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Review



Ning-li Wang，*professor. He is the vice president of Beijing Tongren Hospital，director of Beijing Tongren Eye Center，president of Ophthalmology Academy of Capital Medical University. He has done many pioneering research works in the area of glaucoma：proposed the new classification system of primary angle-closure glaucoma based on the mechanism of angle-closure；proposed the new theories that the high Trans-Lamina Cribrosa Pressure difference can cause optic nerve damage in glaucoma and conduct a series of studies to verify；performed the study on the mechanism of glaucomatous posterior retinal neuron damage，and proposed the concept that glaucoma is a disorder of whole visual pathway；discovered the pathogenesis of exfoliation syndrome in Chinese population is different from that in European and American people，and made the diagnostic criteria of exfoliation syndrome for Chinese people；designed and spearheaded a number of new ophthalmic technologies.*

Editorial note：*Prof Ning-li Wang et al. "The application of translational medicine in ophthalmology" explain the advantage for the research and application of translational medicine in ophthalmology. The paper provides an overview from the respects of genetics，stem cell，adaptive optics and artificial vision，with particular examples of the application of melanopsin and channelopsin－2 as well as anti-VEGF in the clinical practice. The author recommends that the transform of the needs of patients or clinical practice into basic clinical research questions，and further summarizes the needs of raising research questions from clinical practice in order to adjust research emphasis to answer the real-time and real-life clinical problems，and eventually to improve the diagnosis，treatment and prevention of diseases.*

The application of translational medicine in ophthalmology

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Abstract　Similar to other disciplines，there are many diseases have no effective treatment in ophthalmology，so we need promote the clinical applications of basic scientific research. Recently，many translational researches in ophthalmology have gained great achievement，and provided great examples for other subjects，including studies on treatment of angiogenesis by anti-VEGF drugs and degenerative blinding diseases by stem cell and neurotrophic factors，study on gene therapy of Leber congenital amaurosis and artificial vision research，etc.

Key words　translational medicine，ophthalmology，basic research，clinical application

Eye is the most important sensory organ of human body，which is responsible for receiving about 82% external information into brain for signal integration. The ocular diseases causing blindness have direct impacts on human visual functions，resulting in blindness or severe vision loss. The World Health Organization（WHO）reported that around the world as of 2009，314 million people have some forms of visual impairment，with 45 million of those being blind. Common ocular diseases causing blindness can be divided into two main categories：optical eye disease and neurovascular

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eye disease. Of these, optical eye disease can be controlled with the available medical interventions; whereas neurovascular eye disease is becoming a major cause of irreversible blindness due to a lack of effective treatment options. Therefore, there is an urgent need for novel and effective treatment approaches or technologies for people with such diseases.

In recent years, the rapid advance in basic scientific research sheds light on the treatment of these diseases, which mainly includes gene therapy, stem cell replacement therapy, sustained release drug delivery technology, artificial organ reconstruction technology and etc. At present, however, most studies are still in the early phase of animal experiments, with few of them finding their way to clinical use. In light of such a considerable gap between basic research and clinical application, translational medicine becomes a "navigator" in addressing these hard-to-treat diseases.

1 Translational medicine and its development

Translational medicine is a new concept emerging in the international field of healthcare in recent years, along with the rapid development in genomics, proteomics, bioinformatics and other disciplines. Its core target lies in rapid and effective translation of basic research findings into theories, technologies, therapies and medicines for clinical use, so as to build up a bridge from bench to bedside (B2B)[1]. The main purpose of translational medicine is to break the inherent barriers between basic research and clinical medicine, to realize rapid translation of basic research findings into new treatment approaches for clinical practice and medical decisions, and thereby foster the development in clinical medicine and finally offer direct benefits of technologies to our patients. Thus, translational medicine plays an important role in guiding and supporting the development in medical sciences.

In 1992, the American journal *Science* put forward for the first time the concept of "B2B"[2]; in 1996, the term "Translational Medicine" first appeared in *The Lancet*[3]; in 2003, the former director of American National Institute of Health (NIH) Elias Zerhouni published in *Science* his Roadmap for Medical Research, which has facilitated the rapid development of translational medicine[4]. In 2005, Wyeth Pharmaceuticals, four Scottish universities, Scotland's National Health Service, and Scottish Enterprise jointly created the world's first Translational Medicine Research Collaboration (TMRC). Now, American NIH has launched 60 translational medicine research centers and funded these centers with a budget of $ 500 million per year; in UK, a total of £450 million has been invested to fund translational medicine research over five years; and European Commission's budget for such research has totaled 6 billion[5]. As for China, there has been a growing interest in translational medicine research since 2009, and many translational medicine research centers have been launched in Chinese Academy of Engineering, Academy of Medical Sciences, Academy of Military Sciences and some major universities.

