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Industrial Development of Innovative Technology in Cell-Technology-Related Regenerative Medicine in China

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Abstract: The innovative medical technology industry of regenerative medicine has shown significant economic potential and development prospects both at home and abroad over the past decade. After describing the current situation of industrial development in the innovative technology of cell-technology-related regenerative medicine, we investigate, sort, and analyze related policies and regulations, management systems, and existing problems in the United States, the European Union, Japan, Australia, and other developed countries. Subsequently, we study the current development, governmental regulation policies, and management mechanism of this industry in China. Next, we analyze and summarize the industry development trends, characteristics, and existing problems. Finally, based on experts' advice and opinions on breaking through the bottleneck of industrial development, we suggest it is imperative for China to strive and develop the innovative technology industry of cell-technology-related regenerative medicine.

Keywords: regenerative medicine; stem cell; industrial development

1 Introduction

There is an increasing number of innovative medical technologies surfacing due to the rapid development of science and technology. However, some diseases caused by tissue or organ defects that seriously influence human health and some dysfunctional diseases such as tumors, trauma, aging, or genetic factors remain challenging current medical conditions. Notably, the development of regenerative medicine has improved the prospects for those diseases that seriously endanger human health and reduce the quality of life.

In China, regenerative medicine has been chosen as a major field in the medium- and long-term plans of national science and technology research and development. Specifically, a large number of basic research studies and clinical trials in cell-technology-related regenerative medicine have been carried out under three of the Chinese five-year plans. A number of published papers and patent applications have made breakthrough progress. Some of the research results reached an advanced international level and a number of stem cell therapy-based regenerative medicine programs have been implemented to cure clinical diseases. In other words, the technology and products industry for cell-technology-related regenerative medicine has shown large-scale application and development potential.

Regenerative medicine is an emerging discipline among medicine fields, but suffers from lack of suitable and systematic conversion policies and regulatory mechanisms in the process of transforming basic research into clinical practice. Therefore,

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for emphasizing clinical transformation from basic research and adjusting the layout of bio-medical industrialization, some institutions that do not have stem cell clinical transformation qualifications performed clinical applications of cell-technology-related therapies for profit, which causes irreparable damage to this emerging industry and severely hampers its sustainable development.

This study identifies the bottleneck problems that influence regenerative medicine development, putting forward strategic suggestions to promote industry development, and providing scientific evidence for government administrative departments to formulate a development strategy for regenerative medicine.

2 Regenerative medicine as a final solution to solve medical challenges

Numerous studies have proven that stem cells can be used for the treatment of many diseases or injuries, such as cardiovascular disease, autoimmune disease, diabetes, osteoporosis, severe burns, and spinal cord injury. According to incomplete statistics, nearly 1000 cases of stem cell transplantation have been performed abroad and most acquired a satisfactory clinical outcome [1]. At least four types of stem cell drugs (three types in South Korea, one in the United States) and five types of non-drug stem cell products (three types in the United States, one in Australia, one in Belgium) have been approved on the global market [2]. Despite a series of scientific problems and many technological challenges in this field, there is no doubt that regenerative medicine technology based on stem cells has shown application prospects abroad in the treatment of tissue and organ defects, degenerative disease, and a variety of the other intractable diseases. As such, it would be beneficial to protect human health and scientifically and reasonably speed up the clinical transformation of basic research in the field of regenerative medicine, as it may fundamentally change the pattern of the bio-pharmaceutical industry.

The systematic literature inquiry and related foreign personnel communication revealed that foreign countries have in place development programs and management processes for industrial investment in and development of regenerative medicine, which can be attributed mainly to the following reasons.

(1) From the scientific development perspective, cell therapy has become a competitive technology among various countries' governments and scientific and technological circles. In November 2004, the State of California approved a stem cell research and therapy initiative of California (also known as Bill 71), proposed to establish a regenerative medicine institute (CIRM), and claimed it would raise 3 billion USD over the next 10 years to support stem cell research [3].

(2) From the industrial policy perspective, typical countries attach great importance to cell-technology-related therapy and product clinical application management. Governments establish relatively complete policies and regulations, rules, and guidelines in this respect. The division of management agencies, departments, and responsibility is clear and specific. Research and development investment, related legislation, assessment, and supervision function in upstream, midstream, and downstream industrialization are gradually improving.

(3) From the industrial investment perspective, increasing attention is being paid to cell therapy industrialization. Typical developed countries (e.g., the United States, European Union member states, Japan, Australia) have increased economic support for research, clinical trials, and transformation of the regenerative medicine area, such as human cell therapy and tissue engineering technology. State and local governments and enterprises tend to be more reasonable investment. The upstream, midstream, and downstream industrialization achieves balanced development. For example, Pfizer Pharmaceutical Co. Ltd. offered a 3 million USD risk investment to EyeCyte Company in the United States in support of their stem cell research [4].

