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Cochlear Implants: Causes, Effects and Mitigation Strategies for the Foreign Body Response and Inflammation

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Abstract

Cochlear implants provide effective auditory rehabilitation for patients with severe to profound sensorineural hearing loss. Recent advances in cochlear implant technology and surgical approaches have enabled a greater number of patients to benefit from this technology, including those with significant residual low frequency acoustic hearing. Nearly all cochleae implanted with a cochlear implant electrode array develop an inflammatory and fibrotic response. This tissue reaction can have deleterious consequences for implant function, residual acoustic hearing, and the development of the next generation of cochlear prosthetics. This article reviews the current understanding of the inflammatory/foreign body response (FBR) after cochlear implant surgery, its impact on clinical outcome, and therapeutic strategies to mitigate this response. Findings from both in human subjects and animal models across a variety of species are highlighted. Electrode array design, surgical techniques, implant materials, and the degree and type of electrical stimulation are some critical factors that affect the FBR and inflammation. Modification of these factors and various anti-inflammatory pharmacological interventions have been shown to mitigate the inflammatory/FBR response. Ongoing and future approaches that seek to limit surgical trauma and curb the FBR to the implanted biomaterials of the electrode array are discussed. A better understanding of the anatomical, cellular and molecular basis of the inflammatory/FBR response after cochlear implantation has the potential to improve the outcome of current cochlear implants and also facilitate the development of the next generation of neural prostheses.

Keywords

Cochlear implant; foreign body response; fibrosis; biomaterials; inflammation

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1. Introduction

Cochlear implants are highly successful neuroprostheses that provide auditory rehabilitation to patients with sensorineural hearing loss. Since the first single-channel device was implanted by William House and John Doyle in 1961 (Mudry & Mills, 2013), cochlear implants have undergone tremendous technological advancements in electrode design, speech processing strategies, and programming software (Roche & Hansen, 2015). The initially narrow candidacy criteria have broadened to include a myriad of patients affected by hearing loss, including those at the extremes of age, individuals with residual hearing or unilateral hearing loss, and patients with auditory neuropathy spectrum disorder. Improvements in surgical techniques have reduced electrode insertion trauma and rates of electrode array translocation (Ishiyama, Ishiyama, Lopez, & Linthicum, 2019). While modern cochlear implants have relatively low rates of wound infection and tissue flap necrosis, a growing body of literature suggests that a tissue response in the form of a foreign body response (FBR) or hypersensitivity reaction to the implant is not uncommon (Nadol, Eddington, & Burgess, 2008; Noonan, Lopez, Ishiyama, & Ishiyama, 2020; Seyyedi & Nadol, 2014). Importantly, this biologic response can have adverse effects on cochlear implant performance (Kamakura & Nadol, 2016). Herein, we review the current understanding of the inflammatory response that occurs following cochlear implant insertion and the effect of intracochlear fibrosis on clinical outcomes in patients. We will also highlight studies done in animal models that shed further light on the tissue responses within the cochlea to chronic implantation and electrical stimulation. Finally, we will discuss emerging strategies to help mitigate intracochlear fibrosis and hopefully improve clinical outcomes.

2. Histologic evidence of a foreign body reaction to cochlear implantation in humans

Histopathologic temporal bone studies have revealed the presence of an inflammatory tissue response to the electrode array in some patients, involving the formation of densely organized fibrotic tissue and new bone growth (neo-ossification) (see Fig. 1 for three different examples). Several hypotheses have been proposed to explain the chronic local inflammation that occurs following cochlear implantation, including delayed hypersensitivity or a local tissue reaction to the electrode array (Bertuleit, Groden, Schafer, & Leuwer, 1999; Ho, Dunn, Proops, & Warfield, 2003; Puri, Dornhoffer, & North, 2005).

This inflammatory process can lead to electrode extrusion and soft failure of the implant system. Seyyedi and Nadol described a granulomatous reaction to the electrode in 27 out of 28 (96.4%) of temporal bones studied, noting that the inflammatory response to the electrode was significantly greater at the basal turn of the cochlea close to the cochleostomy rather than at the apex (Seyyedi & Nadol, 2014). Other studies have confirmed that inflammatory effects are more severe at the basal turn of the cochlea, suggesting that surgical trauma during the insertion may initiate a cascade of inflammatory effects that organizes itself around the electrode array (Fayad, Makarem, & Linthicum, 2009; P. M. Li, Somdas, Eddington, & Nadol, 2007). There is strong evidence that the

cochleostomy approach can be associated with fibrosis surrounding the ductus reuniens, leading to endolymphatic hydrops of the cochlea (Ishiyama et al., 2019). Additionally, the cochleostomy approach is associated with a significant increased amount of new tissue formation when compared with the round window approach (Danielian, Ishiyama, Lopez, & Ishiyama, 2021). Other studies have documented that round window and extended round window approaches are more likely to result in full scala tympani insertion of electrodes compared to cochleostomy approach (91%, 84% vs 37%) which might explain the higher tissue response in cochleostomy cases. (Wanna et al., 2015)

The round window insertion site typically has a smooth fibrous capsule surrounding the CI electrode (Fig. 2). In cases of the extended round window approach, increased tissue formation occurs at the site of endosteum damage. Cochleostomy insertion is more often associated with fibrosis, and osteoneogenesis often extending from the site of insertion throughout the basal cochlea. Given the strong difference in the reaction, we believe that this increased fibrotic response following cochleostomy is predominantly due to disruption and damage to the endosteum.

Importantly, these responses tend to localize around the electrode array suggesting that interactions with the surfaces of the biomaterials also contribute to the inflammatory and fibrotic responses. Additionally, histopathologic temporal bone studies have shown that translocation of the electrodes, with damage to the lateral wall of the cochlea might be associated with poorer auditory function compared with the group with translocation without lateral wall injury(Ishiyama et al., 2019). They also demonstrated that CI translocation at the time of surgery appears to incite fibrosis and osteoneogenesis, which is qualitatively more prominent when associated with lateral wall injury. A higher degree of translocation injury is associated with longer (21.86 ± 2.55 mm) compared to shorter (18.50 ± 3.33 mm), (mean ± SD) electrodes insertion (student's t test, p =0.03). The patients who had CI translocation with significant lateral wall injury had lower spiral ganglion neuronal counts (6714 ± 4269) compared to those having translocation with localized injury (17300 ± 9415), (mean ± SD), (student's t test, p = 0.015). It has also been shown that translocation with significant lateral wall injury results in poorer auditory performance scores (39.86 ± 15.36) compared to the group with localized (66.55 ± 27.20), (mean ± SD) injury, (student's t test 0.024). However, they have mentioned that use of various types of implants, insertion approaches and auditory function tests among the CI recipients made the comparison difficult which is a significant limitation of the study. Danielian et al. (2021) found that years following implantation as a predictor of osteoneogenesis (r = 0.638, p-value = 0.011), total new tissue formation (r = 0.588, p-value = 0.021), but not of fibrosis (r = 0.235, p-value = 0.399). They also demonstrated that cochleostomy insertion (median, 25.98%) was associated with significantly greater degree of new tissue formation compared to round window insertion (median, 10.34%) (Mann Whitney test, p = 0.018)(Danielian et al., 2021). Thus, the studies demonstrate that soft techniques reflected by slow and atraumatic electrode array insertion, with preference for the round window approach over the cochleostomy approach, when feasible, are important in the goal of achieving best possible auditory performance. In this study, the electrode length was not associated with new tissue formation, although there was a high type II error due to few numbers of shorter electrodes. These studies collectively demonstrate correlation between fibrosis and osteoneogenesis following CI-

surgery. Important factors which are associated with increased degrees of fibrosis and osteoneogenesis which have been identified include insertion techniques, length of time with CI, history of translocation especially with lateral wall injury, and length of the electrode array of the different CIs. None of the very short early electrodes of 10 mm or less exhibited translocation, and all four electrode insertion lengths of greater than 20 mm had translocation injury (Ishiyama et al., 2019).

