An Investigation and Analysis of Literature on Stem Cell and Regenerative Medicine Industry in China

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Abstract. The latest report from the National Bureau of Statistics, “China’s economic and social development in 2016”, shows that the number of people aged 60 and above is approximately 230 million (i.e., 16.7% of the population). By 2050, this age-group will increase to 400 million, accounting for more than 30% of the population. In China, this dramatic aging trend has endangered people’s health. Major disorders such as tissue and organ damage, cardiovascular and other functional organ failures, degenerative diseases, and cancer are closely related to aging. Traditional treatments such as drug therapy and surgery often have little effect on such diseases, and fail to meet the growing medical needs of this age-group. Stem cell-based regenerative medicine is expected to become the third treatment option after drug therapy and surgery. With the increasing financial supports and investments in China recent years, a series of important progress have been made to stem cells and regenerative medicine. In this issue, we investigated the stem cell and regenerative medicine industry in the world and china, such as research literature and research institutions distribution.

1. Introduction
The past 100 years has seen rapid developments in the life sciences and medicine. Advances such as the discovery of the DNA double helix, the invention of the polymerase chain reaction, the establishment of gene editing, and the advent of test-tube baby technology have brought about significant changes in human society. Since the beginning of the current century, the completion of the human genome project, the development of a new generation of low-cost, high-throughput sequencing technologies, the establishment of multi-stem cell technology, etc., have improved people’s understanding of life at the molecular level, particularly with regard to the transformation of cells. Research on the basic theory and technology of regenerative medicine will revolutionize the prevention and treatment of age-related diseases, such as cardiovascular[1] and cerebrovascular diseases[2], cancer[3], diabetes[4], Parkinson’s[5, 6] and Alzheimer’s diseases[7, 8], and will lay the foundation for new disruptive medical technology. In stem cell transformation studies, functional cells that can be used for human transplantation are obtained using directional differentiation or transdifferentiation of pluripotent stem cells to provide an adequate graft supply for clinical disease
treatment. Moreover, gene editing and other technologies can be used to treat genetic diseases that could not be treated previously. Therefore, the development of stem cells and regenerative medicine could provide new solutions for the health needs of the human population. However, regenerative medicine is still in its infancy and faces many problems and technical obstacles, such as ethical disputes, policy limitations, illiberal regulations, and numerous medical barriers.

2. The present situation in the fields of stem cell research and regenerative medicine in different countries

The United States Government regards regenerative medicine as a national strategy, and the American Association for Regenerative Medicine has proposed the “Regenerative Medicine Promotion Act of 2011”. The act seeks to promote government funding, and to boost and regulate the development of American regenerative medicine by “Advancing Tissue Science and Engineering: A Multi-Agency Strategic Plan” through legislation. The National Institutes of Health has invested heavily in supporting regenerative medicine research; in 2010 its investment in stem cell research reached $1,286 million. Moreover, private capital investment is estimated to be 10 times that of government funding.

At the same time, product approval standards in the United States are relatively high. The Food and Drug Administration (FDA) regulates the approval of regenerative medical products through biotechnology product licensing (BLA) and medical device listing applications (PMA). BLA is managed by the Biological Products Review and Research Center, which has three departments: the Cell and Gene Therapy Division; the Human Organization Department; and the Clinical, Pharmacological, and Toxicology Assessment Department.

Japan treated stem cell technology as an excellent opportunity to catch up with the United States and Europe in the life sciences and biotechnology; in 2000 it initiated the “Millennium Century Project” with stem cell engineering as the core technology of regenerative medicine as one of its four major priorities. In 2007, following Shinya Yamanaka’s breakthrough in induced pluripotent stem (iPS) cells, the Japanese Ministry of Education, Culture, Sports, Science, and Technology made the decision to invest 7 billion JPY to support research into regenerative medicine, and to build the Kyoto University iPS Cell Research Center. Japan's Ministry of Economy, Trade, and Industry is promoting the clinical transformation of regenerative medicine, and Japan's Institute of Physics and Chemistry (RIKEN) is an important force in Japanese stem cell research. Japan published a 10-year roadmap for iPS cell research in 2009, with four goals: the discovery of iPS cell initiation mechanisms; the creation and promotion of iPS cell research standards; the creation and identification of iPS cells from patients, with clinical research in favor of drug discovery, and the establishment of an iPS cell bank; and the promotion of research into regenerative medicine, including cell, tissue, and iPS cell differentiation in pre-clinical and clinical studies on tissues.

