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Kanemaru Tissue Engineered Tympanic Membrane Regeneration - Initial Experiences

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Tympanic membrane perforations are a common otological problem, particularly in the various indigenous populations worldwide such as the Aborigines in Australia or the Inuit in Northern America.[1] The incidence in the Australian population is not clearly known, though a study in 2004 by Morris investigating the prevalence of OM in 709 Aboriginal children from Northern and Central Australian communities discovered that 15% of these children were afflicted with a tympanic membrane perforation secondary to suppurative infection.[2] Up to 73% of Indigenous children will suffer from otitis media and its complications by the age of twelve months. Inadequate treatment of otitis media results in significant conductive hearing loss and subsequent speech and language delay. These impediments cause educational problems, social isolation, truancy and eventually early school-leaving and difficulty gaining employment.[3]

Furthermore, limited access to healthcare for rural and remote communities often means that with a large burden of disease a technique to repair the tympanic membrane needs to be fast and easily performed in order to maximise the number of patients that will benefit from the procedure.

To date tympanic membrane reconstruction has not changed substantially in the last 60 years. The standard of repair is generally either an autologous fascia or cartilage graft. Wullstein (1952) and Zollner (1955) attempted repair of the tympanic membrane with skin grafts.[4] The first temporalis fascia tympanoplasty was performed in 1958 by Herrman[4] However, the success rate can be as low as 71% for repairs, and lower if there is poor attention to post operative care.[5] Modern tympanoplasty still requires substantial operating time as well as an incision to harvest the fascia or cartilage required.

The ideal tympanic membrane repair would be quick to perform, reducing operative time from hours to minutes, involve less morbidity and wound healing and reproduce a three layer tympanic membrane.

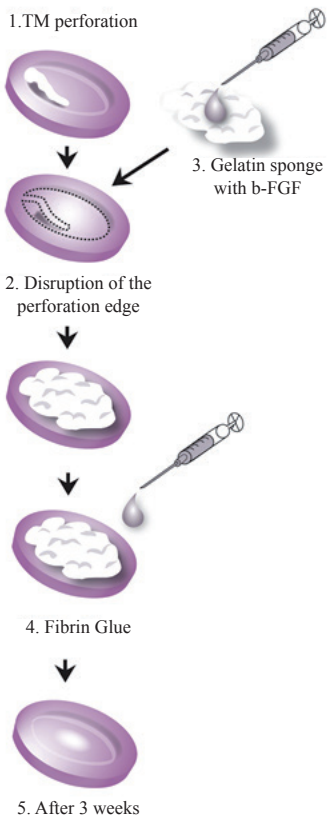
A novel new technique for tympanic membrane repair has been recently proposed by Kanemaru et al involving a minimally invasive approach to repair.[6]

Kanemaru's technique involves the use of basic fibroblastic growth factor (b-FGF) and fibrin glue (Tisseel™) .Tisseel™ is a trademark of Baxter Healthcare Corporation and used here with permission. B-FGF is engineered from E coli and fibrin glue is a commercially available product derived from plasma of screened patients. As a genetically engineered product b-FGF is inherently safe from infectious contaminants. Tisseel™ has been used safely in over 5 million applications since its commercial availability.

The technique involves the usual initial step in tympanoplasty, namely

freshening of the tympanic membrane perforation edges. A Gelfoam® (Gelfoam® is a registered trademark of Pharmacia & Upjohn Company LLC) plug is soaked with the b-FGF and inserted onto the perforation, ensuring this plug is in contact with the edges of the perforation. The Gelfoam® plug is then covered by Tisseel™ glue to provide a waterproof seal. (**Figure 1**)

Figure 1 Schematic diagram showing the method and procedures used in Kanemaru's technique.



Kanemaru's technique can be performed under general anaesthetic but has also been successfully tested under local anaesthetic in adults, thereby saving a general anaesthetic and operating time in suitable patients.

Kanemaru performed a study of this technique enrolling 56 patients with 63 chronic perforations. Fifty-three had the procedure with b-FGF, with 10 in a saline only control group. The age of participants was 10-85 years (mean 55 years).

98% of those in the b-FGF group resulted in complete closure of the tympanic membrane perforation, versus 10% in the control group.