In a study comparing intracochlear fibrosis around the electrode in pre-curved (perimodiolar) half-banded electrodes versus straight (lateral wall) full-banded electrodes, the fibrous sheath was found to be asymmetrically thicker at the medial aspect of the pre-curved electrodes but symmetric around the lateral wall electrodes (Ishai, Herrmann, Nadol, & Quesnel, 2017). Possible causes of the asymmetric pattern of fibrosis around the pre-curved half banded electrodes include asymmetric current flow, which was directed medially given the half-banded design and suggested a potential role of electrical stimulation in fibrotic response, as well as insertional trauma, and differences in the FBR. In addition, intracochlear trauma was more common and more significant in the cochleae implanted with pre-curved electrodes (Ishai et al., 2017).

Despite widespread success with cochlear implantation, the device has the potential to incite a robust FBR within the inner ear. Several researchers have categorized damaged caused by the cochlear implant into acute and delayed components (Foggia, Quevedo, & Hansen, 2019; P. M. Li et al., 2007). Acute injury to the inner ear includes surgical trauma at the insertion site, damage to the cochlea along the path of the electrode, or disruption of cochlear fluid homeostasis. The exquisite sensitivity of the cochlea depends on the endocochlear potential (EP) requires a highly specialized environment. CI surgery cause disturbance of cochlear fluid homeostasis by various mechanisms including: 1) trauma to the spiral ligament and stria vascularis that are important for maintaining the EP, 2) inadvertent damage to the basilar membrane resulting in mixing of the perilymph and endolymph with resultant alterations of the EP (Bas, Dinh, Garnham, Polak, & Van de Water, 2012). In the delayed component, the host responds to biomaterials of the electrode array elicit a FBR manifest as a vigorous inflammatory response of macrophage activation and fibroblast migration that ultimately results in the formation of a fibrous capsule surrounding the implant (Anderson, Rodriguez, & Chang, 2008). Using energy-dispersive-X-ray-spectroscopy, both platinum and silicone from the electrode have both been identified as foreign body materials that are phagocytosed by CD163 positive cells as part of the foreign body response in the fibrous sheath surrounding the electrode (Nadol, O'Malley, Burgess, & Galler, 2014). The severity of the inflammatory response is variable; in some patients, only mild fibrosis occurs, while in others, a robust foreign body granuloma and extensive new bone formation have been described (Nadol et al., 2008).

3. Biologic response to cochlear implantation using immunohistochemical stains in humans

The cellular immunologic response that occurs following electrode array insertion is complex and multifactorial. Using morphological characteristics and expression of

molecular markers, attempts of classifying the macrophages as ‘active/activated/phagocytic’ vs ‘inactive/resting’, ‘proinflammatory (M1)’ vs ‘anti-inflammatory (M2)’ have been made by several authors. O’Malley et al. immunohistochemically identified multiple populations of macrophages in human cochleae using primary antibody stains against CD163, Iba1, and CD68 (markers specific for macrophages) (O'Malley, Nadol, & McKenna, 2016). While all of these are macrophage markers, some functional implications of individual markers have been suggested. Iba1 is a sensitive marker of macrophage/microglia(Kanazawa, Ohsawa, Sasaki, Kohsaka, & Imai, 2002).CD163 is a scavenger receptor that in human has been shown to be involved in transition from pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype of macrophages (Alvarado-Vazquez et al., 2017). CD68, a marker of phagocytic activity, located primarily in the endosomal/lysosomal compartment of phagocytic macrophages, can rapidly shuttle to the cell surface. The role of CD68 as a scavenger receptor is yet to be confirmed, although involvement in antigen processing/ presentation has been postulated(Chistiakov, Killingsworth, Myasoedova, Orekhov, & Bobryshev, 2017). O’Malley et al. has shown that relatively non-specific marker, Iba1, is expressed nearly ubiquitously in human cochlea. However, expression of CD163 and CD68 varies among different parts of cochlea. The implication of diversity of macrophage population in different parts of cochlea is yet to be determined. The proliferation and recruitment of macrophages within the inner ear is an important step in the development of the FBR and histopathological temporal bone studies have demonstrated a greater number of macrophages in implanted ears compared to unimplanted ears (Okayasu, O'Malley, & Nadol, 2019). In a subsequent study, the authors further characterized the macrophages in implanted and contralateral unimplanted ears using anti-Iba1 immunostaining. Activation status of the macrophages was defined by morphological features with ‘ameboid’ morphology as a marker of ‘active/activated/phagocytic’ macrophages while ‘ramified’ morphology was used as marker of ‘inactive/resting’ macrophages (Wilms, Hartmann, & Sievers, 1997). Using these markers, they reported that activated, and phagocytosing macrophages existed within the fibrotic sheath surrounding the electrode array (Okayasu, Quesnel, O'Malley, Kamakura, & Nadol, 2020). Noonan et al. further characterized macrophage populations based on expression of lysosomal marker CD68 considering it as a marker of ‘activation’(Chistiakov et al., 2017). The authors evaluated the distribution and morphology of CD68 positive and Iba1 positive macrophages and qualitatively compared the implanted vs the unimplanted cochlea. They reported that both Iba1+CD68− (resting) and Iba1+ CD68+ (active) macrophages were detected in the fibrous sheath surrounding the electrode array within the cochlea (Noonan et al., 2020). In the implanted cochlea, there were Iba1+CD68+ ‘active’ macrophages lining the fibrous sheath surrounding the CI, in areas of fibrosis in the scala tympani and scala vestibuli, in the spiral ganglion and in the modiolus. These data potentially suggest ‘activation’ of macrophages in response to foreign body (CI). An increase in numbers of Iba1+CD68+ ‘active’ macrophages in areas of fibrosis was observed in the case of translocation with lateral wall damage suggesting further activation in response to damage (Noonan et al., 2020). However, with a small number of samples, without control for multiple confounding factors including age and sex of the deceased person, years following CI surgery, co-morbid conditions, a quantitative comparison of distribution of Iba1+CD68+ (active) and Iba1+CD68−(resting) macrophages among implanted cochleae, non-implanted sides, and hearing control cochleae was not

made in this study. In the implanted cochlea without translocation and round window insertion, Noonan et al. found no evidence for pathological foreign body giant cells or inflammation. In addition to changes related cochlear implantation, they observed Iba1+ ramified macrophages with spider-like extensions (resting), in both the unimplanted and implanted spiral ganglia and indicated that these macrophages might be involved in spiral ganglion neuronal homeostasis and innate immune response. Several human studies suggest that cochlear implantation may result in loss of inner and outer hair cells and innervating peripheral distal processes of spiral ganglion neurons. In a study of 14 patients with unilateral cochlear implants, Kamakura et al. compared stained sections of the implanted side with the unimplanted side (Kamakura, O'Malley, & Nadol, 2018). The authors found reduced populations of inner and outer hair cells and reduced density of the peripheral neural processes in the osseous spiral lamina in the implanted cochleae compared to the contralateral unimplanted cochleae. While animal studies (described in section 7) and *in vitro* experiments (described in section 5) have suggested that post-CI inflammation might play a role in this degeneration, human studies supporting this notion are still rare. Okayasu et al. has described higher density of macrophages and specifically higher density of 'activated' 'ameboid' macrophages in osseous spiral lamina (OSL) of implanted cochlea compared to unimplanted counterparts that supports a possible role of immune activation in the post-CI neurodegeneration (Okayasu et al., 2020). Noonan et al. also described infiltration of Iba1+CD68+, 'activated' macrophages in the organ of Corti and osseous spiral lamina (OSL) of implanted cochlea, although a quantitative comparison with unimplanted or normal hearing cochlea was not reported. (Noonan et al., 2020),