2 Translational medicine in ophthalmology

Due to the unique physiological and anatomical characteristics of eyes, ophthalmology has been a pioneer in the utilization of translational medicine research. Firstly, owing to structures like blood-retina barrier, eye is a relatively independent organ, and delivery of drugs, foreign genes or cells is less likely to produce immune response, indicating some degree of immune privilege. Secondly, the volume of eyeball tissue is relatively small, with a constant and small number of cells, and thus the required dosage of drugs, genes or cells for treatment is relatively low, which may be associated with fewer side effects. Thirdly, as an external organ of human body, eye is relatively easy to operate on; since the dioptric media of eyes is transparent, most procedures on eye tissues are visible (or visible via minimally invasive methods). Moreover, the visual functions and the physiological characteristics of eyes are relatively easy to observe and analyze; most structures and tissues of eyes can be directly observed by using slit lamp microscope, ultrasonic device, fundus camera and other equipments; real-time recording and objective evaluation of the changes in visual functions are also feasible by using visual electrophysiology, fundus fluorescein angiography, optical coherence tomography (OCT) and other techniques. Finally, because each person has a pair of eyes, the unique feature of self-comparability of eyes makes it possible to assess the efficacy of therapies in clinical studies.

2.1 Translational research of genetics in ophthalmology

The completion of the human genome project and the widespread application of relevant genetic techniques have led to a new revolution in the understanding of the nature of diseases, and have also offered a new hope for molecular typing, biological diagnosis and gene therapy of diseases.

With an increasingly comprehensive understanding of eye diseases, more and more pathogenic genes are being discovered. To date, a total of 192 pathogenic genes and thousands of mutation loci associated with hereditary retinal diseases have been identified[6]. Chinese researchers have made some progress in studies of families with con-

genital cataract as well as genetic studies of Leber congenital amaurosis (LCA), retinitis pigmentosa, age-related macular degeneration, glaucoma, exfoliation syndrome and etc[7-10], which has laid a theoretical basis for genetic diagnosis and treatment of eye diseases in Chinese population.

A number of clinical trials on gene therapies for retinal diseases have been reported in recent years, including retinitis pigmentosa, age-related macular degeneration, retinoschisis and color blindness. Of these, the gene therapy for LCA has been regarded as a good example in the field of translational medicine research.

LCA is considered as one of the most serious hereditary retinal diseases, however, there are currently no effective treatments available, and new therapeutic techniques and methods are urgently needed. Along with the widespread application of genetic studies, 14 pathogenic genes associated with LCA have been discovered[11]. A study of basic medicine indicated that of these genes, *RPE*65 was the only gene that conferred retinal pigment epithelium (RPE) -specific expression, and the protein it encoded involved in the metabolic circulation of optical signals[12]. And then, researchers designed a vector-based technology to deliver *RPE*65 into the host RPE cells and let its functions perform, which has led to some degree of visual recovery in LCA models of both small and big animals[13,14]. In 2008, American and British ophthalmologists successfully administered a low-dose gene therapy for LCA patients in phase I clinical trials, and significant improvements in visual acuity were observed in patients who received the gene therapy; the results were published in *New England Journal of Medicine*, these novel findings ushered in a new era of gene therapies for gene-related eye diseases[15,16]. Now, an international working group on LCA gene therapy has been launched to conduct multi-center and large-scale clinical trials, and many Chinese ophthalmology centers are actively applying for participation. But translational medicine research did not stop here. In clinical trials, researchers found that the expression of the inserted genes was not as efficient as expected, and then they went to seek better ways to improve the efficiency and stability of gene expression, including vector reconstruction techniques and others[17], so as to further promote clinical translation.

Thus, the research on LCA gene therapy reveals a two-way road of translational medicine: first a question is raised from clinical practice and answered by relevant basic studies; then the findings of the basic studies are transformed for clinical application; after that, further questions may be raised from clinical practice and then back to basic studies again, with an ultimate goal of solving all questions in the end.

