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Current Situation and Development Strategy of Bioengineering in Visual Science and Ophthalmology in China

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Abstract: With the largest number of blind people in the world, China is home to more than 12 million people who are blind. The most promising research direction in the bioengineering field for the treatment of blindness involves searching for bioengineering materials to restore visual function, particularly by using stem cell and biochip technology. This paper introduces the development situation of bioengineering research in ophthalmology and visual science in China, and it analyzes the main problems facing the current bioengineering researchers in the field of corneal and retinal diseases. We also present strategies and recommendations for research and development directions, the approval system, achievement translation, and the construction of a research platform, based on the current situation in China

Keywords: ophthalmology and visual science; bioengineering; current situation; strategy

1 Introduction

According to the World Health Organization (WHO) report, cancer and cardiovascular and eye diseases are the leading causes of reduced quality of life in humans. China has the largest number of blind people in the world: about 12 million Chinese are blind, which accounts for 18% of the global total. Approximately 450 000 people become blind each year in China, with one new blind patient almost every minute; blindness poses a heavy burden on individuals, families, and the society [1]. The major causes of blindness are eye diseases, including cataracts, keratopathy, ocular trauma, glaucoma, age-related macular degeneration, diabetic retinopathy, and retinal pigment degeneration. The treatment of various eye diseases costs the United States about 60 billion USD, and it costs the United Kingdom up to 8.8 billion pounds annually. Although China does not have statistics, its population is approximately four times as large as that of the United States; therefore, injuries and losses due to eye diseases are immeasurable. The Chinese government has signed into the "VISION 2020—The Right to Sight" initiative that was launched by WHO, which promises to eliminate avoidable blindness in China by 2020. The government has made tremendous progress in the prevention of blindness associated with cataracts. However, there remains a gap between China and the European and American countries with respect to the treatment of corneal, retinal, and optic nerve diseases.

The research focus in blinding diseases is shifting based on the changes in the national conditions and the disease prevalence in different countries. Neurological blinding diseases, such as diabetic retinopathy, age-related macular degeneration, and retinal pigment degeneration, are more important in Europe and the United States. Although drugs and surgery can delay disease development, retinal neuronal cell injury eventually leads to irreversible damage to vision. In terms of corneal diseases, China

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is facing a problem that is different from what other countries are facing. The limited availability of donated corneas is the key hindrance for the recovery of corneal blindness. The developments of bioengineered materials, especially those using stem cell and biochip technology, seems to be promising areas, and it has become a hot focus for research.

2 Current situation of ophthalmology and visual science bioengineering in China

2.1 Cornea

Corneal diseases are one of the leading causes of blindness in China. Results of a survey in 10 provinces in China organized by Professor Xie Lixin showed that there were about 3.015 million people with corneal blindness; 80% of these patients can recover their vision through corneal transplantation. However, a severe shortage of donor corneas in China seriously limits the transplantation such that less than 10 000 patients can undergo the operation, and this cannot meet the clinical needs [2–3]. Therefore, the development of tissue-engineered corneas has a promising prospect for clinical application. Nowadays, the alternative materials for keratoprostheses, such as tissue-engineered corneas and bioactive amnion membranes, are commonly used clinically. In addition, the research in tissue-engineered corneal epithelium and stroma has made remarkable progress in recent years [4].

2.1.1 Keratoprosthesis

A keratoprosthesis (KPros) is a special refractive apparatus made of alloplasm-shaping material that is designed to replace the turbid corneal tissue and achieve a certain vision. In 1947, Stone was the first person to use polymethyl methacrylate (PMMA) to make KPros; this breakthrough greatly promoted the development of KPros. The recent progress in Kpros technology has mainly focused in the innovations in material selection, processing and design methods. Currently, two types of Kpros, AlphaCor and Dohlman-Doane (Boston), are certified by the United States Food and Drug Administration (FDA) for clinical application. Boston, which is currently one of the most widely used and effective Kproses, was approved by FDA in 1992. AlphaCor was approved in 2003. China has no independently developed KPros products approved for clinical use.