4. Correlation between cochlear implant performance and presence of intracochlear fibrous tissue in human

Cochlear implants are excellent prostheses that have the ability to restore speech perception in the vast majority of patients. Delayed failure following cochlear implantation may be attributable to device failure "hard failure" or a gradual performance decline unexplained by integrity testing "soft failure." Intracochlear fibrosis is one mechanism that may explain some cases of delayed device failure (Nadol et al., 2008). Additionally, the FBR/ hypersensitivity reaction is hypothesized to be a potential source of delayed loss of residual acoustic hearing.

In one illustrative case, a patient was implanted with a Nucleus Hybrid S8 implant with initially preserved residual low-frequency hearing subsequently followed by delayed loss of residual hearing after implantation (Quesnel et al., 2016). On histopathological review, using traditional microscopic quantification techniques, there was no obvious evidence of post-implantation degeneration of hair cells or spiral ganglion neurons. The authors proposed multiple hypotheses to explain the delayed loss of residual hearing: 1) inflammatory response, 2) excitotoxicity from electrical stimulation, 3) delayed degeneration of hair cells or spiral ganglion neurons, 4) delayed effects of surgical trauma to the cochlea, and 5) changes in the cochlear mechanics due intracochlear fibrosis and/ or neo-osteogenesis. Consistent with this association of fibrosis and loss of residual acoustic hearing after cochlear implantation, Scheperle, et al. noted that increased impedances temporally

correlated with a delayed decrease in acoustic hearing in patients with initially preserved hearing after cochlear implantation (Scheperle et al., 2017).. Several authors have studied the effect of fibrosis within the cochlea on electrical impedances and have suggested that the presence of a fibrous capsule on the electrode array or new bone formation increases electrode impedance (Shaul et al., 2019; Tykocinski, Cohen, & Cowan, 2005).

It is unclear whether intracochlear fibrosis has a significant negative impact on the clinical outcomes in cochlear implant recipients with profound deafness. Kamakura et al. reported that postoperative consonant-nucleus-consonant (CNC) word scores negatively correlated with the percent volume of new bone within the cochlea, but not with the percent volume of fibrous tissue (Kamakura & Nadol, 2016).

5. Animal models and *in vitro* findings

To investigate the mechanisms of FBR after cochlear implantation, various animal models have been used. These include guinea pig, rat, cats, mouse, gerbil, and macaque. Additionally, in vitro studies have also been performed both in organotypic cell culture models (explant cultures) and in cell culture models. In the following sections, we highlight findings from these different animal and *in vitro* models.

5.1 Histological and cellular findings in guinea pig models

As in humans, histological findings after cochlear implantation have been described as inflammatory, fibrotic, and new bone formation with a temporal relationship between implantation and the FBR. One to two days after cochlear implantation in a guinea pig model, hematoxylin and eosin staining revealed accumulation of fibrin, blood clot and infiltration of leukocyte (primarily neutrophils and macrophages) in the scala tympani. Fibroblast infiltration occurred later, around 7 days after surgery. By that time, red blood cells and neutrophils in scala tympani diminish. In this model, new bone formation occurred much later, ~16 weeks after implantation (Tanaka, Nguyen-Huynh, Loera, Stark, & Reiss, 2014). Foreign body giant cells form in guinea pig models and their presence is significantly correlated with extent of the tissue reaction, new bone formation and injury to the osseous spiral lamina (OSL) (O'Leary et al., 2013). Using quantitative nanomechanical atomic force microscopy (QNM-AFM), Choong et al. has recently demonstrated that stiffening of the basilar membrane after cochlear implantation occurs over time, even at sites far apical to a cochlear implant electrode array (Choong et al., 2020).

5.2 Molecular and gene expression profile in guinea pig models

ICAM-1 (Intercellular Adhesion Molecule 1)/CD54 promotes the adhesion of immune cells to endothelial cells and their migration to tissue and is upregulated in guinea pig cochlea 24 hours after implantation. ICAM-1 expression is most prominent in the lateral cochlear wall with highest expression in the basal turn suggesting an important role of these regions in the immune cell infiltration (Kel, Tan, Eastwood, Wongprasartsuk, & O'Leary, 2013). Chemokine receptor (CXCL1) expression, involved in infiltration of immune cells (primarily neutrophils), is upregulated around the same timeframe (24-72 hours) and gradually declines thereafter (Zhang, Stark, & Reiss, 2015). Other inflammatory genes including IL-1β, TNF-

α, and Tnfrsf1a/b are also upregulated. While the expression of some inflammatory genes as well as connective tissue growth factor (CTGF) gradually declines by the end of the first week, tissue remodeling genes (TGF-β, MMP2, MMP9) are upregulated as early as 24 hours post implantation and their expression is maintained at a high level until the end of second week (Zhang et al., 2015).

5.3 Histological and cellular findings in mouse models

Pronounced tissue response around the electrode track is universally seen in chronically implanted stimulated and unstimulated mouse cochleae (Claussen et al., 2019; Irving et al., 2013; Mistry, Nolan, Saeed, Forge, & Taylor, 2014) (Fig. 3). Six weeks after implantation, histology shows varying degrees of cochlear damage, hair cell and spiral ganglion neuron loss, fibrosis and in some cases new bone formation (Colesa et al., 2021). Monocyte/macrophage (F4/80 positive cells) infiltration to the cochlea shows biphasic pattern: one peak at 3 days and the second at 14-28 days post-implantation (Bas et al., 2015). Fibrotic tissue developing within the scala tympani has been demonstrated by deposition of alpha-SMA positive cells and type I collagen after electrode analog insertion trauma (Bas et al., 2015). Like their unstimulated counterparts, chronically stimulated mouse cochleae show evidence of a FBR manifested as fibrosis and new bone formation in the basal turn (Irving et al., 2013) . In this special issue, Claussen, et al. report that the immune and fibrotic response within the scala tympani of mice depends on the presence of the electrode array and is largely absent from cochleae following surgical insertion and withdraw of the electrode array. This implies that the biomaterials used for the electrode array (platinum and silastic) contribute to the ongoing inflammatory and fibrotic response.

