**Recovering lost sight**

**Dr Tadao Maeda** has expertise in the visual cycle that underlies pathology of degenerative retinal disorders. He is using this knowledge to develop an innovative regenerative medicine for patients with age-related eye diseases.

Working as an ophthalmologist in Japan fuelled my interest in the pathology of retinal degenerative diseases. I joined Dr Krzysztof Palczewski’s lab in 2001, where I was given the opportunity to study the ‘visual cycle’ – an essential chemical reaction that occurs between photoreceptor cells and retinal pigment epithelium (RPE) that enables us to maintain our vision. In this lab, I learnt about the design of therapeutic molecules for retinal diseases and, following the completion of a highly successful project in this field, I decided I wanted to be involved in drug development. After forming a collaboration with Dr Masayo Takahashi to study the retinoid cycle in human induced pluripotent stem cell-derived RPE (iPS-RPE), I was introduced to Healios KK. I then joined this company to develop iPS-RPE as a promising regenerative medicine.

What are the main aims and objectives of the work being carried out at Healios KK?

Our main aims are to establish iPS-RPE, which is absolutely safe and stable physiologically, possessing RPE-specific characteristics that are important in the treatment of retinal degenerative diseases. Our objective is to optimise procedures and materials that differentiate RPE from iPS cells and manufacture iPS-RPE cell products in order to comply with regulations. Our research team at Healios is utterly committed to the establishment of the safest and most effective iPS-derived regenerative medicine.

**Healios KK** is a commercial biotechnology venture company in Japan. It hosts a dynamic group of scientists who are pushing new boundaries in regenerative medicine in the context of ophthalmic research.

**AS A PERVASIVE** and unprecedented phenomenon, population ageing represents a major challenge for governments and societies throughout the world. Largely caused by rising longevity and declining birth rates, it puts pressure on the jobs market and imposes major socioeconomic burdens on health and social services. Unsurprisingly, population ageing correlates with a rise in the incidence of age-related diseases.

One such age-related disease is macular degeneration (AMD), a condition that results in the loss of vision in the centre of the visual field caused by damage to the retina. As one of the leading causes of sight loss in elderly individuals in developed countries, its social and economic impacts are increasing – and it is projected that this disease will become a more widespread cause of blindness in the future. AMD is a particular cause for concern in Japan, where population ageing is thought to outweigh all other countries. There is, therefore, an urgent need for research that focuses on innovative diagnostic and therapeutic strategies that target this devastating condition.

**VISIONARY REGENERATION**

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**RISING TO THE CHALLENGE**

Dr Tadao Maeda is a prominent and forward-looking researcher who is attempting to respond to the challenges presented by AMD – along with other retinal degenerative diseases including retinitis pigmentosa and diabetic retinopathy. As the Research Director of ophthalmic studies at Healios KK – a thriving and progressive biotechnology company – he focuses on the pathologies that underpin retinal degeneration and the development of therapies involving small compounds and regenerative medicine using induced pluripotent stem (iPS) cells. “Key technological advances mean that we can now study the pathology of retinal diseases more precisely and test the efficacy of therapies for AMD and other retinal degenerative diseases, as well as conventional ophthalmic examinations,” points out Maeda. “This in turn enables us to develop well-informed treatments.”

**RESEARCH DEVELOPMENTS**

Previous research conducted by Maeda and his colleagues at the Visual Sciences Research Center at Case Western Reserve University, USA, has shown that retinal pigmented epithelial (RPE) cells taken from human iPS cells have functional visual cycle enzymes, both in vitro and in vivo. Additionally, the researchers have found that retina-specific proteins carry out the majority of the visual cycle, with any disturbances to this important sequence of reactions potentially triggering varying degrees of blindness. Drawing on these findings, they are currently attempting to develop the world’s very first human iPS-RPE cells as regenerative medicine for patients with progressive retinal disorders.

