Breaking the silence

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IMPACT

This chapter summarizes the relevance and impact of the present thesis in a clinical and commercial context. It highlights how the research findings of this work can be translated in the future to address some of the current clinical gaps in tympanic membrane regeneration.

RELEVANCE

The primary goal of translational research is to bridge the existing gaps between fundamental science and its practical applicability towards the improvement of human health. Tissue engineering, in this regard, has emerged as a promising field to integrate the latest advancements in biology, materials science, and engineering, for addressing the current challenges in organ transplantations. Tremendous progress has been made in the last decades for artificially regenerating a wide array of tissue injuries affecting for instance the skeletal, muscular, and nervous systems of the human body [1]. However, among them, regenerative therapies for otologic tissues have remained largely unexplored up until recently.

The latest 2023 report from the World Health Organization estimates that by 2050, over 2.5 billion people will be affected by some degree of hearing loss, with at least 700 million of them requiring hearing rehabilitation [2]. The number is expected to rise from the current 5% of the global population (432 million adults and 34 million children) to 10% in the next couple of decades [2]. Tympanic membrane (TM) perforations are one of the most widespread injuries to the human ear, often leading to an impaired hearing ability due to inadequate sound conduction. The primary etiologies for TM perforations include physical or acoustic trauma and microbial infections such as otitis media. The middle ear inflammation caused by otitis media affects approximately 740 million symptomatic patients every year, making it the most prevalent reason for medical consultations, antibiotic prescriptions, and surgical treatments in high-income countries [3].

Most clinical interventions addressing the repair of perforated TMs have predominantly relied on conventional myringoplasty therapies, involving microsurgical placement of autologous tissue grafts [4]. However, these grafting tissues, commonly derived from the temporalis fascia and perichondrium, often lack the necessary properties for an effective vibro-acoustic transmission, leading to suboptimal restoration of the hearing capacity [5]. Moreover, in cases of recurrent perforations, surgeons frequently face a shortage of sufficient grafting materials for the successive myringoplasties. Therefore, this thesis aimed to provide promising alternatives to the current strategies available for repairing and reconstructing the damaged TM by developing nanoengineered 3D scaffolds. The subsequent sections of this chapter discuss the potential impact of the conducted research, focusing on its scientific, economic, and societal implications within the field of otology and beyond.

SCIENTIFIC IMPACT

The first efforts towards a biomimetic construction of the human TM were reported in 2015 [6, 7]. Multiple biofabrication approaches have been investigated in this regard since then [8-13]. Yet, the fundamental questions involving geometry, mechanical response, immunomodulation, drug delivery, and most importantly, extracellular matrix (ECM) modeling within the context of TM replacements remained unexplored prior to this thesis. Significant progress in this direction has been achieved through the research conducted and published as part of the present compilation. Moreover, the results highlighted in these studies have played a critical role in drawing the attention of tissue engineers towards the current challenges of TM regeneration. This is clearly evidenced by the number of scientific articles published on 'tympanic membrane tissue engineering' every year (**Figure 1**). A rising volume of publications has been observed recently, following a temporary decline between 2017 and 2019.

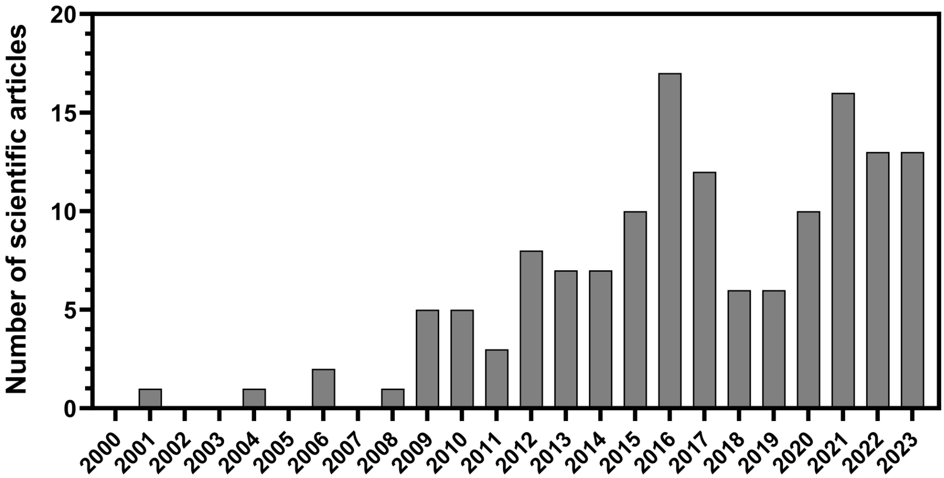

Figure 10.1: The number of scientific articles published on **'tympanic membrane tissue engineering'** every year since 2000. PubMed search, December 2023.