5.4 Molecular and gene expression profiles in mouse models

Molecular classification of the macrophages infiltrating the implant site has been attempted in mouse model. Historically, macrophages have been phenotypically categorized as either M1 or M2 responses (Mills, Kincaid, Alt, Heilman, & Hill, 2000), although it is now recognized that this broad categorization fails to fully account for the varied responses and phenotypes of macrophages. M1 macrophages, characterized by IL-1β production, are linked to cytotoxic function. M2 macrophages, indicated by Arg1 production, are associated with healing functions (Ley, 2017). In the cochlea, at the site of implantation, IL-1β and Arg1 expression overlap during the first 4 weeks after implantation suggesting the presence of both M1 and M2 macrophages. In lateral wall and the organ of Corti, IL-1β is increased with a biphasic pattern: one early (3 day) and one late (14 day) peak after implantation. By the end of a month post-implantation, Arg1 remained higher than IL-1β suggesting predominant M2 response in organ of Corti and lateral wall at that time. In the spiral ganglion, Arg1 expression predominated over that of IL-1β levels, indicating dominant involvement of M2 responses (Bas et al., 2015). Gene expression profile from the mouse model also demonstrated proliferative, fibrogenic changes after implantation. Matrix metalloproteinase-3, TIMP metallopeptidase inhibitor 1, and collagen type III alpha 1 are some example of genes involved in fibrogenic response that are upregulated by 7 days after implantation (Bas et al., 2015). WNT signaling pathways mediate many cellular mechanisms including development, proliferation, and migration; involvement of these WNT associated signaling pathways has been assessed in cochlear implant models using TOPGAL Balb/c

transgenic mice. Expression of genes involved in both cell migration (*Cd44, Nrp1, Ctgf, Fn1, Fgf7, Gdnf, Igf1, Jag1, Il6, Nrcam*, and *Twist1)* and cell cycle control *(Ccnd1, Cdkn2a, Ahr, Igf1, Id2*, and *Ptgs2*) *are* upregulated following cochlear implantation (Bas, Anwar, & Van De Water, 2020).

5.5 Histological and cellular findings in other animal models of cochlear implantation

Tissue responses similar to those seen in humans, guinea pigs and mice are observed in implanted cat cochleae, both stimulated and unstimulated (Shepherd, Matsushima, Martin, & Clark, 1994; Xu, Shepherd, Millard, & Clark, 1997). Gerbils have been implanted after various forms of ototoxic insult such as noise (Choudhury et al., 2014; Choudhury et al., 2011) or aminoglycosides (Hessel et al., 1997), although FBR in this model has not been described in detail. Because of the anatomical similarity to human cochleae, sheep has been proposed as a good model for cochlear implantation with human sized cochlear implants and, like the other models, sheep develop intracochlear fibrosis after implantation (Han et al., 2021; Kaufmann et al., 2020). In macaque, minimal insertion trauma has been reported, mainly rupture of the basilar membrane in the transition area between the basal turn and the first cochlear turn (de Abajo et al., 2017).

5.6 *In vitro* models of cochlear implant

Rat cochlear explant culture model: Inflammatory and fibrotic responses have been described in a rat explant model of electrode insertion. Electrode insertion trauma to organotypic tissue culture (explant) models from neonatal rat cochleae have shown increased leukocyte recruitment and intercellular interaction associated with higher expression of chemokines and cell adhesion molecules on cochlear tissues and leukocytes (Bas et al., 2015). Pro-inflammatory cytokines (i.e., TNFα and IL-1β), inducible enzymes (i.e., iNOS and COX-2), markers of oxidative stress (i.e., CellROX) and apoptosis pathways (i.e., caspase-3, apoptosis induced factor and Endonuclease G) are upregulated due to electrode insertion trauma in the rat explant model which is followed by upregulation of growth factors (i.e., TGFβ1, TGFβ3 and CTGF) and WNT signaling pathways involved in cell proliferation and migration (Bas et al., 2020; Bas, Gupta, & Van De Water, 2012).

Cell culture models: Platinum corrosion products from cochlear implants induce cell death, mitochondrial disintegration and swelling of endoplasmic reticulum in NIH 3T3 and SH-SY5Y cell lines suggesting cytotoxic damage to respiratory chain (Wissel et al., 2018). In this special issue, Jensen, et al. use *in vitro* cultures to compare the effects of platinum and silastic on macrophage and fibroblast activity and proliferation.

6. Factors affecting FBR after implantation in animal models

6.1 Factors related to surgery

In guinea pig models, round window insertion has been linked to be more traumatic histologically compared to cochleostomy approach (Rowe et al., 2016). The round window approach has been linked to delayed, low frequency hearing loss which appears to be unrelated to extent of FBR in scala tympani (Rowe et al., 2016). However, opposite results were described in the macaque model (Shepherd, Clark, Xu, & Pyman, 1995).

Importantly, in humans electrode array insertion through the round window appears to result in reduced trauma and fibrosis compared to cochleostomy or extended round window insertion (Ishiyama et al., 2016; Richard, Fayad, Doherty, & Linthicum, 2012) and currently most surgeons favor the round window approach for hearing preservation in humans. In guinea pigs, intraoperative, intracochlear bleeding is associated with fibrosis and ossification (Radeloff et al., 2007; Ryu et al., 2015). Further, the extent of cochlear trauma and depth of electrode array insertion have positive relationship with fibrosis and post implantation hearing loss in guinea pig model (Lo et al., 2017). However, in one study in a cat model, fibrosis, new bone formation, hair cell loss, and spiral ganglion neuron loss were not affected by different surgical approaches, extent of surgical trauma, bleeding, bone dust, or electrical stimulation (Clark, Shute, Shepherd, & Carter, 1995). 'Soft' arrays caused less tissue response compared to ‘hard arrays’ in guinea pig model (Choong et al., 2019).

6.2 Factors related to electrical stimulation

Electrical stimulation may play a role in modulating the FBR. Chronic electrical stimulation using charge balanced biphasic current pulses in hearing, 8-week-old kittens, implanted with scala tympani electrodes did not damage cochlear structures when compared with implanted, unstimulated control cochleae (Ni et al., 1992). Hair cell loss was restricted to regions adjacent to the electrode array and is unaffected by level of electrical stimulation. Similarly, spiral ganglion neuron density is also unaffected by level of electrical stimulation (Ni et al., 1992). Direct currents (DC), on the other hand, causes extensive pathological and functional changes: spiral ganglion cell loss, new bone growth, altered morphology of the electrically evoked auditory brainstem response (EABR) with higher response threshold (Shepherd, Matsushima, Millard, & Clark, 1991). Aminoglycoside deafened kittens stimulated with bipolar electrodes showed higher response amplitudes and were associated with more fibrosis in cochleae compared to that with monopolar electrode (Shepherd et al., 1994). In this, deaf cat model, chronic focused multipolar (FMP) stimulation does not affect electrode impedance, ECAP and EABR thresholds, or spiral ganglion neuron survival. However, it significantly increases the tissue response. Finally, there was no evidence of Pt corrosion following long-term FMP stimulation; stimulated electrodes exhibited the same surface features as the unstimulated control electrodes (Shepherd, Wise, Enke, Carter, & Fallon, 2017). In adult hearing cats, spiral ganglion neurons are not adversely affected by long term intracochlear electrical stimulation (Shepherd, Clark, & Black, 1983). Similarly, high-rate electrical stimulation using monopolar and bipolar electrode configurations does not affect spiral ganglion neuron or hair cells survival (Shepherd et al., 2021; Shepherd et al., 2020; Xu et al., 1997). However, it results in significant increase in tissue response, much higher corrosion of platinum from electrode evident by increased charge storage capacity and charge injection limit, and accumulation of platinum within the tissue capsule surrounding the electrode array compared with implanted, unstimulated control cochleae (Shepherd et al., 2021). Some corroded platinum has been found in the kidney, but not in liver or brain (Shepherd et al., 2021). Platinum corrosion can be decreased by charge recovery using capacitive coupling (CC) alternating leading phase (AP); however, this does not reduce tissue response (Shepherd et al., 2020). In hearing guinea pigs, intracochlear electrical stimulation with an intensity equal to or above electrically evoked compound action potential (ECAP) threshold decreased the excitability of auditory nerve (Q. Li, Lu,

