in the application of biomaterials to create a regenerative microenvironment within the injured spinal cord.

Another area of research geared towards clinical applications is the success in producing functional sperms *in vitro* by coaxing embryonic stem cells to undergo meiosis (Zhou, Q. *et al. Cell Stem Cell*, **18**: 330–40, 2016). It's important for two reasons. First, a better understanding of meiosis has been difficult because there are limited materials. If we can create this process *in vitro*, then we could study how meiosis is regulated and how haploids are generated from diploids. Second, it's great news for patients who can't produce functional sperms. We can really envisage the day when those patients could have genetically related offspring.

NSR: What's the situation in terms of clinical trials using stem cells?

Zhou: In April, we launched clinical trials for Parkinson's Disease and macular degeneration, which are two of the eight clinical-research projects involving stem cells that have been registered with China's Food and Drug Administration (FDA) and health ministry. The pre-clinical studies were done in my lab and our clinical partner is the First Medical Hospital of Zhengzhou University in Henan province. These are the first embryonic stem-cell clinical studies in China that adhere to new regulatory rules.

In both cases, we have to differentiate embryonic stem cells into desired cell types—dopamine neurons for treating Parkinson's Disease and retinal pigment epithelium for macular degeneration. We have to have very good cell lines, which have to be tested in animal models and undergo strict evaluation. The pre-clinical studies are very rigorous. For instance, we have been working on primate models of Parkinson's Disease for over five years—not counting the amount of times spent to develop those models—which have yielded very promising results, such as reducing the severity of shaking and delaying disease progression.

NSR: What are the key research directions in China's 13th five-year plan between 2016 and 2020?

Zhou: China has a major programme called Stem Cell and Translational Research, with a budget of about 2.7 billion yuan. Compared to the previous five-year plan, it focuses more on clinical applications, especially in areas of neurological conditions, cardiovascular diseases, liver regeneration and reproductive health. CAS is a major player in this. There are also initiatives at the municipal and provincial levels. Beijing, for instance, has launched a major programme on stem-cell research and regenerative medicine. Regarding basic research, the emphasis is on how to obtain functional cell types from stem cells and how they can be affected by the *in vivo* environment after transplantation.

NSR: Gene-editing research in China has attracted a lot of attention worldwide. What's the plan in the coming years?

Zhou: China plans to do three things. First, it hopes to develop novel tool kits with its own intellectual-property rights, especially new and effective gene-editing systems, which is crucial for developing commercial therapeutics. Both CAS and the Ministry of Science and Technology have funded projects to search for new gene-editing enzymes and develop novel technologies. Second, Chinese scientists are carrying out transfer research using existing technologies to, for instance, generate animal models of human diseases. Such examples include pig models of haemophilia and primate models of autism and Parkinson's diseases. Finally, there are also attempts to repair mutations in patients with genetic diseases using existing gene-editing technologies.

NSR: Last October, China became the first country to conduct clinical trials involving gene editing. What is it about?

Zhou: This is the only case of clinical application of gene editing in China at the moment. It's carried out by the West China Hospital in Chengdu, capital of Sichuan province, for treating patients with metastatic non-small cell lung cancer. It involves taking immune cells from patients' blood and delete a gene that normally tempers with their ability to attack cancer cells. The modified cells will be amplified in the lab and transfused back into the patient's bloodstream, where the team hope they will help kill the cancer.

It's controversial because some researchers don't think there are sufficient pre-clinical studies to demonstrate that the approach is safe and effective. While gene editing is very promising, we must move forward cautiously. We really should take lessons from gene therapy—which suffered from serious setbacks at the early stage of clinical application because people rushed into it without properly assessing its safety. Let's hope history will not repeat itself.

NSR: What's the state of research on mitochondrial replacement therapy that aims to prevent mothers from passing down harmful genes through their mitochondria?

Zhou: The best known case internationally is John Zhang, a physician at New Hope Fertility in New York City, who led a team that created a baby boy last year using this technique—which involved transferring the nucleus of the mother's egg with diseased mitochondria to the egg of a healthy donor. The procedure, which is not permitted in the US at the moment, was performed in Mexico. Several Chinese groups have carried out similar work. I do think this technique could have significant clinical potentials, as this may be the best and only solution for women with mitochondria diseases to have genetically related healthy offspring.