2.2 Translational research of stem cell in ophthalmology

Due to its potentials of "infinite" proliferation and multi-directional differentiation, stem cell has brought new hope for tissue repair and regeneration as well as the treatment of major diseases, including cardiovascular disease, diabetes, neurological disease, liver disease and etc. However, although basic studies on stem cell have been increasingly developed, very few of the initial " ideas" actually make it to clinical trials. Most of the studies that have advanced into human testing are related to the treatment of eye diseases, which may help to direct the translational application of stem cells in other specialties.

In recent years, induction and differentiation of various stem cells into ocular cells have been tried in experimental studies, and photoreceptor cells, RPE, retinal ganglion cells and other major neurons have been successfully obtained. In the meantime, cell transplantation experiments on several kinds of animal models with eye diseases have been conducted, with a detailed assessment of long-term safety and effectiveness[18]. Finally, in October 2010, a research team on prevention of blindness of the University College London obtained an approval to conduct clinical trials in patients with macular degeneration; by using tissue engineering techniques, the differentiated human embryonic stem cells (ESC) were attached to poly fiber membrane to build RPE membrane[19]. In November 2010, an American company Advanced Cell Technology Inc. was granted a approval to conduct a phase I clinical trial on stem cell (ESC-derived RPE cell) transplantation in the treatment of Stargardt disease. In this trial, 12 patients were recruited to receive the novel treatment[20], which was the second clinical trial on ESC therapy approved by US Food and Drug Administration (FDA). This year, the company also received a clinical trial approval to treat macular degeneration with stem cell transplantation[21], which further expanded the indications of stem cell therapy in treating eye diseases. Moreover, the Southwest Hospital of The Third Military Medical University has also conducted a clinical trial of treating retinitis pigmentosa with human embryonic photosensory precursor cell transplantation. These trials are currently ongoing and the results have not yet been released.

The studies presented above have accelerated the clinical translation and application of stem cell therapy, and ophthalmology may represent a real breakthrough of stem cell entering into clinical practice. This will certainly bring about a revolution in medical science or even the

entire pharmaceutical industry, provide a reference for treating all other diseases that are viewed as "incurable disease", and thus impose a profound impact on human health.

2.3 Translation of basic research findings into clinical application in ophthalmology

The application of translational medicine requires both clinical application specialists who pay constant attention to basic research findings, and basic research scholars who are well aware of the clinical demands. Particularly, the "top talents" with a combination title of clinical application specialist and basic research scholar are most preferable. Thanks to such a group of prominent experts, a great number of research findings of basic medical science are being translated into clinical application in ophthalmology, entering into the "B2B" pathway directly.

2.3.1 Application of melanopsin and channelopsin-2

Recent studies identified a type of intrinsically photoreceptive ganglion cells across the entire retina, whose primary role were to regulate non-image-forming visual functions, such as circadian rhythm and pupillary light reflex. These findings were named by the leading magazine *Science* as one of the top ten scientific breakthroughs of 2002[22,23]. This type of cells contains a new opsin-melanopsin, a photopigment which activates endogenous light sensitivity. We and other international investigators have done a lot of studies regarding the function of these cells and their changes in patients with eye diseases[24].

In 2008, based on the rationale of gene therapy, researchers inserted melanopsin gene into the third-order retinal neurons-ganglion cells in mice lacking rods and cones, which restored the photoperceptivity of these blind mice whose leading cause of blindness was the death of the primary neurons (rods and cones)[25]. This trial provided a basis for the application of melanopsin in clinical treatment and confirmed that even though the primary neurons (rods and cones) are dead, the visual functions of patients could be regained by reconstructing the remaining second and/or third-order neurons.

The same strategy also facilitated the application of channelopsin-2 gene. Researchers inserted the vision forming gene channelopsin-2, a gene found in green algae, into the ganglion cells of blind rats whose leading cause of blindness was the death of photoreceptor cells, which successfully promoted the repair of the rats' visual functions[26]. Now encouraging progresses have been made in primate models[27].

Such a strategy has broken away from the traditional pattern in which a specific pathogenic gene must be targeted in gene therapy. It seems that this therapeutic strategy is universally applicable, which is of great clinical and commercial value, especially for those patients with advanced retinopathy or significant apoptosis of rods and cones.