Zhang, Hansen, & Li, 2020). Furthermore, the number of synapses between inner hair cells and afferent spiral ganglion neurons also decreased after electrical stimulation with higher intensities. However, no significant change was observed in the packing density and perikaryal area of SGNs or the number of hair cells (Q. Li et al., 2020). These observations suggest that intense levels of electrical stimulation may evoke synaptopathic changes similar to those seen after noise trauma (Kujawa & Liberman, 2015).

7. Effects of FBR on outcome of cochlear implants in animal models

7.1 Loss of residual hearing, hair cells and SGN

Hearing loss occurs early after implantation in guinea pig model, peaking at 3 days with some recovery by the end of first week (Zhang et al., 2015), reaching the best recovery by the end of 4 weeks. This recovery is limited by the extent of tissue response in scala tympani, outer hair cell count and damage to osseous spiral lamina (Shepherd et al., 1991). Fibrous tissue growth in cochlea after implantation correlates with hair cell loss in cat (Clark et al., 1995) and in guinea pig models (O'Leary et al., 2013). MMP9 upregulation is qualitatively associated with changes in hearing thresholds which is consistent with the role of tissue remodeling in loss of residual hearing (Zhang et al., 2015). In guinea pig model, Eshraghi et al. has demonstrated that electrode insertion trauma (Bertuleit et al.) causes programmed cell death (PCD) of support cells (SCs) initially, followed by followed by PCD in hair cells (HCs) while activation of caspase-3 was observed only in SCs following EIT (Eshraghi et al., 2015). In a mouse model, there is increase in threshold in the base of the cochlea (Mistry et al., 2014; Soken et al., 2013), with maintained low frequency hearing in most instances (Claussen et al., 2019) and no apparent damage to SGNs (Kopelovich et al., 2015). Organ of Corti damage in mice is correlated with rate of hearing loss early (0–2 weeks) but not late (2–22 weeks) after implantation (Kopelovich et al., 2015). Cochlear implantation in macaques induces hair cell loss adjacent to the electrode array, but apical hair cells and cochlear structures are preserved (Shepherd et al., 1995). Interestingly, electrode array removal and reimplantation in these animals does not appear to adversely affect the apical hair cell population (Shepherd et al., 1995). This is consistent with the ability to preserve low frequency hearing following reimplantation of failed electrode arrays in humans (Dunn, Etler, Hansen, & Gantz, 2015).

SGN loss is associated with electrode insertion trauma and inflammation in hearing cats (Xu et al., 1997). In partially deafened cat model, chronic electrical stimulation does not cause degeneration of residual hair cells apical to the electrode array or increased SGN survival (Coco et al., 2007). In deaf kitten, on the other hand, SGN survival has been reported to have positive correlation with fibrosis in scala tympani, but negative correlation with degree of organ of Corti degeneration (Araki et al., 2000). There are variable reports on protection of SGN by electrical stimulation in deaf animals: with reports of protections in deafened guinea pigs (Mitchell et al., 1997; Shepherd, Coco, & Epp, 2008), deafened kittens (Leake, Hradek, & Snyder, 1999), suppression of apoptotic signaling in rat (Kopelovich, Cagaanan, Miller, Abbas, & Green, 2013). Others have seen a lack of SGN protection by electrical stimulation in deafened cats (Araki et al., 1998; I. Chen, Limb, & Ryugo, 2010; Shepherd et al., 1994), deafened guinea pigs (L. Li, Parkins, & Webster, 1999), and deafened mice

(Irving et al., 2013). Taken together, these animal models support the findings in human temporal bones that atraumatic electrode array insertion does not significantly damage hair cells or spiral ganglion neurons apical to the electrode array, confirming that it is feasible to place electrode arrays within the scala tympani and preserve apical cochlear structure and function.

7.2 Effects on impedance

Animal model findings: The resistance between the stimulating electrode and the return electrode is manifested as electrode impedance and reducing electrode impedance is expected to allow for improved function and battery life. A correlation between the extent of the FBR after cochlear implantation and electrical impedance changes has been documented in guinea pig (Wilk et al., 2016), kitten (Ni et al., 1992), cat (Clark et al., 1995; Xu et al., 1997) and macaque models (Shepherd et al., 1995).

In *vitro* model: Under standard tissue culture conditions, when monolayers of different cell lines were grown over electrode surfaces, impedance directly correlates with the extent of cell coverage of the electrode. Impedance also depends on the type of cells grown (Newbold et al., 2004). Electrical stimulation to cell-covered electrodes causes decrease in number of cells covering the electrode and immediate lowering of impedance. During inactive period, the number of covering cells increases and impedances rises back to recovery to pre-stimulation levels(Newbold et al., 2004) . Overall, this suggests that number and type of cells encasing the electrode array and electrical stimulation might affect the impedance. In *vitro* studies also demonstrated that presence of blood within the cochlea can increase impedance(Bester et al., 2020). Inhibiting fibroblast adhesion pharmacologically decreases the impedance *in vitro*(Aliuos et al., 2014).

7.3 Effects on ECAP

The ECAP represents the synchronous response from auditory nerve fibers when they are electrically stimulated. In hearing guinea pigs, ECAP amplitude growth function declines and ECAP thresholds increase over first few days after implantation, followed by slow increase in ECAP amplitude growth function and decline in thresholds over weeks. In case of deafened guinea pigs with relatively poor SGN survival, ECAP growth function slopes do not recover. Healthy SGN density appears to be the main determinant of ECAP amplitude growth function and cochlear implant insertion trauma can impair the function of a healthy SGN population (Pfingst et al., 2015; Schvartz-Leyzac et al., 2020). A positive correlation between ECAP threshold, fibrosis and new bone formation was found in guinea pig model (Simoni et al., 2020). However, simple impedance measures were weakly related to ECAP amplitude growth function (Schvartz-Leyzac et al., 2020; Schvartz-Leyzac et al., 2019). In aminoglycoside deafened guinea pig model, correlation between the FBR and the ECAP measures (amplitude growth function and IPG effect) was not found; these measures were affected by SGN density (Swiderski, Colesa, Hughes, Raphael, & Pfingst, 2020). Similarly, SGN density, and not the FBR, affects several psychophysical measures of implant functions (Swiderski et al., 2020). Non-deafened implanted animals show greater SGN survival, higher ECAP amplitude growth functions, peak amplitude values and interphase gap than the deafened, implanted guinea pigs (Schvartz-Leyzac et al., 2019), suggesting improved

SGN survival and function in cochleae with hearing and highlighting the importance of preserving cochlear function and structure during and after cochlear implantation.