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Overall, this thesis addresses some of the prominent knowledge gaps within the domain of TM reconstruction by investigating tissue-engineered scaffolds possessing the appropriate 3D geometry (**chapter 3**), mechano-acoustic characteristics (**chapter 4**), immunomodulatory response (**chapter 5**), antimicrobial properties (**chapters 6, 7**), and biomimetic ECM (**chapter 8**). Furthermore, this thesis reports the development of novel TM-relevant techniques, such as macro-indentation mechanical testing (**chapters 3, 4,**

7) and air-liquid interface acoustic stimulation (**chapter 8**), to advance the present state of regenerative therapeutics for TM. All future investigations in this direction are expected to benefit immensely from these innovations.

ECONOMIC IMPACT

The latest Grand View Research report has valued the global hearing loss disease treatment market size at 13.62 billion US dollars in 2023 [14]. Moreover, it is estimated to further grow at a compound annual growth rate of 5.25% from 2024 to 2030 [14]. This coincides with the recent entry of several biomaterials-based grafting approaches into the market, serving a wide range of tissue applications, including the treatment of otologic injuries. Some of the commercial products addressing TM perforations are the Biodesign® Otologic Repair Graft from Cook Medical and PhonoGraftTM from Desktop Health. Among them, the Harvard-based PhonoGraftTM technology is being developed and commercialized, leveraging their prior research and patent on the 3D printed TM replacements [7, 15]. Inspired by these translational advancements, this thesis aimed to further enhance the existing technologies for producing clinically relevant TM replacements with improved auditory outcomes.

Furthermore, in addition to the primary goal of regenerating the damaged TM, the current thesis demonstrated the fabrication of an acoustic bioreactor capable of stimulating the in vitro tissue constructs at an air-liquid interface. The bioreactor platform is currently under patent application, where a few potential licensees such as Corning, Thermo Fisher Scientific, Greiner Bio, and Sarstedt have been identified to commercialize the production of these plug-and-play setups. If approved, the technique can be implemented for triggering stem cell differentiation to treat diverse medical conditions requiring tissue regeneration.

SOCIETAL IMPACT

The previous sections discussed how this thesis has contributed towards elevating the scientific and economic aspects of TM regeneration, especially within the domain of biofabrication-assisted tissue reconstruction. However, as stated earlier, the ultimate goal of all translational research is to positively influence human health. This impact is not limited to finding groundbreaking cures for terminal diseases, but also entails the enhancement of existing medical technologies to make them more accessible and affordable for people from all socioeconomic backgrounds.

In developing countries, the presence of poor socioeconomic conditions in the form of poverty, overcrowding, poor hygiene, and malnutrition, has often been linked to a higher prevalence of chronic suppurative otitis media [16]. Moreover, most patients lack the financial capacity to undergo the required clinical interventions, thereby resulting in a further decline in their quality of life. The use of biomaterial-driven strategies has demonstrated tremendous potential in recent years to create patient-specific solutions in an accessible and affordable fashion. Additionally, when combined with biofabrication techniques, it aims to simplify the complicated myringoplasty surgeries that demand highly specialized skills and precision [4], consequently reducing the overall workload of otologists worldwide by providing off-the-shelf medical devices. Alternatively, the biofabricated TM scaffolds can be combined with a patient's own cells as an advanced therapeutic medicinal product (ATMP), potentially improving their auditory response. The choice between the medical implant strategy and the ATMP will largely depend on the regulatory and socioeconomical factors, although they both offer a clear alternative to the currently available therapies. Furthermore, the fabrication of these TM replacements with tunable drug-releasing capabilities promises to create patient specific treatments, thereby minimizing their exposure to high doses of antibiotics.

Thus, in conclusion, the research findings presented in this thesis further strengthened the growing potential of tissue-engineered TM scaffolds as a promising alternative to the traditional autografts and allografts.

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