As China has the largest population worldwide, the number of patients with tissue and organ defects or dysfunctions caused by trauma, disease, genetic defect, and aging is also the largest worldwide [5]. There are around 300 000 patients waiting for liver transplantation each year in China, while only about 3000 have the opportunity to obtain it [6]. Further, the prevalence rate of adult diabetes was estimated at 11.6% [7] and there are a large number of common burn and scald patients each year. These patients cannot obtain effective treatment only through traditional medical approach. Cell-technology-related regenerative medicine treatments mainly consisting of stem cell therapy will thus become an important supplement of traditional therapies.

3 Current situation and existing problems in the industrial development of cell-technology-related regenerative medicine in China

3.1 Current industrial development of cell-technology-related regenerative medicine

The basic research and industrial development of cell-technology-related regenerative medicine developed rapidly in China. The number of published scientific papers and their citing frequency increased every year, a number of technologies obtained patents, and some clinical trials have made a breakthrough progress. The statistics of Chinese clinical trial registration centers show that 116 stem-cell-related clinical trials have been registered and declared. A number of stem cell therapies have also been applied in the clinical treatment of diseases. China accounted for two seats among the 62 global listed companies in the stem cell field [8]. Human cartilage regeneration technology led by academician Lu Shibi and skin regeneration technology led by academician Fu Xiaobing were highly acknowledged internationally.

However, there is a hidden danger in the Chinese stem cell market. *Xinmin Weekly* published a lengthy report titled "stem cell truth" in September 2007, where the cooperation between some local hospitals and technical companies was disclosed. More than 20 types of diseases were treated by stem cell therapy, such as cerebral palsy, cerebral infarction, and amyotrophic lateral sclerosis. The treated number of patients reached 1000, even attracting many foreign patients specifically coming to China for therapy [9]. This phenomenon caught the attention of the international scientific community. *Nature* also paid attention to the progress of Chinese stem cell therapy in 2012 and reported on it [10].

Relevant state administrative departments begun to create order in the chaos of the stem cell industry. For instance, the Ministry of Health issued *Notification of Promoting Self-Check Working in Terms of the Stem Cell Clinical Research and Application* on December 26, 2011. The National Health and Family Planning Commission decided to cancel third-class medical technology clinical application access approval in July 2015 but maintained the specifications and consolidation of cell-technology-related industries.

The current situation marks the coexistence of two important phenomena. On one hand, some institutions with rigorous scientific attitude and owning advanced technology strictly followed regulations but could not obtain legal policy support. As such, they reluctantly chose to register on the US clinical trial registration website in hope to obtain some support for their research. On the other hand, there are still some institutions that do not have stem cell clinical transformation qualifications and are ignoring the relevant provisions of the state, avoiding regulations, and, in the name of "clinical research," carrying out the expensive cell therapy applications.

3.2 Problem analysis for the industrial development of cell-technology-related regenerative medicine

Through extensive research and sorting, our research group agreed that the key issues that will affect the industrial development of cell-technology-related regenerative medicine include the following aspects.

3.2.1 Unclear subordinate regulatory relations

China released the first regulatory documents in this field in 1992, and after reviewing the entire regulatory process, we find that the key link—management of clinical trials and application of research—in the industrial chain faced the following problems: the government agencies and departments exhibit long-term cross-management, dispersal of functions, unclear responsibilities, and other defects.

3.2.2 Regulatory laws and regulations fail to form a system

By studying the 23 normative documents, including the *Administrative Measures of the Umbilical Cord Blood Hematopoietic Stem Cell Bank (trial implementation)* and *Limited Clinical Application of Medical Technology (2015 edition)* released by the Chinese government from 1999 to 2015, the current laws and regulations in terms of stem cell research, clinical application, and product regulation are lagging behind, incomplete, or even nonexistent. Meanwhile, the existing rules lack operability.

3.2.3 Government and enterprise investment versus industry downstream lack of consideration

The investment in cell-technology-related regenerative medicine industry mainly depends on the state, while enterprises account for a small proportion of investment and low enthusiasm, being unable to provide effective support for the development of the stem cell industry. The government has greatly increased spending for each link of the regenerative medicine industry to carry out basic research, while there is limited investment for supporting the clinical trials and clinical application research in regenerative medicine technologies and products. There is no doubt that it will affect the industry's sustainable development.

3.2.4 Lack of collaborations among the industry's main bodies

The development of the stem cell industry involves various main bodies. In the upstream industrial chain, the government departments include medical administration, science and education, laws and regulations, and supervision departments and professional associations, all failing to reconcile in terms of the policies, regulation formulation, and supervision aspects. The inner industrial chain has no effective means of translating basic research into clinical research and enterprise development into clinical application among the various departments and various organizations. Persisting in department duties and safeguarding local demand interests are bound to impede industry development.

4 Countermeasures and suggestions for promoting the industrial development of cell-technology-related regenerative medicine in China

To speed up the development pace of cell-technology-related regenerative medicine industry, remove the subjective and objective obstacles that seriously influence industry development, strengthen and perfect the top-level design of regenerative medicine development, and guarantee healthy development of the regenerative medicine industry, suggestions are presented in the following.