8. Mitigation Strategies for FBR in animal models

Various mitigation strategies have been investigated to modulate the foreign body response post-CI: in animal models and in clinical trials. Broadly two major approaches have been in these studies: pharmacological approaches and cochlear implant biomaterials. A description of some significant studies will follow in this section. In addition, table 1 summarizes the role of different approaches for mitigation of FBR post-CI in *in vivo* animal studies, *in vitro* models of CI, and clinical trials and quantitative comparison of effects. Table 2 summarizes the proposed mechanisms of action of the experimental interventions to mitigate the FBR post-CI. Moreover, figure 4 summarizes the molecular targets for experimental therapeutic interventions used in animal models *in vivo, in vitro* models of cochlear implantation, clinical trials, and standard clinical practice. Some of the interventions involve more than one mechanism of actions.

8.1 Pharmacological approaches: Anti-inflammatory drugs

8.1.1 Local or systemic glucocorticoids *in vivo*—Dexamethasone eluting CIs preserve and recover auditory function, protect hair cells and neural elements, decrease the FBR, decrease fibrosis and bone growth, and decrease electrical impedance after implantation in hearing guinea pigs in a dose dependent manner (Ahmadi et al., 2019; Bas et al., 2016; Liu et al., 2015; Simoni et al., 2020; Van De Water et al., 2010; Wilk et al., 2016) without affecting SGN density (Simoni et al., 2020). Similar effects are seen in guinea pigs exposed to noise trauma (Eshraghi et al., 2019). In guinea pigs, dexamethasone eluting implants reduce the inflammatory response including fibrocyte, macrophage, and giant cell infiltration at early (day 3) and infiltration of lymphocyte, macrophage infiltration, and capillary formation at later (day 13) time points (Farhadi et al., 2013). In non-human primate model, 6 months after post implantation, dexamethasone-eluting implants resulted in lower mean ABR threshold shift, lower mean impedance value, lower ECAP threshold, and higher ECAP amplitude, less tissue reaction (fibrosis and ossification) compared to conventional CI (Manrique-Huarte et al., 2020). Dexamethasone eluting rods also has similar effect on the FBR and auditory functions in guinea pig models (Astolfi et al., 2016; Simoni et al., 2020). Taken together, these studies point to an ototoxic role of the inflammation caused by cochlear implantation which can be mitigated, at least in part, by dexamethasone elution.

8.1.2 Preoperative local or systemic dexamethasone—Beyond elution from an electrode array, dexamethasone and other corticosteroids are used frequently by surgeons during cochlear implantation in humans. These can be delivered locally and/or systemically and at various times in the perioperative period. Several animal studies have attempted to address the efficacy, route of delivery, and timing of dexamethasone for cochlear implantation.

Preoperative local dexamethasone: In some studies using guinea pigs, short-term, preoperative, round window delivery of dexamethasone protects residual hearing (James,

Eastwood, Richardson, & O'Leary, 2008) with higher dose and duration of treatment giving better protection (Eastwood, Chang, et al., 2010). Other studies with a guinea pig model showed reduced FBR but not preservation of hearing following cochlear implantation (Lo et al., 2017).

Preoperative systemic dexamethasone: Extended preoperative systemic steroid for 5 days preserves high frequency hearing, SGNs in base of cochlea but does not inhibit implant induced fibrosis (Kuthubutheen et al., 2015).

8.1.3 Postoperative local or systemic steroid—Both local and systemic dexamethasone delivery improves ABR thresholds, whereas only systemic dexamethasone has been reported to reduce the tissue response around the electrode (Lee et al., 2013). More effective hearing protection and antifibrotic effect by systemic steroid is achieved when administered for at least a week after CI (Chang, Rah, et al., 2017; Rah et al., 2016). Different results were found in another guinea pig study that demonstrate that local dexamethasone delivery is more effective in reducing intracochlear inflammation and hearing preservation (Lyu et al., 2018).

8.1.4 Dexamethasone *in vitro*—Dexamethasone released from cochlear implant coatings with a protein repellent hydrogel layer, sPEG, inhibits fibroblast proliferation on implant *invitro* (Wrzeszcz et al., 2014). Biopolymer-released dexamethasone prevents TNF alpha-induced loss of auditory hair cells *in vitro* (Dinh et al., 2008; Haake, Dinh, Chen, Eshraghi, & Van De Water, 2009). In rat cochlear explant, inflammatory, proliferative-fibrosis responses are inhibited by dexamethasone (Bas, Gupta, et al., 2012). Rat explant studies also show that dexamethasone treatment requires both Akt/PKB and NFkB signaling for protection of hair cells which upregulates expression of anti-apoptosis related genes (i.e., Bcl-2, Bcl-xl) and down regulation of pro-apoptosis related genes (i.e., Bax, TNFR-1) (Van De Water et al., 2010). Additionally, combination therapy of dexamethasone and L-NAC shows additive effect in prevention of hair cell loss caused by electrode insertion trauma (Bertuleit et al.) in rat cochlear explant studies (Eshraghi et al., 2020) whereas combination of dexamethasone, NAC and mannitol improves the protection of hair cells upto nearly 96% (Eshraghi et al., 2016)

8.1.5 Other anti-inflammatory drugs—Beyond corticosteroids, other anti-inflammatory drugs have also been investigated for their ability to protect residual hearing and mitigate fibrosis. The tumor necrosis factor alpha receptor antagonist, etanercept, has been reported to preserve of acoustic hearing after cochlear implantation in guinea pigs (Ihler, Pelz, Coors, Matthias, & Canis, 2014). In this study, 1 mg/ml Etanercept was added to artificial perilymph and auditory brainstem responses (Rejali et al.) was performed prior to and 3, 5, 7, 14, 28 post-CI to assess hearing. Compared to controls, hearing thresholds were significantly lower in etanercept-treated animals on day 28 at 8 kHz and from day 3 onwards at 4 and 2 kHz. Systemic lipoic acid administration preserves acoustic hearing, protects SGN and prevents intracochlear fibrosis in guinea pig model of cochlear implantation (Chang, Gwon, et al., 2017). Guinea pigs received intraperitoneal lipoic acid for 4 weeks following insertion of silicone electrode-dummy through the round window. ABR measurements prior

to and at 4 days and 1, 2, 3 and 4 weeks after electrode-dummy insertion showed that lipoic acid prevents loss of acoustic hearing at 2kHz.

8.1.6 Immune/inflammatory modulating drugs and growth factors—Implant insertion trauma can be attenuated and recovered with hydrogel-coated, growth factor (IGF1, HGF)-releasing CI electrodes (Kikkawa et al., 2014) while IGF1 might attenuate loss of low-frequency hearing after cochlear implantation (Yamahara et al., 2018). Tissue-type plasminogen activator (tPA), an antithrombotic medication, can potentially reduce fibrosis after cochlear implantation in guinea pig models (Choong et al., 2019). Laminin-coated electrodes preserve acoustic hearing, SGN and neurites in guinea pig model (Bas et al., 2019).

8.1.7 Anti-apoptotic compounds—Inhibition of the c-Jun N-terminal kinase (JNK) signaling cascade protects acoustic hearing in an acute insertion trauma model (Eshraghi et al., 2006; Eshraghi et al., 2010). Thus, the JNK inhibitor, AM-111/brimapitide, preserves hair cells, SGNs, and Schwann cells by inhibiting programmed cell death and preserves acoustic hearing in guinea pig model (Eshraghi et al., 2013).