Professor Takashi Yamamoto cooperated with ReproCELL, TAKARA Bio, and Takeda, a Japanese pharmaceutical giant, to invest 10 billion JPY in subsequent drug research and regenerative medicine product development. Takeda will provide long-term financial support and research management advice, and will provide facilities at Japan's Fujisawa Shonan Research Center.

Britain has always recognized the importance of stem cell research; British scientists created the world's first mouse and rat embryonic stem cell lines, developed somatic cell nuclear transfer, created “Dolly” the sheep, and have made many other important advances with a solid foundation in research. They have promulgated the “British Stem Cell Plan”, and introduced a new strategy for regenerative medicine. Ahead of the United States, the United Kingdom was the first country to legalize cloning research in 2001, allowing scientists to create cloned embryos for stem cell research. In 2012, the British Technical Committee, the Medical Research Council (MRC), and the Biotechnology and Life Sciences Research Council (BBSRC) jointly launched the “UK Regenerative Medicine Development Strategy”, with clear objectives and implementation programs aimed at rapidly advancing life science research into clinical practices that benefit patients and the economy. The aim was to conduct scientific research at the existing research centers, and facilitate the early transformation of a regenerative medical research platform and the commercial transformation of cell therapy centers. There was an emphasis on the safety assessment of regenerative cells and quality control in manufacturing.
Germany prohibits embryonic stem cell cloning, but does permit the import of stem cells that have been obtained from embryos before May 2007. To a certain extent, it limits the development of German stem cells. At present, German research is mainly sponsored by the Max Planck Institutes, the Helmholtz Federation, the German Federal Ministry of Education and Research, and the German Science Foundation. Germany has been more active in the fields of neural stem cell research, tissue engineering, and the biological re-engineering of organs; for example, it has successfully developed skin and cartilage.

In China, the National 973 Program supported two stem cell-related projects in the Population and Reproductive Health Sector in 2001, marking the systemic layout of the foundation and transformation of research into stem cells in China. The following year, the special 863 program of “organization and organ engineering” was initiated, which concerns the layout of stem cells and regenerative medicine technology research. In 2005, stem cell research was included in the key areas of support through the national “Eleventh Five-Year Plan” outline. The “National Medium and Long-term Science and Technology Development Plan (2006–2020)” clearly sets out to vigorously develop biotechnology, and "stem cell-based tissue engineering technology” is listed as one of its five cutting-edge biotechnology directions. Stem cell research is an important part of developmental and reproductive research in the four major national scientific research programs. In 2010, work carried out by the national major scientific research program for stem cell research, born out of developmental and reproductive research, ranked as one of the six special areas of research. In 2011, the Chinese Academy of Sciences launched a stem cell and regenerative medicine research strategic pilot, relying on the Chinese Academy of Sciences stem cell and regenerative medicine research network to carry out research.

In 2015, the National Natural Science Foundation listed regenerative medicine research as a “major research program”. "China's public health science and technology road map 2050", published by the Chinese Academy of Science, and "China's long-term development of science and technology research report", published by The Chinese Academy of Engineering both point out that regenerative medicine is an important area for the future. In the "Chinese transformation medical road map", published by the Chinese Academy of Engineering, regenerative medicine and biological therapy are the main areas of interest. The industrialization of regenerative medicine is part of the "12th Five-Year Plan", and its development will have an important impact on economic growth. Scientists in the field of regenerative medicine discussed the philosophical problems, the scope of application, and the key breakthroughs and issues in the development of regenerative medicine in China at the Xiangshan Science Conferences held in 2005, 2010, and 2015. The organizers of the Xiangshan Conference also arranged a special seminar to discuss stem cell biology and cloning, gene therapy and biological material research and development strategies, and tissue engineering in regenerative medicine. Statistics were only collected during the "12th Five-Year Plan" period; China supported nearly 170 major stem cell-related scientific research projects, and financial support amounted to more than 2.4 billion.