2.1.2 Tissue-engineered cornea

The whole tissue-engineered cornea contains the epithelium, stroma, and endothelium. Early research showed that the immortalized human corneal epithelial cells, stromal cells, and endothelial cells could be used to construct all layers of the tissue-engineered corneal substitutes using the scaffold of glutaraldehyde cross-linked with collagen materials. The transparency and response to external stimuli of these tissue-engineered cornea were close to those of the normal cornea, but there have been no reports of their clinical studies [5]. Because of the uncertainty of the safety of immortalized cells and of the long-term effect of the scaffold materials, further studies are still needed in the development and application of the whole tissue-engineered cornea.

Tissue-engineered corneal epithelium requires suitable sources of epithelial stem cells and carrier materials. Nowadays, the treatment of limbal stem cell deficiency by using in vitro cultured limbal and oral mucosa epithelial cell sheets has been approved for clinical application in Japan, Italy, South Korea, and China Taiwan, and it has been confirmed to have significant beneficial short-term and long-term effects [6–9]. Research progress in the development of corneal epithelial cells from other stem cells may provide new stem cell sources for the construction of tissue-engineered corneal epithelium [10].

Corneal stroma, which accounts for 90% of the thickness of the cornea, is the main structural basis for its transparency. The development of a stromal substitute with a natural transparency is one of the key points in the research of tissue-engineered cornea. Present studies focus on removing the cellular and antigen components while maintaining the composition, structure, and transparency of corneal stroma. The first product of acellular corneal stroma, "Acornea," was approved by the CFDA in April 2015; this was the first stromal substitute in the world that completed the clinical trials [11]. Similar products have subsequently been approved or are undergoing clinical trials, but their long-term safety and effectiveness after clinical application needs further observation [12].

Human corneal endothelium exhibits limited regeneration in vivo and amplification in vitro; acquiring an adequate amount of functional source cells for corneal endothelium is the most difficult challenge in the construction of tissue-engineered cornea. In recent years, researchers have not only optimized the amplification methods for adult human corneal endothelial cells in vitro, but also induced the generation of functional corneal endothelial cells from the embryonic stem cells or other adult stem cells. However, the former is difficult to realize in an industrial scale; the safety and effectiveness of the latter need to be clarified. Meanwhile, there is no specific marker to identify corneal endothelial cells; the identification and functional evaluation, especially for the differentiated corneal endothelial cells, remains unsolved.

2.1.3 Bioactive amnion membrane

An amniotic membrane is one of the most widely used biological materials in the treatment of corneal diseases. The products of bioactive amnion membranes have been used in clinical treatment in United States. However, there are no listed products in China. Only one company developed a freezing-dried amniotic membrane, which was inferior to the bioactive amnion membrane.

2.2 Retina

Pharmacotherapy cannot help blind patients with retinitis pigmentosa, macular degeneration, or severe ocular trauma whose retinas or optical nerves have been permanently damaged. Considerable efforts have been directed toward development of visual prosthetic devices, and a number of publications have indicated that significant progress has been achieved [13]. Several different approaches are currently being developed to restore vision in the blind. The visual pathway extends from photoreceptors in the retina to the visual cortex in the brain. Since loss of vision can results from the alteration of any element of the visual pathway—from the eye to the visual cortex in the brain—the approaches currently being exploited as visual prostheses have been classified as cortical, optic nerve, or retinal implants depending on their position in the visual pathway. Each one of these approaches has its own attraction [14–16].

2.2.1 Cortical visual prosthesis

Starting in the 1960s, there has been notable research in the development of a visual prostheses that stimulate the visual cortex. Since then, the best result that has been reported is a case of a traumatically blind volunteer who could routinely recognize a 6 inch square "tumbling E" at five feet, which corresponds to a visual acuity of approximately 20/120, after the implantation of the cortex prosthesis. He has retained the implant for more than 20 years without infection or other problems [13]. But the progress has been hampered by its inherent disadvantages, such as the difficulty in the selection of stimulation parameters and the induction of epilepsy. The rather high surgical risk that a patient with an otherwise healthy brain needs to take is another reason why the cortical approach has not been welcomed as compared with other approaches. Consequently, no large sample clinical trial has been conducted to date despite a large number of scientists who have intended to do so.