8.1.8 Antioxidants—The antioxidant, N-acetylcysteine (NAC), appears to reduce post-implant chronic inflammation and preserve residual hearing, although at the expense of increased new bone formation in guinea pigs (Eastwood, Pinder, et al., 2010). Treatment with taurodeoxycholic acid, a bile salt, provides significant hair cell protection in a dose-dependent manner by decreasing oxidative stress and activity of apoptotic pathway (Shah et al., 2020).

8.1.9 Neurotrophic factors—Electrode arrays engineered to elute brain derived neurotrophic factor (BDNF) preserve SGNs in base of the cochlea in guinea pig model (Rejali et al., 2007). Investigators in this study transduced guinea pig fibroblasts with an adenovirus with a BDNF gene cassette insert. After confirming that these cells secreted BDNF, they attached BDNF-secreting cells to the cochlear implant electrode via an agarose gel and implanted the electrode in the scala tympani. BDNF expressing electrodes preserved significantly more SGNs in the basal turns of the cochlea after 48 days post-CI, an effect that decreased in the apical cochlear turns.

BDNF released from the fibroblast cell line NIH3T3 grown on silicone elastomers enhances survival of SGN *in vitro* and in vivo (Warnecke et al., 2012). Likewise, neurotrophin-3 expressed using viral vectors (AAV.Ntf3) injected into the inner ear at the time of cochlear implantation protects SGNs in deaf guinea pigs and ameliorate the reduction of ECAP growth function (Pfingst et al., 2017).

8.2 Cochlear implant biomaterials

In vivo: Flexible “electrode” arrays comprised of the housing material but devoid of contacts or wires has been demonstrated to better preserve the integrity of inner ear than more rigid electrode arrays that contain active contacts and wiring(Choong et al., 2019; Giordano et al., 2014; Kopelovich et al., 2015). When cochlear implants were coated with hydrogels created from hyaluronic acid and gelatin, a decrease in capsular tissue responses,

looser collagen distribution, reduced cytokine expression on the hydrogel-coated surface was observed in guinea pig skin model and *in vitro* (Joo et al., 2021). Rats implanted with laminin coated electrodes have significantly lower electrical auditory brain response (eABR) and acoustic auditory brain response (aABR) thresholds at selected frequencies, a greater number of SGNs, neuritic processes projecting into the scala tympani compared to animals with uncoated electrodes ($p<0.05$). (Bas et al., 2019)

In vitro: Laminin coating on the electrode arrays attracts Schwann cells and neurites augmenting growth and survival of SGN in rat cochlear explant culture (Bas et al., 2019). A silicone fiber coating can reduce fibroblast growth on electrode surfaces (Dencker et al., 2017).

8.3 Clinical trials on mitigation strategies for FBR post-CI

In a double blinded placebo-controlled trial, systemic methylprednisolone (1 gm, intravenous) for hearing preservation during cochlear implant surgery was not effective in prevention of loss of residual hearing, improving speech perception, or lowering electrode impedances (O'Leary et al., 2021). In another clinical trial, three treatment groups were compared: 1) standard intravenous dexamethasone (0.1 mg/kg body mass twice a day); (2) intravenous dexamethasone (0.1 mg/kg b.m. twice a day) and oral prednisone (1 mg/kg body mass/24 h), and (3) no steroid therapy. This study demonstrated that steroids did not protect residual hearing in cochlear implant recipients (Skarzynska, Kolodziejak, Gos, & Skarzynski, 2021). These clinical trials contradict with the findings of *in vivo* and *in vitro* experimental studies.

A randomized, placebo-controlled clinical trial investigating the effect of antioxidant vitamins A, C and E and a vasodilator, Mg, on overall safety and residual hearing preservation in CI patients suggests that perioperative oral administration of these agents is safe and may provide protection of residual hearing in CI patients (Scheper et al., 2016; Scheper et al., 2020).

9. Challenges and prospects in animal models of cochlear implants

9.1 Lesson learned from other implant models

Host reactions following implantation of biomaterials include injury, blood-material interactions, provisional matrix formation, acute inflammation, chronic inflammation, granulation tissue development, foreign body giant cell formation and fibrosis/fibrous capsule development. These events have been reviewed in detail by Anderson et al. (Anderson et al., 2008). One important feature of such response to biomaterials is that the response evolves over time. Initially, humoral factors e.g. proteins like albumin, γ globulin, fibrinogen, fibronectin, vitronectin, complement and others adsorb to the biomaterial and modulate host cell mediated responses. Acute inflammatory response is characterized by recruitment of neutrophils. This phase is also associated with mast cell degranulation and release of chemical mediators. Macrophage adhesion to biomaterials follows. Inflammatory cells release several cytokines and chemokines including IL-1, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IL-18, IL-36, TNF-α, TGF-β, MCP-1, MIP-1α/β, among many others.

In the chronic phase, macrophages fuse with each other and form foreign body giant cells (FBGCs). The chronic phase is also characterized by recruitment of lymphocytes and their interactions with macrophages (Anderson et al., 2008). Recent studies have shown a dynamic change in the type of inflammation after biomaterial implantation: starting as innate immune response and later involvement of adaptive immune pathways (Chung et al., 2020). Moreover, stromal cells, once believed to be passive effectors in the inflammation, has been shown to have regulatory role in the inflammatory process (Chung et al., 2020).

9.2 Challenges in animal models of cochlear implant, recent advancements, and future directions

In recent years, our understanding of the tissue and FBR within the cochlea after implantation has advanced significantly. However, challenges still exist. In many tissues, mouse models have been used extensively to characterize and manipulate the immune system. In particular, investigators have leveraged knockout and transgenic mouse models and reliable antibodies against mouse immune markers to investigate inflammatory/FBR to implanted biomaterials. However, primarily due to surgical and technical challenges associated with small cochleae and the manufacturing of durable, very small electrode arrays, studies involving cochlear implantation seldomly take advantage of mouse models. Longitudinal, in-depth analyses of the cellular and humoral immune responses after cochlear implantation are limited and experiments involving genetic manipulation are virtually absent in cochlear implant studies. Additionally, unlike most other implanted biomaterials, a cochlear implant is electrically stimulated. This poses an additional variable in the investigation of the inflammatory and FBR to cochlear implantation. Our lab recently has recently developed a mouse model of cochlear implantation with chronic electrical stimulation (Claussen et al., 2019). As reported by Claussen, et al, in this special edition, a transgenic reporter (CX3CR1-GFP, Thy-1 YFP) mouse model enabled us to quantitatively assess macrophage and neuronal response to cochlear implantation. Future studies leveraging the malleable mouse genome will enable rigorous mechanistic studies of the contribution of specific cellular activities to the FBR after cochlear implantation.

Another issue faced with animal models is that the electrode array designs need to be customized to match the cochlear size constraints of cat, guinea pig, rat, and mouse cochleae, among others. These design requirements likely yield electrode arrays with different mechanical properties (e.g., flexibility) than those used in humans. To this end, larger animal models (e.g., sheep and pigs) may prove useful to the extent that they enable the use of human electrode arrays(W. Chen et al., 2017; Kaufmann et al., 2020; Trinh, Cohen, Boullaud, Cottier, & Bakhos, 2021).