In November 2015, the National Key Research and Development Program released six pilots of the "stem cells and transformation research" special set, comprising eight key topics including pluripotent stem cell dry maintenance, tissue stem cell acquisition and function determination, stem cell-based organ regeneration, stem cell transformation and applications, etc. The overall aim was to perform stem cell-based research related to product application development, product and technology transformation integration, and deployment of innovative change, and to translate that research into industrial standards. Basic research should be improved to make it more relevant to clinical applications and industrialization. The translation of research into stem cell applications is inevitable, and with China's appropriately qualified personnel and basic reserves, the time has come to implement research and apply the results.
3. Analysis of literature on stem cell research

3.1. Global stem cell research literature
The number and level of stem cell research papers reflects interest in stem cell research. Stem cell research literature included in the Web of Science database between 2000 and 2016 was investigated, and the results of the analysis were visualized using Thomson Data Analyzer (TDA) software. A global search of the Web of Science database revealed 319,672 items related to stem cell research in the literature. The time series of stem cell research, the national and regional distribution, and the main research and development institutions were investigated to produce a comprehensive evaluation.

Figure 1. Time distribution of global stem cell research literature
Figure 1 shows the development trend of stem cell literature from 2000 to 2016. For more than 15 years, the volume of stem cell research literature has been growing rapidly. Since 2010, the volume of literature published per year has exceeded 20,000 items. The volume of literature in 2014–2016 exceeded 30,000 per year, indicating that international research into stem cells is increasing.

Figure 2. International stem cell research literature by country or region
An analysis of the country/region distribution of international stem cell research literature on the Web of Science database is shown in Figure 2. The number of documents issued in the United States was 118,982, accounting for 37% of the total statistical literature—far ahead of other countries. China, Germany, Japan, and the United Kingdom ranked No. 2 to No. 5. Between 2000 and 2016, China issued 35,305 articles—more than Japan (26,486)—to become the second largest country in the field of stem cell research literature, but it is still far behind the United States in terms of volume.

3.2. Stem cell research literature published in China
The distribution of literature on domestic stem cell research in China is shown in Figure 3. Between 2000 and 2016, 35,305 domestic stem cell research articles were published. China has always attached importance to stem cell research, and has given its support to the "973" program, the "863" plan, the Natural Science Foundation, etc., which has rapidly advanced China's stem cell research effort. Since 2001, the volume of literature published in the field of domestic stem cells has grown linearly. A slight increase in 2011 may have been related to the suspension of stem cell research in China. The number of available stem cells in China rose rapidly between 2012 and 2016, and more than 6,000 stem cell research papers were published in 2015. These were mainly issued by the Chinese Academy of Sciences, followed by Shanghai Jiaotong University, and Sun Yat-sen University (Figure 4).

Figure 3. International stem cell research literature by country or region

Figure 4. International stem cell research literature by country or region
4. Conclusion
As China’s economy and people’s living standards continue to improve, there is an increasing demand for health- and biomedicine-related technology products. At the same time, China's aging population poses a serious problem, and the proportion of people aged 65 or more comprises 9.1% of the population. In 2011, the World Health Organization quantitatively assessed the global burden of disease and the impact of various diseases and injuries on human society, and noted that the most significant diseases that have an impact on human health are undergoing dramatic changes, some of which are caused by aging. The social burden of degenerative diseases accounts for 19% of the total burden of all diseases—more than cardiovascular disease (11%) and cancer (7%). Neurodegenerative disease is a neurological affliction characterized by the gradual loss of the structure and function of neurons, and ultimately leads to death. Owing to the complexity of the pathogenesis of these disease and the limitations of research methods, the treatment of these diseases remains problematic. The traditional medical means of treating these diseases have little effect, and are usually a temporary solution. These factors coupled with China's large population base mean that population aging is a serious consideration, so the establishment and development of new treatments is imperative. In addition to the clinical treatment of blood system diseases, there is also a huge demand for stem cell regeneration medicine. Hematopoietic stem cell transplantation is widely used in the treatment of hematological diseases, and is an effective means of curing leukemia, lymphoma, and other malignant diseases, but the shortage of hematopoietic stem cells seriously affects the extensive application of transplantation technology, and a large number of patients urgently require transplant donors. Moreover, clinical considerations such as the scarcity of rare blood type donors and blood pollution are also a major problem. In addition, access to safe and adequate blood products is also an issue related to national strategic security. Therefore, there is a national demand for a solution to the problem of insufficient hematopoietic stem cell transplantation. Regenerative medicine based on stem cells has brought the solution to these increasingly serious problems closer. The use of stem cells to produce cells that function in vitro to replace dead, aging, or diseased cells has great potential for the clinical treatment of various diseases.

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