2.2.2 Optic nerve prosthesis

The optic nerve serves as a pathway for image information delivered from the retina to the brain. An optical nerve prosthesis is intended to produce visual perception by stimulating the optic nerve using a special system. Clinically, only 3 cases in the world have been reported widely by Belgian scientists. Three profoundly blind persons with retinitis pigmentosa (RP) reported visual perception after placement of an optical nerve stimulator [17,18]. These preliminary results displayed the potential feasibility of optical nerve prostheses. Professor Ren Qiushi, chief scientist of "Project 973" in China, and his team has conducted some research in this field. They have made significant progress in many aspects, such as visual information processing, image capturing and processing, assessment of the interaction mechanism between multi-electrode array and optical nerve, development of the multi-electrode array and its modifications, as well as understanding of the related basic medical issues. Animal experiments have also been conducted. A focal response was recorded on the cortex successfully while the optical nerve was stimulated through the implanted electrode, which confirmed that the implanted prosthesis can induce a visual experience [19]. Professor Ren Qiushi and his team are planning to find some volunteers whose retinas and optical nerves are partially preserved to conduct clinical trial in small sample size. Hopefully, the prosthesis can make blind people experience the sensation of light, movement, and a silhouette, and it can enable them to recognize simple words.

2.2.3 Retinal prosthesis

Retinal prosthesis is the most intensively investigated technology, and it is believed to be most effective in restoring damaged vision when compared to cortical and optical nerve prosthesis [20–22].

(1) Retina chips

Argus II is now commercially available in the United States and some European countries. It was developed by The Artificial Retina Team, which is composed of 6 state laboratories, 4 universities, and a private company. In the spring of 2011, after more than two decades of research and development in the field of visual prosthesis, Argus II was approved for clinical and commercial use in Switzerland, France, and the United Kingdom. Second Sight Company launched the product later the same year. Three major US government funding agencies (National Eye Institute, Department of Energy, and National Science Foundation) have supported the work. The clinical trial involved 30 subjects who were totally blind due to RP, and it spanned 10 sites in 4 countries. The preliminary results showed that the Argus II system provided some functional vision to these blind subjects [23]. Another commercially available retinal prosthesis named Alpha-IMS was launched in Germany in 2013. Currently only some preliminary research is being carried out in the development of retinal chips in China. We have a lot of difficulties to overcome in catching up with the western world in this aspect.

(2) Bioengineering retina

Bioengineering retina is a newly developed technique in the attempt to restore vision in blind subjects; the technology is based on the rapid progress in stem cell technology. Bioengineered retina is composed of seed cells and scaffolds. With respect to the stem cell technology of the retina, China is still in the beginning stage. Professor Yin Zhengqin, Professor Ge Jian, and Professor Xu Guotong have conducted a great deal of research and achieved some original innovations; they have demonstrated the possibility of using stem cell transplantation in visual function restoration. A number of clinical trials are currently underway in foreign countries to use stem cells in the treatment of atrophic age-related macular degeneration, Stargardt's disease, retinal pigment epithelial degeneration, and diabetic retinopathy [24].

2.2.4 Protein biological agents

Currently, biological agents are mainly used in neovascular retinal disease. Anti-neovascular biological agents are classified into two types based on their molecular structure: monoantibodies (ranibizumab and bevacizumab) and fusion proteins (aflibercept and conbercept). They are all commercially available internationally and domestically. Among them, Conbercept ophthalmic injection (Lumitin, Chengdu Kanghong Pharmaceutical Group Co., Ltd.) was approved for the treatment of neovascular AMD by the China Food and Drug Administration (CFDA). Conbercept has exhibited excellent therapeutic effects. Moreover, Conbercept is the first national Class I original new biological drug for which the company holds independent intellectual property rights.