2.3.2 Application of anti-VEGF

The final common pathological process of visual loss caused by many ocular fundus diseases is retinal and/or choroidal neovascularization. Basic medical studies revealed that vascular endothelial growth factor (VEGF) was one of the main regulatory molecules involved in the process of vascularization and angiogenesis[28]. Afterwards, researchers confirmed that suppressing the expression of VEGF could effectively inhibit neovascularization in cell and animal experiments[29]. Consequently, anti-VEGF drugs were successfully developed, which have restored the visual functions and improved the quality of life of a large number of patients with relevant disorders. Currently, there are two FDA-approved drugs available for clinical use, i. e. Bevacizumab (Avastin) and Ranibizumab (Lucentis). The main mechanism of anti-neovascularization of these drugs involves preventing the binding of VEGF to VEGFR1 and VEGFR2 receptors on the surface of endothelial cells, thus disabling the bioactivity of endogenous VEGF, inhibiting the mitosis of endothelial cells, reducing the permeability of blood vessels and then inhibiting neovascularization[30]. In China, many clinical studies have demonstrated that these agents are effective in the treatment of neovascularization in patients with macular degeneration, macular edema in patients with diabetic retinopathy, neovascularization of the iris and etc [31,33]. Researchers from the Ophthalmology Department of West China Hospital of Sichuan University conducted a clinical trial on full-length humanized antibody-like fusion protein (KH902, an anti-VEGF agent, with an independent intellectual property right in China) in patients with wet macular degeneration. The results of the trial showed that more than 95% of the treated patients achieved an improvement in visual acuity. Presently KH902 owns 7 international patents and has entered into late-stage clinical trials [34]. Studies on VEGF have also been regarded as one of the most successful models of translational medicine in ophthalmology.

2.3.3 Application of CNTF

Currently, there is still no effective treatment available for retinal degenerative disease. A wide range of approaches have been tried, of which the neuroprotective effects of neurotrophic factors have drawn lots of concern. Among the numerous neurotrophic factors, studies on ciliary neurotrophic factor (CNTF) well reflect the strategies of translational medicine.

A basic study found that retinal neurogliocyte could secrete an endogenous neural factor-CNTF, which might

play a protective role for retinal neurons via several pathways[35]. And then, researchers further carried out a study to confirm the safety and protective effects of CNTF in animal models of photoreceptor cell apoptosis, and results showed that animals in the treatment group had an increased thicknesses of the outer nuclear layer and decreased damage of photoreceptor cells, which laid a foundation for CNTF entering into clinical practice[36]. In a subsequent clinical trial, however, researchers found that the traditional administration routes (intravitreal injection or subretinal injection) were really invasive and repeated procedures were always required, which could result in decreased tolerance of patients, unstable therapeutic effects, and probably a series of complications as well [37]. Therefore, by integrating tissue engineering with cell engineering techniques, the US company Neurotech developed an encapsulated cell technology (ECT) and manufactured a sustained-release delivery system NT-501 for continuous and controllable release of CNTF, which further promoted the clinical application of CNTF [38]. A pilot clinical trial showed that NT -501 could produce a biological effect on patients with retinitis pigmentosa and macular degeneration, mainly manifested as an increased thickness of the retinal photoreceptor layer, which reflected the neuroprotective effect of the system. And a phase II clinical trial is ongoing now[39].

2.4 Translational research of adaptive cptics

Adaptive optics (AO) is a servo system that utilizes deformable lens to adjust atmospheric turbulence in real time, which contains deformable lens, wavefront sensor and effective control elements. The concept of AO was first brought up by H. W. Babcock[40] in 1953, and then it has been gradually applied in astronomy and military affairs, such as astronomical adaptive optics telescope, laser guide star adaptive optics system, large space adaptive optics telescope, adaptive optics resonant cavity, laser nuclear fusion adaptive optics system, space adaptive laser communication system and etc.

Since the1990s, the technique of AO has been applied for civilian use. In vivo human cone cells were successfully identified with AO technique by Professor David R. Williams and his colleagues of Rochester University of US in 1997. The visual quality of human eyes was also significantly improved after aberrational correction [41]. In recent years, the application of AO in ophthalmology has been further expanded. For example, adaptive optics OCT and adaptive optics fundus camera can monitor human visual cells, gangliocytes and capillaries in vivo, which may help early diagnosis and treatment of various eye disorders so as to eliminate diseases at the initial stage [42,43].

