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Cultivated oral mucosal epithelial transplantation for severe ocular surface disease

The Translational Research Informatics Center (TRI) was founded in 2002 as the first data center in Japan to promote academia-originated medical innovation. The Academic Research Organization (ARO) network was established in 2013 by TRI and is now transforming into an Asian ARO network in conjunction with Korea, Taiwan and Singapore. Furthermore, we plan to expand this network globally to Europe and the United States. Ultimately, our aim is to develop an infrastructure to support the launch of global clinical trials of academia-originated medical technology, drugs and instruments and to obtain regulatory approval worldwide. This *Nature Outline* on cornea regeneration describes one of the leading regenerative medicine treatments promoted by TRI, which contributes to our goal of providing new therapeutic options for a number of intractable diseases.

The eyes are the windows of the soul. Important external sensory information is gained through eyesight, and humans have developed a complex vision system. Severe damage to corneal epithelial stem cells results in devastating ocular surface disease (OSD), ultimately closing a patient's visual window. Severe OSDs are typically bilateral, and ophthalmologists usually perform allogeneic corneal transplantation. However, intensive and prolonged postoperative immunosuppresive therapy markedly reduces a patient's quality of life and affects the clinical outcome. Those drawbacks prompted us to investigate an innovative reconstructive method using an autologous mucosal epithelium of non-cornea origin. In patients with severe OSD, both the corneal and conjunctival epithelial stem cells, as well as the underlying stroma (substrate), are severely damaged. The accomplishment of the above-described treatment objective depends on two factors: the epithelial stem cells, which have high proliferative capacity with extensive longevity, and the substrates, which determine the environmental niche and cell character. Based on these two considerations,

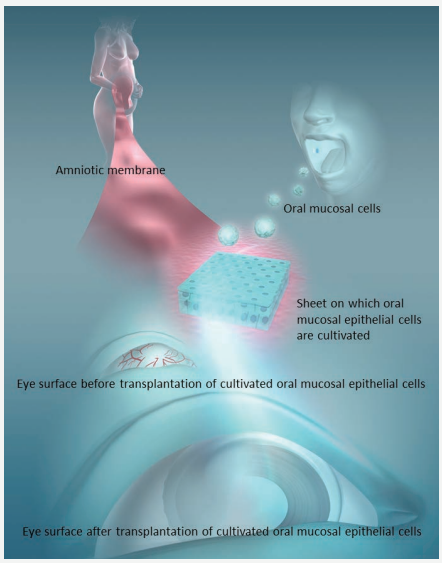

Figure 1. Cultivated oral mucosal epithelial transplantation protocol. *Oral mucosal epithelial cells from a patient's mouth are cultured on an amniotic membrane. In the next stage, an epithelial cell sheet is transplanted on to the surface of the patient's eye.*

we theorized that oral mucosal epithelial stem cells cultivated on amniotic membrane (AM) could be substituted for corneal epithelial cells and normalize the underlying substrate[1]. After complex investigations, we generated well-stratified and differentiated rabbit- and human-cultivated oral mucosal epithelial cell sheets that are similar to normal *in vivo* corneal epithelium, allowing us to perform autologous cultivated oral mucosal epithelial transplantation (COMET) (**see Fig. 1**).

To clarify the usefulness of COMET, we analyzed clinical data[2] from the first 72 consecutive patients treated since 2002. This retrospective study demonstrated that COMET is safe and effective for the visual prognosis of patients with severe OSD. The primary advantage is that the tissue-engineered graft can be used for not only treating the corneal surface, but also the conjunctival fornix, demonstrating that COMET using AM as a carrier can be used to reconstruct the entire ocular surface. The high proliferation potential of oral mucosal cells is advantageous for obtaining long-term survival of cells transplanted under the abnormal ocular environment; that is, severe dryness of the ocular surface and chronic inflammation. These advantages are essential for the treatment of severe OSD, such as Stevens–Johnson syndrome and ocular cicatricial pemphigoid. Following approval by the Japanese Ministry of Health, Labour and Welfare, COMET rose as a novel advanced medical treatment, with favourable results.

To minimize the associated risks of infection from the use of xenobiotic materials such as mouse-derived 3T3 feeder cells and fetal bovine serum, we developed a novel technique for creating the COMET graft that uses a feeder-free and serum-free culture system[3]. We established a safe culture protocol for the next generation of corneal regenerative therapy. Clinical data from more than 100 cases demonstrated that COMET produces benefits for treating cases of end-stage blindness. Our newly developed tear-exchangeable rigid contact lens can enhance the improved vision obtained by COMET, thus establishing a standard protocol for the management of postoperative ocular conditions. We believe that greater knowledge of the proposed and developed novel methods, including a thorough understanding of stem-cell behaviour and pathophysiological conditions, will lead to a 'reopening of the window' in patients with severe OSD.

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