But, again, I think we must move forward cautiously. There are several scientific and technical issues that need to be resolved before it could be moved into clinical application. One major hurdle is that current techniques can't avoid carrying over a small percentage of diseased mitochondrial into the donor egg.

Some worry this could have a negative health impact, especially if this proportion rises as the embryo develops.

Even if it's possible to replace all diseased mitochondria, there are still concerns about the long-term impact—not only on individual children but future generations. It's now clear that mitochondria do not just produce energy, but are involved in many biological processes, such as cell death and immune responses. And cross-communication between mitochondrial and nuclear genomes could be important in ways that are yet to be fully appreciated. Therefore, it remains to be seen whether and how mitochondria replacement therapy could affect these poorly understood processes in the long run.

NSR: What's the regulatory framework in China regarding mitochondria replacement therapy?

Zhou: This is lacking in China at the moment. It's such a new technology we don't have rules to say that it can't be done, but I believe the health ministry is looking into it. Ethical guidelines proposed by professional societies such as the US National Academies of Sciences, Engineering and Medicine recommend limiting initial clinical investigation to women at risk of transmitting a serious mitochondrial disease—in an attempt to prohibit the expansive use of the technology in treating age-related infertility. They also suggest that only male embryos should be brought to term, thereby preventing passing the donated mitochondria to their descendants (because children inherit mitochondria only from their mother).

Moreover, informed-consent forms should describe the procedures in detail and be explicit about the uncertainties and the potential risks of using the techniques to create a child. And it's absolutely essential to follow up the children—at least through their early childhood years—to determine long-term safety and efficacy.

NSR: How is stem-cell research regulated in China?

Zhou: In August 2015, the country's FDA and healthy ministry jointly issued a set of rules to regulate stem-cell clinical research. A key highlight is that stem-cell research is regulated according to the same principles as drugs and biological products—as opposed to the previous framework for medical technologies. The new rules specify the standard of clinical-grade stem cells and stipulate that stem-cell clinical research can be carried out only in 30 authorized top-ranking hospitals, which must have certificates to carry out drug trials, have proven track-record of stem-cell research, and have sufficient equipment and platforms.

Research groups planning to conduct stem-cell clinical trials have to register with the agencies. Clinical-grade stem cells have to go through third-party evaluations. And there have to be sufficient pre-clinical data from basic research and animal models. So far, only eight projects have been given a go-ahead—involving conditions such as Parkinson's Disease, macular degeneration and cerebral palsy.

It's a step in the right direction, but is imperfect in several ways. Military hospitals, for instance, are not obliged to adhere to the rules because they are not under the jurisdiction of China's FDA or health ministry. The penalties for breaking the rules are also not clear. It's likely to be transitional regulation. There should be further amendments, in my view.

NSR: Has this helped stop the practice of unproved stem-cell therapies in China?

Zhou: Certainly. There are major improvements compared to the situation before—when numerous hospitals and companies advertised and offered unproven stem-cell therapies. In 2012, the country's health ministry banned all stem-cell therapies and clinical trials as it began to draft the new guideline to step up the regulation. But China is a massive country. There may be hospitals and companies that continue to offer unproven stem-cell therapies, but at least they wouldn't be doing this blatantly. I want this to be clear: there are no proven stem-cell therapy in China.

NSR: What are the opportunities for China's stem-cell research and regenerative medicine?

Zhou: We certainly have a few advantages. If China determines to do something, it can coordinate and integrate and make it happen quickly. The major stem-cell programme at CAS, for instance, has been able to integrate scientists' individual research interests and focus on important areas. China's investment in research and development has steadily increased in recently decades—in contrast to the situation in Europe and the US where research funding and capacity have been going downhill. Moreover, there has also been a major rise in the number of talented Chinese scientists who return to China after having been trained in the West.

The permissible climate for primate research in China is also an opportunity for us. In the West, it's much more expensive to carry out such research and is getting increasingly difficult because of animal-rights movement. I'm concerned that people here may be more interested in publishing papers than how to leverage the tools to advance clinical applications—as experimental designs would be rather different with or without a well-thought-out clinical endpoint.

Another opportunity is that China now places more emphasis on application and technology transfer, across all research fields, including stem-cell research and regenerative medicine. While basic research is still encouraged, it's more interested in the kind of research that sets an eye for applications. As individual scientists, we need to be guided by China's focus and regulatory framework, steering our research in areas that are more relevant to the clinical setting—to better serve the national interests and the needs of the people.

Jane Qiu writes for NSR from Beijing.