Stem Cells and Regenerative Medicine Research Postprint

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Abstract

The "Stem Cell and Regenerative Medicine Research" Strategic Priority Program (hereinafter referred to as the "Stem Cell Priority Program") was among the first Category A priority programs launched by the Chinese Academy of Sciences (CAS) in January 2011. Hosted by the Institute of Zoology, CAS, the program brings together 17 institutes across the academy spanning life sciences, materials science, chemistry, biomechanics, and other disciplines, along with multiple leading extramural institutions, focusing on major challenges impeding the field' s development through collaborative innovation and integrated research efforts. After five years of arduous efforts, the program has achieved a series of original achievements widely recognized by the international academic community, established multiple core technologies with independent intellectual property rights, and applied these technologies to conduct extensive preclinical and clinical translational research, forming a nationwide stem cell research and medical translation network, and achieving the expected goal of leading China' s stem cell research and applications into the international first echelon.

Full Text

Preamble

The Chinese Academy of Sciences (CAS) Strategic Priority Research Program (Category A) titled "Stem Cell and Regenerative Medicine Research"(hereinafter referred to as the "Stem Cell Pilot Program") was one of the first Category A programs launched by CAS in January 2011. Based at the Institute of Zoology, CAS, the program integrates 17 CAS institutes and several external partner units from life sciences, materials science, chemistry, biophysics, and other disciplines, focusing on major problems hindering field development through collaborative innovation and concerted research efforts.

After five years of intensive work, the program has produced a series of internationally recognized original achievements, established multiple core technologies with independent intellectual property rights, and applied these technologies in numerous preclinical and translational studies, forming a nationwide stem cell research and medical translation network that has achieved the goal of leading China' s stem cell research and applications into the international first tier.

With program support, CAS has formed approximately 100 excellent stem cell and regenerative medicine research teams, cultivating a group of internationally influential academic leaders, including two academicians and a large number of outstanding young stem cell research talents, creating a well-structured, multi-tiered talent pipeline. Additionally, the program has significantly enhanced China' s international influence in the stem cell field, with over 400 person-times serving in international academic organizations or journals, including the program' s chief scientist being elected as President of the International Stem Cell Forum (ISCF) during the project execution period. Funded by the program, over 360 person-times have presented at international academic conferences or conducted exchange visits, with related achievements reported more than 210 times.

Given its significant importance for national health security and economic and social development, stem cell and regenerative medicine research has become a strategically competitive field of high concern and substantial investment by governments, scientific communities, and industries worldwide, with unprecedentedly fierce international competition. China, as a populous country, must face both health issues common to developing countries and new challenges brought by modernization, making the demand for stem cells and related products and technologies particularly urgent. Under these circumstances, CAS timely launched the Category A Strategic Priority Research Program "Stem Cell and Regenerative Medicine Research."

1. Project Background and Overall Progress

Stem cells can self-renew, proliferate extensively, and further differentiate into various cells to form tissues and organs, holding enormous potential for cell replacement, tissue repair, and disease treatment, and capable of solving many medical challenges facing humanity. Stem cell and regenerative medicine represent the frontier of contemporary life sciences and the core of the new medical revolution, leading profound transformations in medical paradigms and often serving as a measure of a nation' s life science and technology level.

2. Brief Introduction to Representative Achievements

2.1 Top 10 Scientific Advances in China

(1) Revealing the important role of Tet dioxygenase in mammalian epigenetic regulation. The research revealed that Tet3-mediated DNA hydroxylation

regulates paternal DNA epigenetic reprogramming in fertilized eggs and also affects somatic cell nuclear reprogramming in animal cloning. This work provides important guidance for understanding epigenetic regulation in early development, the causes of totipotency in fertilized eggs, and improving the efficiency and quality of animal cloning. This achievement was selected as one of the "2011 Top 10 Scientific Advances in China."

(2) Discovery of cell surface marker genes for mammary gland stem cells. For the first time, the existence of undifferentiated stem cells in adult mammary organs was discovered. These stem cells specifically express the protein C receptor gene, revealing this molecule' s high expression characteristics in triple-negative breast cancer and its significant correlation with patient prognosis, providing new ideas for targeted breast cancer therapy and laying a foundation for application (Figure 1 [Figure 1: see original paper]).