2.3 Lens

In some mammals, a new lens can be regenerated after its removal if the capsule remains [25]. It is generally believed that the remaining epithelial lens cells in the capsule are the source of lens regeneration. The cooperative research between Zhongshan Ophthalmic Center, Sun Yat-Sen University and University of California confirmed there can be functional lens regeneration by stimulating the endogenous stem cells; further tests were conducted in infants with congenital cataract in infants [26]. However, the regeneration of the mammalian lens is not a simple repetition of the development of the lens; the problem of the incidence of a posterior cataract needs to be solved.

3 Existing problems in the bioengineering research in ophthalmology and visual science

3.1 Cornea

Acellular corneal stroma products have obtained the registration certificate of medical devices from CFDA. With regard to the bioengineered corneal products containing cells, particularly bioengineered corneal epithelium, close collaboration is needed among companies, research institutes, and hospitals. Moreover, the availability of artificial cornea is still dependent on importation because of the lack of products with independent intellectual property rights for clinical use in China.

3.2 Retina

Research on optic nerve prosthesis has attained the advanced stage that is seen at the international level; however, many problems still need to be solved in the clinical application of these prostheses. With regard to the bioengineered retina, breakthroughs and original innovations are mostly possible in preclinical research. Clinical trials in China fall behind those in the developed countries.

4 Strategies for the bioengineering research of ophthalmology and visual science

4.1 R&D in accordance with national conditions

Take the bioengineered cornea for example. The rate of corneal donation is high in developed countries. In the United States, 1/3 of the donated corneas are used for clinical transplantation, 1/3 for laboratory research, and 1/3 for export to other countries. Although corneal donation in China is gradually increasing and the donor corneal utilization rate is also improving, most patients with corneal blindness do not have an opportunity to undergo keratoplasty. Use of bioengineered corneas is the main approach to solve the shortage in donor corneas. Bioengineered corneal epithelium and stroma are most likely to be applied in clinical practice, and they are associated with a lower risk compared to other tissues. It is suggested that the Ministry of Science and Technology and the National Natural Science Foundation of China should provide more funding support and policy guidance to alleviate the serious shortage of donor corneas in China.

4.2 Development of national approval system

At present, the basic research on stem cells and tissue engineering in China is at the same level as that in other countries, but the transformation and application of the relevant research results are apparently lagging. A national policy is important in the management of stem cell transplantation. However, unclear legal and policy-related regulations at the national level may impact on the development of ophthalmic products related to stem cells and tissue engineering. It is worth noting that the government has been trying to formulate policies to guide clinical trials of stem cells and issue a series of regulations and norms. Owing to the rigorous requirements for basic and clinical technology, it is necessary to establish specific stem cell clinical trial bases. Although the third-class medical technology has alleviated the disadvantages of product conversion to a certain extent, the scale of its application and future transformation cannot be compared with that of product conversion. It is suggested that the health authorities and the State Food and Drug Administration should formulate and issue standardized approval policies and systems as soon as possible, and they should avoid imitating the foreign systems.

4.3 Positive policy for achievement transformation

The bioengineering research in ophthalmology and visual science mostly depends on the state funding, and most of the research results only end in the laboratory and publications; they are not translated into industrial and clinical use. There are many reasons for this. The current system of achievement evaluation

limits the progress of industrialization and clinical application in some degree. For example, the number of published papers is often emphasized in the "973" programs, but the downstream process is not evaluated. The 5-year research cycle is too hasty for the transformation. On the other hand, the related state policy available is not yet positive enough, which hinders the enthusiasm of researchers. Japan's experience in the industrialization of stem cells deserves to be borrowed. Business companies partly participate in the research and development of the product, and this is followed by the investment of a venture capital, which helps speed up the industrialization. It is recommended that the science and technology authorities should formulate and issue standardized approval policies and regulations as early as possible.

4.4 Establishment of the national engineering technology research platform

It suggested that the Ministry of Science and Technology should organize a national engineering technology research and development platform of ophthalmology and visual science that can meet the need of domestic patients and medical institutions; this platform should focus on resource integration and translation medicine and development of tissue engineering ophthalmic products with independent intellectual property rights. Through the promotion of new engineering products and innovative techniques, the rate of avoidable blindness can be reduced, more blind patients may recover their vision, and China's academic position in the international arena of preventable blindness research can be further enhanced.

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