4.1 Relevant government departments for establishing and improving relevant laws and regulations system in regenerative medicine

4.1.1 Setting up independent government regulatory agencies

The government needs to set up independent regenerative

medicine technology management institutions in terms of the human cells-related technology or other technologies under the leadership of the national health administrative department. Under the hosting of these institutions, the experts and scholars from the medical administration, science and education, drug administration, medical ethics, scientific research, finance, and legislation will be called to establish related strategic decisions, carry out industry legislation, and exercise the recording and supervision responsibilities.

4.1.2 Establishing and improving relevant laws and regulations system in regenerative medicine

Formulating laws and regulations needs to conform to cell-technology-related regenerative medicine industry characteristics. Utilizing legal thinking and methods can thus provide a solid guarantee for the healthy development in cell-technology-related regenerative medicine industry and promote rapid development in regeneration medicine.

4.2 Establishing an innovative management system and mode in cell-technology-related regenerative medicine industry

4.2.1 Establishing a strict record and access system for innovative technologies and products of cell-technology-related regenerative medicine

The National Health and Family Planning Commission or the State Food and Drug Supervision and Administration Bureau is the main regulatory body and can set up an expert committee, namely the national advisory body, establish a review center, simplify the process, perform strict access system, or set up an authoritative third-party certification body. They should also strengthen supervision and the efforts to investigate illegal events.

4.2.2 Establishing grading, classification, and staging management system for the innovative technologies and products of cell-technology-related regenerative medicine

The innovative technologies and products of cell-technology-related regenerative medicine need to perform risk classification management. According to the various technology and product risk levels, for the qualification of medical institutions carrying out technology research and application, different requirements will be put forward, including hospital level, scientific research and clinical personnel proportion, or former related research results.

They could also perform classified management according to the different characteristics of cell technology. The application of autologous cells is managed by the National Health and Family Planning Commission in accordance with medical technology. Allogeneic cells and their derivatives are registered and managed by the State Food and Drug Supervision and Administration Bureau.

The various processing stages and usage stages will be staging the management according to the individualized progress of regenerative medicine development. For example, the State Food and Drug Supervision and Administration Bureau will be responsible for the regulation of cell preparation steps and product management, while the National Health and Family Planning Commission will be responsible for the clinical application management of medical implants technologies.

4.2.3 Establishing "the special disease with special treatment" policy in cell-technology-related regenerative medicine based on target-driven strategy

According to the target-driven concept, special laws and regulations for innovation medicine as well as operation specifications need to be introduced. When faced with diseases threatening patients' life or serious illness for which the current medical treatment cannot do anything a "the special disease with special treatment" policy will allow for the controlled use of technologies that have been validated in basic research or in small sample clinical trials.

4.2.4 Implementing the application or products demonstration mechanism of treatment technology in cell-technology-related regenerative medicine

Under the leadership of the national medical and health department, experts were gathered to identify innovative cell technologies and diseases. Multi-center clinical trials were carried out in an orderly manner under the close examination of regulatory authorities. Further, product technical standards and demonstration mechanisms were gradually improved from the first demonstrations.

4.3 Inspiring innovative thinking, promoting cell-technology-related regenerative medicine industry synergetic and leap-type development

4.3.1 Improving the risk management mechanism of cell-technology-related regenerative medicine

Risk-sharing mechanisms need to be established at all levels. Government supervision departments, expert committees, medical institutions, and enterprises will share responsibility and risks to prevent the situation in which government supervision departments independently share risks.

4.3.2 Formulating scientific and feasible cell-technology-related regenerative medicine technology specification, promoting integrated development of research, and application and industrialization in cell-technology-related regenerative medicine

Medical technological specification modules recognized by the expert group according to different diseases need to be identified. They will mainly consist of two parts:

(1) Preparation and storage management: such as cell source and collection specification, preparation and conservation specification, quality control specification, transportation specification, terminal-using specification, and stop and release specification in terms of supervision and follow-up.

(2) Clinical trials and application management: such as patient indications, contraindications, observation indexes, assessment methods, and treatment procedures.

Original industrialization studies with high-level scientific research results, support of joint research and development between state-owned and private organization, and integrated development of research, application, and industrialization in cell-technology-related regenerative medicine need to be encouraged.

4.3.3 Establishing state-level innovative technology implementation alliances in cell-technology-related regenerative medicine and using big data to promote industry development

There is also a need to take full advantage of the system superiority, set up industry cooperation mechanisms and form a national cell technology clinical trials and application research alliance. For example, medical institutions can jointly carry out multi-center clinical trials or unify the treatment indications and treatment paths. Further, experts in the industry from different scientific research areas, enterprises, clinical, management, or law and ethics need to jointly establish relevant technological standards.

Intra-industry data sharing and analysis mechanisms need to be proposed and different types of data related to technologies and products of cell-technology-related regenerative medicine collected from basic research, clinical transformation, and the process of clinical practice. Using big data to develop the intra-industry data sharing and analysis and further promote the healthy development of each link of this industry from basic research to clinical transformation is also important.

In conclusion, basic research is witnessing rapid development, and clinical applications are broad in regenerative medicine. As such, it is imperative to design corresponding policies and regulations suitable for Chinese regenerative medicine transformation, with reference to foreign experiences in clinical transformation and based on the characteristics of medical and pharmaceutical laws and regulations in China.

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