(3) Successful conversion of mouse fibroblasts into functional hepatocyte-like cells. For the first time, it was confirmed that under the premise of inhibiting cellular senescence mechanisms, transferring three transcription factors that play important roles in mouse liver development and function can convert fibroblasts from mouse tails into liver cells. This achievement was selected as one of the "2011 Top 10 Scientific Advances in China."

(4) Demonstrating that haploid androgenetic stem cells have the ability to replace sperm and rapidly transmit genetic modifications. Through collaboration among multiple research teams, the program achieved an important theoretical breakthrough in the field of haploid embryonic stem cells—establishing the first international haploid embryonic stem cell line from androgenetic blastocysts and achieving the first healthy transgenic mammals using gene-modified haploid embryonic stem cells. This achievement was selected as one of the "2012 Top 10 Scientific Advances in China."

(5) Creating a new type of stem cell, subverting traditional reproductive theory. A new type of stem cell was created—interspecific hybrid diploid embryonic stem cells—the first artificially created, stably existing interspecific hybrid embryonic stem cells in diploid form, providing a novel and powerful tool for studying molecular mechanisms of trait differences between evolutionarily distinct species and X chromosome inactivation.

2.2 Second Prize of National Natural Science Award

(1) Major breakthroughs in somatic cell reprogramming mechanism research. Major breakthroughs were achieved in vitamin C's ability to improve reprogramming efficiency and cell quality, and in the regulatory mechanisms of cell transitions between mesenchymal and epithelial states during reprogramming. This series of achievements won the 2013 National Natural Science Award Second Prize.

(2) Major breakthroughs in establishment and regulation mechanisms of mammalian pluripotent stem cells. Multiple breakthroughs were achieved in induced pluripotent stem cells and human embryonic stem cell acquisition and cell reprogramming mechanisms. Using induced pluripotent stem cell technology, healthy animals from non-embryonic sources were obtained for the first time, promoting the establishment, popularization, and application of this technology and improving developmental biology theory. This series of achievements won the 2014 National Natural Science Award Second Prize.

2.3 Major Breakthroughs in Frontier Basic Research

(1) Construction of three-dimensional cell lineage in early embryos. Combining advanced technologies such as laser microdissection and single-cell sequencing, a fine three-dimensional molecular atlas of mouse embryos during mid-gastrulation was mapped, revealing spatial transcriptomic characteristics, transcription factors, and signaling pathway regulatory networks during the establishment of mouse cell lineage blueprint, providing a novel perspective and theoretical guidance for understanding stem cell pluripotency and differentiation potential.

2.4 Establishment of Multiple Original Systems for Core Key Technologies

(1) Novel gene editing technology and disease treatment. Haploid androgenetic and parthenogenetic embryonic stem cell lines were successfully established, and primate Parkinson’ s disease treatment was conducted (Figure 3 [Figure 3: see original paper]). CRISPR-Cas9 technology was successfully used to treat mouse cataract genetic diseases, and development of CRISPR-Cas9 therapeutic systems for other diseases continues. Through joint research on these novel genome editing technologies, technical possibilities have been provided for stem cell therapy and gene correction for related diseases.

(2) Establishment of long-term in vitro culture system for muscle stem cells, achieving muscle stem cell expansion in vitro. A system for long-term in vitro expansion and passaging of muscle stem cells was established, in which muscle stem cells that originally could not be passaged can now be continuously passaged 40 times in vitro, with cell numbers increasing by 1×10^35 fold. Additionally, four cytokines that can help muscle stem cells maintain their stemness during in vitro passaging were identified, laying a foundation for providing solutions to muscle degenerative diseases.

(3) Completion of China’ s first near-infrared-II small animal fluorescence imaging system and realization of export of domestic biomedical imaging equipment to the United States. The spectral response range of the near-infrared-II in vivo imaging system was extended to 400–1,700 nm, covering

current mainstream visible light and near-infrared-I fluorescence imaging, as well as near-infrared-II fluorescence imaging. The system has provided imaging services for multiple research institutions and signed a sales contract with Emory University' s Department of Biomedical Engineering in the United States, realizing the export of domestic biomedical imaging equipment.