Similarly an ongoing pilot study by Rajan et al confirmed similar findings.[7] The same technique was used in 17 patients so far. (5 paediatric, 12 adults). Four out of 5 paediatric patients had a successful closure and associated improvement in hearing. Five adult patients to date have a completely healed TM with 6 in the healing phase showing ongoing closure of the perforation. The one failure in the paediatric cohort was due to water contact in the immediate postoperative period and one adult failure due to upper respiratory tract infection and ear discharge during recovery. Mean operating times for the paediatric patients was 6 minutes under a general anaesthetic and 7 minuted under local anaesthetic for the adults.

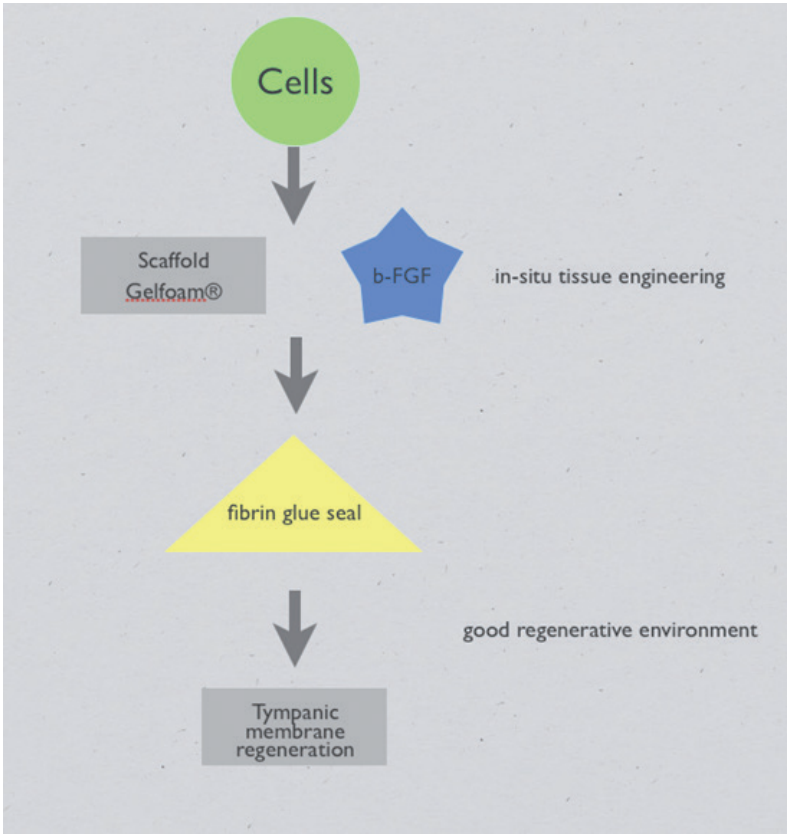
Mechanism (**Figure 2**)

The mechanism for this remarkable work is thought to be due to the provision of 3 elements – viable cells at the perforation edge, a Gelfoam® "scaffold" and the provision of regulatory factors in the form of b-FGF.

b-FGF is a polypeptide mitogen that stimulates proliferation of epidermal and connective tissue cells.

The Gelfoam® acts as a sustained release substrate for the b-FGF

Figure 2 – Proposed mechanism for repair



Concerns

There is no data on whether there may be an increased risk for cholesteatoma formation or if there is any oncogenic potential for this technique. However there is no evidence to suggest this to be any more the case with this technique than with traditional methods. b-FGF has been used safely in healing leg ulcers for many years.[8]

Advantages

The Kanemaru technique has enormous potential to reduce both morbidity and improve hearing with minimal risks. Invasive incisions to harvest graft are avoided. All size perforations can be tackled with this technique. The procedure time is greatly reduced to an average of 6-7 minutes from at least 30-60 minutes. Thus far the success rate has been significantly higher than that of traditional tympanoplasty techniques. Even factoring in material costs the reduction in operating time and possible repair under local anaesthetic suggests this technique is cost effective over traditional tympanoplasty (**Figure 3**).

Figure 3 – Summary of advantages and concerns

ADVANTAGES	Potential Concerns
Quick procedure	? increased risk for cholesteatoma (no data)
Can be performed under local anaesthetic in-office	cost
No skin incision required	? oncogenic potential (no data)

Further trials are ongoing at Princess Margaret Hospital and Fremantle Hospital, Western Australia to further evaluate this technique in collaboration with Professor Kanemaru's unit in Kyoto.

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