In 2006, professor Jiang Wenhan from the Institute of Optics & Electronics of Chinese Academy of Science, a pioneer in the research of AO in China, and professor WANG Ningli et al. from Beijing TongRen Eye Center undertook the Chinese National 863 Project of "Manufacturing technology and equipment research on implantable and individualized higher-order aberration corrective lens for human eyes". They have successfully developed an AO-based individualized higher-order aberration evaluation and correction system for human eyes and a high precision measuring instrumentation for higher-order aberration corrective lens, which own independent intellectual property rights in China. This breakthrough provides a strong hardware support for real individualization of aberration correction[44,45]. It is expected that this will lead to mass production and clinical application of individualized higher-order aberration corrective lens for human eyes through industrialization and commercialization.

2.5 Translational research of artificial vision

Artificial vision often refers to a visual prosthesis made of microelectrode elements. Its rationale is to transform the external visual signals into electrical signals, and then stimulate neurons or nervous tissues on each part of the visual pathway to induce vision formation, and eventually help some blind people regain or partially regain their functional visions. Thanks to the multidisciplinary efforts involving medical bioengineering, material science, electronic engineering and visual science, the introduction of artificial vision will help to address some serious blinding eye diseases that have no effective treatment as yet.

In the 1920s, researchers found that the electrical stimulation on the occipital cortex could induce blind people see some light spots[46], which indicated that it was possible to restore visual functions via electrical stimulation and promoted the research and development of visual prosthesis. A large number of clinical trials have confirmed that with the placement of an artificial visual prosthesis, blind patients can regain some degree of visual functions [47,48]. Then, however, several questions were raised from clinical practice, e. g. how is the stability of a visual prosthesis? Will it result in morphological and functional changes of nerve cells? What is the relationship between stimulus pattern and mapping of real objects? Since then, a series of experiments have been performed on animal models[49], and dramatic progress has been made in the manufacturing techniques and miniaturization of artificial prosthesis, such as the encapsulation technique of microelectrodes, energy supply technique of prosthesis placement, and methods of image capture[50]. Among

these, a dome-shaped three-dimensional flexible microelectrode array for neural stimulation, jointly developed by the Biomedical Engineering Department of Shanghai Jiaotong University and Institute of Microsystem of Chinese Academy of Science, has made a great contribution in ensuring the long-term safety of electrode operation by improving the contact between electrode site and target cells as well as optimizing the effects of stimulation[51]. It is expected that with the continued and concerted efforts of researchers from relevant fields, an artificial visual prosthesis that is capable of providing blind patients with visual functions will finally be developed.

3 Future prospects

As an emerging discipline, the translational medicine in ophthalmology is still in its initial stage despite these early achievements. Now, we still have a long way to go to translate more basic research findings into clinical application in ophthalmological practice so as to benefit more patients.

It is required that we make real efforts to implement the concept of translational medicine. Firstly, the fundamental purpose of scientific research is to meet the needs of patients or clinical demands, rather than publishing papers or winning awards. Secondly, the essential pathway of scientific research should base on the clinical demands and raise clinical questions to determine the direction of basic researches; we should develop clinically effective treatments through basic researches, and then summarize further questions from clinical practice in order to timely adjust our research directions to resolve the real-life clinical problems, and eventually to improve the diagnosis, treatment and prevention of diseases. This is a two-way progressive research process. More importantly, we should realize that the development of translational medicine requires the cultivation of many interdisciplinary talents, thus it is necessary to establish an incentive mechanism to promote the cultivation of translational research talents, who should be equipped with professional and board knowledge of both clinical and basic medicine, also with good communication and coordination skills; based on these, some high-level research teams on translational medicine could be formed. Meanwhile, we may also launch an open platform for translational medicine in ophthalmology through resource integration and cooperation among the major eye centers in China; reinforce and promote the combination of basic and clinical medicine, and avoid the disconnection among research institute, hospital and industry; set up an administrative mechanism for multi-entity and multidisciplinary cooperation and resource sharing; and actively involved in the international competition and cooperation by making full use of our advantages in clinical and human resources and policy priorities.

It is believed that along with the implementation of translational medicine, mutual promotion and development will be realized between the ophthalmology-related basic research and clinical application to reach the ultimate goal of benefiting more patients.

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