2.5 Notable Progress in Clinical Translation Research

(1) Establishment of China' s first clinical-grade stem cell bank. China' s first clinical-grade stem cell bank—the Beijing Stem Cell Bank—was established, obtaining China' s first clinical-grade embryonic stem cell lines tested by the China Food and Drug Administration' s Institute for Drug Control, and conducting standardized clinical trials based on clinical-grade stem cell lines. This provides a standard reference system for clinical-grade stem cell testing in China, reserves important stem cell resources needed for basic research and clinical translation, and vigorously promotes the development of clinical stem cell applications in China (Figure 2 [Figure 2: see original paper]).

(2) Treatment of macular degeneration with clinical-grade embryonic stem cell-derived RPE cells. The world' s first clinical transplantation study using clinical-grade stem cell-differentiated retinal pigment epithelium for hemorrhagic age-related macular degeneration and China' s first case of juvenile macular degeneration was conducted. By December 2015, three cases of hemorrhagic bilateral age-related macular degeneration and five cases of juvenile macular degeneration surgeries had been successfully completed. All patients' visual obstruction disappeared, and three patients receiving hESC-RPE transplantation showed improved vision. The program will further evaluate the safety and effectiveness of these clinical transplantation studies.

(3) Successful birth of babies after endometrial injury regeneration and repair. Collagen biomaterials capable of guiding endometrial regeneration were developed, a pig model of full-thickness uterine injury was created, and small and large animal experiments for uterine wall injury repair were completed, confirming that intelligent biomaterials promote uterine wall regeneration and improve pregnancy rates. In collaboration with Nanjing Drum Tower Hospital, clinical research on uterine wall injury repair was conducted, resulting in the first baby born from intelligent biomaterial-repaired uterine injury, with multiple babies successfully born subsequently (Figure 3 [Figure 3: see original paper]).

(4) Novel bioartificial liver using transdifferentiated human hepatocytes. Based on transdifferentiating human fibroblasts into functional hepatocytes (hiHep cells), these cells were successfully expanded to clinically therapeutic quantities and loaded into a bioartificial liver. The survival

rate of acute liver failure pigs treated with hiHep cell-based bioartificial liver reached 80%. In early 2016, the first clinical treatment experiment based on the hiHep cell bioartificial liver system was completed, saving a patient with a 40-year history of hepatitis B who had recently developed liver failure. The patient' s liver function indicators recovered well, and the critical period was successfully passed.

(5) Regeneration and repair of chronic complete and acute spinal cord injuries. Functional biomaterials capable of guiding spinal cord regeneration were developed, type testing of neural regeneration collagen scaffolds was completed, and multiple batches of functional biomaterial transplantation experiments were conducted on rats and dogs with complete transection spinal cord injuries. Based on this, clinical research on neural regeneration collagen scaffold transplantation for acute and chronic complete transection spinal cord injuries was carried out. Results showed good biomaterial and surgical safety, with acute spinal cord injury subjects showing significant motor function recovery and chronic injury subjects showing improved sensory and motor nerve function, yielding encouraging preliminary results (Figure 4 [Figure 4: see original paper]).

3. Management and Organization

3.1 Goal-oriented Collaborative Research

At the program' s launch, although CAS had made some progress in stem cell research, the overall research workforce was relatively small, and most researchers were accustomed to conducting studies through "free exploration," with awareness of demand-oriented and goal-oriented research not yet formed. Under the leadership of CAS and its bureaus, the program boldly reformed the original project-based horizontal field layout, eliminated hierarchical project management, and integrated superior forces from basic research, technology development, and translational application fields. Research teams were established around scientific questions and clinical goals, with key tasks deployed and classified management implemented. Simultaneously, adopting a project management model similar to engineering projects, task objectives, technical processes, and time nodes were strictly defined, with application orientation and translational research as the export, realizing an innovative value chain from basic research to clinical application, thereby catalyzing the new layout of the "Stem Cell-Based Regenerative Medicine Research" program.