The iPS-RPE cell therapy was initially developed by Dr Masayo Takahashi, a Japan-based pioneer in stem cell medicine with expertise in visual disorders. For instance, it was Takahashi’s group that designed the iPS-RPE sheet, a monolayer of RPE cells with a basal membrane that mimics key functions of RPE cells in situ. However, in the early days of this treatment, autologous RPE cells were harvested from the eyes of individual patients with AMD and then transplanted back into their eyes. Outcomes tended to vary as it was impossible to test the quality of these cells...
The two-photon microscope is state-of-the-art technology that enables us to obtain live cell images localised in deep regions with minimum cell damage. I have used this microscope to observe RPE cells in retinal degeneration mouse models to study the subcellular pathology in the progression of retinal diseases and analyse the therapeutic effects of candidate therapeutic molecules. So far, this technology is only used for research purposes but it is my hope that it will be used for clinical purposes in the near future.

**To what extent are international and multidisciplinary collaborations important for your work?**

The development of regenerative medicine is highly challenging and we have partnerships with both academia and industries. Our partners contribute to the research in different ways – indeed, each role is specialised and indispensable. Importantly, the Japanese Government is also supportive. We welcome two new laws announced on 25 November 2014: the Act for the Promotion of Regenerative Medicine, Revised Japanese Pharmaceutical Law, and the Act to Ensure Safety of Regenerative Medicine.

**Are there any significant challenges that you have had to overcome in your research?**

When I first joined Healios, there were many challenges. As I didn’t have a background in regulatory science, I had to develop a comprehensive understanding of regulatory issues in regenerative medicine in Japan, the US and the European Union. In contrast to basic and translational research – where my original expertise lies – the purpose of regulatory science is to evaluate the efficacy, safety and stability of the materials that are medicine candidates, using scientific methods with high reproducibility. Furthermore, data acquisition and storage is also strictly controlled by regulation. In these somewhat stressful and complex circumstances, we are developing innovative iPS-RPE products. We thoroughly check the composition of reagents used for manufacturing and we are currently testing the various reagents and compounds one after another in order to deliver the safest products for patients. In addition, we need to consider cost issues as well – indeed, cost in the field of regenerative medicine is one of the major issues to overcome. Going forward, close collaboration with our research partners is of utmost importance.

**VISION FOR THE FUTURE**

Maeda and the rest of his colleagues at Healios are planning to continue collaborating with their academic and industrial partners to further the efficacy, safety and cost-effectiveness of iPS-RPE regenerative medicine. Since their innovative treatment can be applied to any retinal diseases underpinned by RPE dysfunction or degeneration, it promises to have a significant, widespread effect on patients who suffer with these diseases. “We are currently devoting 100 per cent of our efforts to the development of effective iPS-RPE therapeutic products for degenerative retinal patients all over the world,” Maeda asserts. “We are very hopeful that the results of future clinical trials will show that our iPS-RPE products result in remarkable and life-changing effects.”

**INTELLIGENCE**

**HEALIOS KK**

**OBJECTIVES**

- To study the importance of the vitamin A metabolism (visual cycle) in vision and various diseases of blindness, such as age-related macular degeneration and retinitis pigmentosa
- To develop the world’s first human induced pluripotent stem cell-derived retinal pigment epithelium (iPS-RPE) products as regenerative medicine at Healios KK by utilising research experience about retinal pigment epithelium

**KEY COLLABORATORS**

- Dr Masayo Takahashi, MD, PhD, Riken Center for Developmental Biology, Japan • Dr Krzysztof Palczewski, PhD, Case Western Reserve University, USA • Dr Grazyna Palczewska, MSc, ME, Polgenix, Inc. • Dr Akiko Maeda, MD, PhD, Case Western Reserve University, USA

**PARTNERS**

- Ajinomoto • Case Western Reserve University • Nikon • Riken Center for Developmental Biology • Shibuya Kogyo • Shin Nippon Biomedical Laboratories • Sumitomo Dainippon Pharma

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DR TADAO MAEDA has previously held a postdoctoral position in the Palczewski lab at Case Western Reserve University, USA, and was subsequently a senior instructor of the Visual Sciences Research Center at the same institution. Maeda has been Ophthalmic Research Director at Healios KK since 2014; his research interests involve studying pathology and therapies of retinal degeneration by abnormal retinoid cycle with live-cell images, and developing therapies involving small compounds, regenerative medicine and induced pluripotent stem cells.