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Novel regenerative treatment for the tympanic membrane

The Translational Research Informatics Center (TRI) was founded in 2002 as the first data centre in Japan to promote academia-originated medical innovation. The Academic Research Organization (ARO) network was established in 2013 by TRI and is transforming into an Asian ARO network in conjunction with Korea, Taiwan and Singapore. We plan to expand the network globally to Europe and the United States. Our aim is to develop an infrastructure to support the launch of global clinical trials of academia-originated projects and to obtain regulatory approval worldwide.

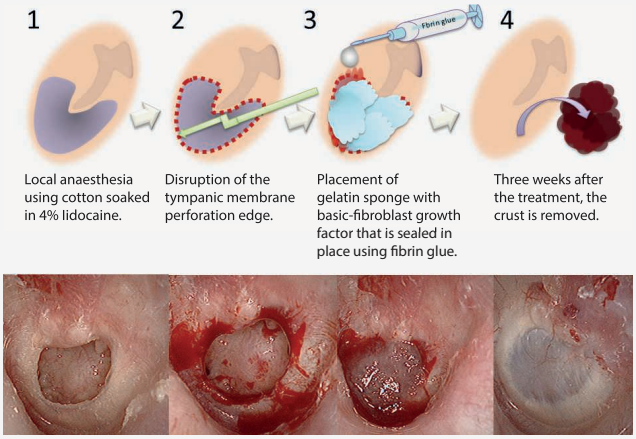

Figure 1. A schematic (top) and photographs (bottom) showing the procedure developed to regenerate the tympanic membrane.

More than 1.5 billion people around the world have tympanic membrane perforation. Chronic tympanic membrane (TM) perforation is a common cause of conductive hearing loss and often requires surgical repair to restore hearing and prevent recurrent infection. Although various treatments for TM perforation have been developed, almost all of them, especially in the case of large TM perforation, are surgical treatments such as myringoplasty or tympanoplasty. Such treatments require a skin incision and harvesting of autologous tissue as material with which to repair the TM. For patients, surgery can involve discomfort and inconvenience including anaesthesia, hospitalization, bed rest, medical fees, and restriction to their daily life during the recovery process. Surgery to treat TM also has risks, such as development of iatrogenic cholesteatoma, otitis media and sensorineural hearing loss, and taste loss.

Acute small perforation of the TM heals spontaneously in 77– 94% of patients. Chronic large TM perforation will also be able to regenerate if adequate arrangement of a scaffold and a growth factor is in place to promote spontaneous healing. Recent progress in regenerative medicine has included the development of scaffolds and growth factors that make it possible to accelerate tissue repair. In this treatment, we selected gelatin sponge as a scaffold and basic-fibroblast growth factor (b-FGF). Creating a mechanical disruption of the TM perforation edge is a trigger for the activation of tissue stem cells for repair of the TM.

Figure 1 shows a schematic of the procedure and photographs of a 67-year-old female who had chronic otitis media with subtotal perforation for 40 years. Perfect regeneration of the TM was achieved with one treatment, and auditory recovery improved from 58.3dB to 30dB. The female patient had no use for a hearing aid.

Had complete closure of the TM perforation not been achieved, the treatment could have been repeated up to four times. In a pilot study, we performed this treatment on 220 patients (age 18 to 96 years) and achieved 82% closure and 80% hearing improvement. There were no severe adverse events. We also performed Phase III Investigator Initiated Trial (IIT) in three Japanese hospitals: Foundation for Biomedical Research and Innovation in Kobe, Kyoto University Hospital in Kyoto, and Keio University Hospital in Tokyo. In this IIT, TM closure rates and hearing improvement rates are 75% and 100%, respectively.

We developed the novel therapy for the large or total TM perforation without conventional surgical treatment by using a tissue-engineering method. The non-surgical procedure can be performed in 20 minutes and is a straightforward outpatient procedure. It is possible to fully regenerate normal TM morphology and achieve ideal hearing recovery.

The otologic surgery will be thought to meet the development of the new stage by this innovative regenerative therapy for the TM perforation. Using this novel treatment, it will not be necessary to perform operations such as myringoplasty and simple tympanoplasty. Moreover, the combination use of an endoscope instead of a conventional microscope will extend the range of applications of middle ear surgery. It will be possible to perform many middle-ear surgical operations through the external auditory canal without a skin incision, harvesting auto-tissues and with no side effects.

Regenerative treatment is cost-effective and easy to use and for this reason has the potential to be used in developing countries where equipment and funds for otolaryngology–head and neck surgery are scarce.

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