3.2 Top-level Design and Forward-looking Layout

As a rapidly developing and highly concerned new field in modern life sciences in recent years, the stem cell and regenerative medicine field has no ready-made experience to replicate, with every progress accompanied by scientific and technological innovation and breakthroughs, where challenges and opportunities coexist. Facing increasingly fierce international competition, the program' s chief scientist team carefully designed and, after more than a year of scientifically rigorous feasibility studies, expert demonstrations, and systematic evaluations, condensed and deployed a large number of internationally forward-looking and pioneering research directions, including cell lineage research, stem cell technology development, intelligent biomaterial research, and comprehensive stem cell clinical strategies. Through systematic layout, concentrated research efforts, and interdisciplinary approaches, the comprehensive and institutional advantages of the CAS system were fully utilized. After five years of arduous efforts, a batch of internationally remarkable major theoretical and technological breakthroughs were achieved, reflecting systematic and advanced scientific research planning.

3.3 Innovative Mechanisms and Strict Management

Under the circumstances that CAS has no directly affiliated clinical hospitals and obvious translation bottlenecks, the program innovated project organization and implementation methods, enabling clinical units to intervene early through collaboration and establishment of special sub-projects, seizing translation opportunities. Additionally, the program emphasized strengthening management and strict evaluation during execution, such as conducting review and summary through "two inspections and two meetings," regular supervision and forming closed-loop feedback, conducting third-party international expert committee evaluations, mid-term assessments, and Ministry of Finance key performance evaluations. Simultaneously, funding was dynamically adjusted based on performance to ensure major outputs. For example, when funding support was substantially reduced in 2014, based on the principle of "protecting key points, protecting urgent needs, protecting critical aspects," the program reviewed and deployed key tasks around overall objectives, innovated funding allocation, and invested 70% of funds into key tasks.

4. Building on Past Achievements and Setting Sail Again

Since its implementation five years ago, the Stem Cell Pilot Program has achieved a series of internationally recognized original results, forming a nationwide stem cell research and medical translation network that leads China' s stem cell and translational research into the international first tier. With program support, CAS has formed a complete echelon and rationally structured talent team, constructing systematic innovation platforms centered in Beijing, Shanghai, Guangzhou, and Southwest China, generating important influence both domestically and internationally. Under the program' s leadership, stem cell research has received high-level national attention, with the National Key R&D Program investing 2.7 billion yuan during the "13th Five-Year Plan" period to support stem cell basic research and translational research.

Based on the Stem Cell Pilot Program, CAS established the "Stem Cell and Regenerative Medicine" Innovation Research Institute in 2015 to further accelerate the construction of an international first-class talent highland and scientific and technological innovation center in the life and health field. Looking to the future, relying on the Stem Cell Innovation Research Institute and based on CAS' s already cultivated institutionalized stem cell research advantage teams, the institute will absorb superior teams, conduct thorough discussions, and layout new CAS stem cell field pilot programs, continuing to lead the future development of Chinese stem cells and further maintaining and consolidating China' s leading position in international competition in stem cell and translational research.

(Undertaking unit: Institute of Zoology, Chinese Academy of Sciences)

Expert Commentary I: Chen Xiangmei

Chen Xiangmei, Member of the Chinese Academy of Engineering, Director of the State Key Laboratory of Kidney Diseases, Director of the National Clinical Research Center for Chronic Kidney Disease, Director of the National Kidney Disease Medical Quality Control Center, Director of the PLA Institute of Nephrology, President of the Chinese Association of Integrative Medicine, Executive Director of the Chinese Medical Association, and President of the Nephrology Branch of the Chinese Medical Doctor Association. She has led or participated in over 20 prospective multicenter clinical trials or expert consensus formulations at home and abroad, served as chief scientist for the "973" Aging Project, chief expert for the National "12th Five-Year" Science and Technology Support Program, and academic leader of the "Innovative Research Group" of the National Natural Science Foundation of China and the PLA "Science and Technology Innovation Group" award. She has published over 1,000 papers at home and abroad, edited 15 monographs, and won 1 first prize and 4 second prizes of the National Science and Technology Progress Award as the first completer, 2 first prizes of the Beijing Science and Technology Award, 3 first prizes of the Chinese Medical Science and Technology Award, 1 first prize each of the Chinese Association of Integrative Medicine Science and Technology Award and the PLA Science and Technology Progress Award, the Ho Leung Ho Lee Award, and the 2014 National Science and Technology Progress "Innovation Team" Award as the first completer.

Stem cells and regenerative medicine can solve many medical problems in cell replacement, tissue repair, and disease treatment, holding significant importance for health security and economic and social development. The "Stem Cell and Regenerative Medicine Research" Strategic Priority Research Program implemented by CAS is particularly urgent for stem cell and related product and technology research and translation worldwide. Based on CAS' s advantages in stem cell and regenerative medicine research, the program has cultivated a complete echelon and rationally structured talent team, including a group of internationally influential academic leaders headed by the President of the International Stem Cell Forum (ISCF) and a large number of outstanding young scientific talents. It is their leading scientific work that has enabled the program to publish numerous high-level papers, obtain a series of original patents and internationally significant breakthroughs, with multiple studies selected as "Top 10 Scientific Advances in China." Not only in basic research but also in clinical translational research, the program has achieved a batch of breakthroughs with major clinical application prospects, successfully solving difficult clinical treatment problems for major diseases. These are not only tremendous scientific achievements but also vigorously promote internationally standard modern translational application research with demonstration effects.

Based on the program' s outstanding research achievements and advanced management in all aspects, it has led China' s stem cell research and applications into the international first tier, placing it at the international leading level.

Expert Commentary II: Meng Anming

Meng Anming, Professor at the School of Life Sciences, Tsinghua University, developmental biologist. He has long been engaged in embryonic development research, revealing important molecular mechanisms regulating early development of vertebrate embryos. He has received the "Qiushi" Outstanding Young Scholar Award, the National Outstanding Young Scientist Fund, the Ho Leung Ho Lee Science and Technology Progress Award, and the Tan Jiazhen Life Science Achievement Award. He was elected as a member of the Chinese Academy of Sciences in 2007 and a member of the Academy of Sciences for the Developing World (now the World Academy of Sciences) in 2008.

In 1998, James A. Thomson et al. first reported human embryonic stem cell lines, demonstrating for the first time the feasibility of preserving and expanding human stem cells in vitro. In 2006, Shinya Yamanaka' s research group successfully expressed four transcription factors to convert adult mouse fibroblasts into induced pluripotent stem cells (iPS), greatly expanding stem cell sources and demonstrating broad prospects for using stem cells to treat human diseases. Since then, stem cell research has entered the fast lane, with developed countries competing to invest heavily in stem cell research to dominate the potential huge market of stem cell-based gene and cell therapy. CAS seized this strategic opportunity and timely launched the "Stem Cell and Regenerative Medicine Research" Strategic Priority Research Program in 2011. Seventeen CAS institutes and some external superior units actively participated, conducting collaborative research on major theoretical and technical bottlenecks facing stem cell medical applications, achieving a large number of important original research results. For example, internationally, the first haploid stem cell lines were established, and healthy mammalian individuals were obtained through fertilization using gene-modified haploid stem cells; interspecific hybrid diploid embryonic stem cells were created for the first time; vitamin C was discovered to significantly improve iPS efficiency and its mechanism was elucidated; fibroblasts were directly transdifferentiated into functional hepatocytes in vitro, and the bioartificial liver system prepared with these cells has shown clinical efficacy;

clinical-grade stem cell-differentiated retinal pigment epithelial cells have shown initial effectiveness in treating age-related and juvenile macular degeneration; etc. The pilot program has achieved remarkable results, placing China in the international forefront in the field of stem cells and regenerative medicine and forming an internationally competitive research team. We expect that the pilot program will continue to produce new major achievements and play a leading role in the field of regenerative medicine.

Note: Figure translations are in progress. See original paper for figures.