10. Conclusions

Following the trend of the last few decades, cochlear implant technology is likely to undergo significant advancements in the near future with peservation of the residual hearing and improving the interface between electrodes and neurons they stimulate being major foci of developments. From human and animal model studies, both observational and interventional, it is evident that inflammation and the FBR are critical determinants of

important outcome measures; they will also impact the performance of future advancements in neuroprosthetic technologies. While some aspects of the inflammatory/FBR resoponse might be desirable, others are likely detrimental. Fundamental understanding of the cochlear immune system and its response to injury and implanted biomaterials, at anatomical, cellular, and molecular levels, are prerequisites for developing selective and optimal modulatory therapies that can improve the outcomes of cochlear implants. This highlights the urgent need for additional studies involving human temporal bones from recepients of modern cochlear implants and the ongoing development of model systems and therapuetic strategies to characterize and modulate the cochlear tissue response to implanted electrode arrays.

While non-specific anti-inflammatory compounds, steroids, have been widely tested in animal models, extensive clinical trials are required to determine whether they will be useful in clinical practice. At the same time, in addition to fundamental research to discover the molecular and cellular mechanism of FBR post-CI, there is an urgent need for continued and diversified effort to identify novel small molecules to modulate the inflammatory process. Integration of data from various ‘omics’ sources such as genomics, proteomics, and metabolomics can potentially unravel the intricate working of systems biology underlying the inflammtory process(Reel, Reel, Pearson, Trucco, & Jefferson, 2021). Use of machine learning methods can enhance the integrated analytic process and augment the search of potential ‘biomarkers’ and ‘druggable’ molecular targets. Moreover, studies on combination therapies needs to be prioritized to decrease effective concentration of individual therapies and consequent potential adverse effects.

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Highlights:

- Foreign body response (FBR) following cochlear implantation affects the residual hearing and efficiency of cochlear implant.
- Cellular, molecular, anatomical, and systemic aspects of foreign body response following cochlear implantation in human subjects, animal models and in vitro has been reviewed.
- Pharmacological approaches, surgical techniques, implant materials, and the degree and type of electrical stimulation to mitigate the foreign body response has been highlighted.

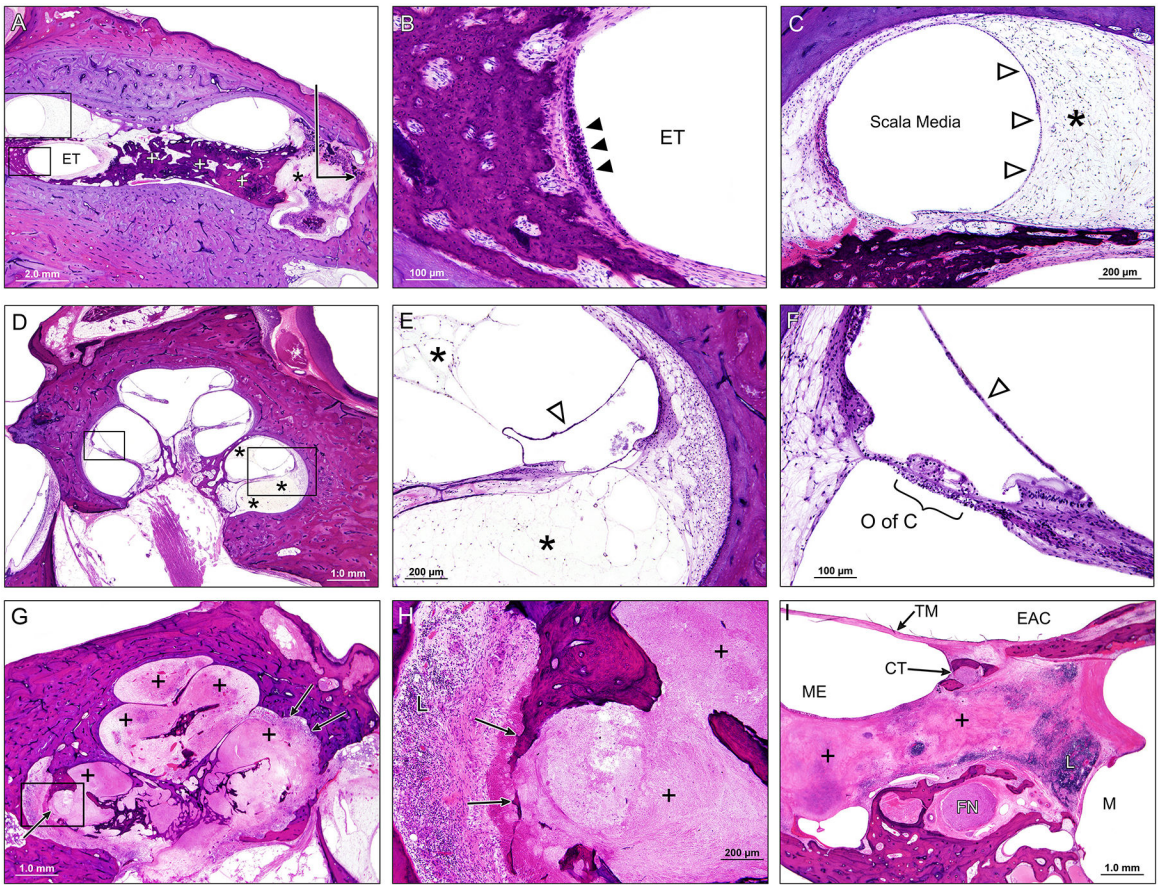

Figure 1. Human temporal bone specimens from 3 patients who were implanted during life, stained with Hematoxylin and Eosin.

A, B, C are from an 89 year-old man who was implanted in his right ear 3 years prior to death with a pre-curved electrode with good performance (CNC score of 74% with his right cochlear implant. In **A**, "+" represent new bone growth in the basal turn of the cochlea; right angle arrow points to the cochleostomy site with adjacent fibrosis; boxes indicate higher magnification images shown in **B** and **C**. In **B**, the electrode track "ET" is shown with surrounding fibrous capsule, and sold arrowheads point to multinucleated giant cells. In **C**, the scala media is shown with hydrops and distended Reissner's membrane (open arrowheads), and loose fibrosis in scala vestibuli ("*"). **D, E**, F are from a 70-year-old man implanted at age 63 years old in the left ear with an electroacoustic cochlear implant with good initial hearing preservation and subsequent delayed loss of residual hearing. In **D**, a mid-modiolar section shows an atraumatic placement of the electrode with no basilar membrane or spiral ligament injury; "*" indicate loose fibrous tissue in the scala tympani and scala vestibuli; boxes represent areas of higher magnification shown in **E** and **F**. In **E**, the lower basal turn shows loose fibrous tissue (*) and slight distension of Reissner's membrane (open arrow). In **F**, the upper basal turn is notable for no direct disruption of the Organ of Corti or spiral ligament due to the implantation. **G, H, I** are from a 71 year old man who was implanted at age 59 in the right ear with initial good performance and then rapid decline and development of facial twitching. **G** shows a massive granulomatous process ("+") filling the entire cochlea, with osteolytic changes of the bone surrounding the cochlea

(arrows); boxes show high magnification views shown in **H** and **I**. In **H**, the osteolytic area and adjacent lymphocytic infiltration (L) in the basal turn is shown. In I, the middle ear (ME) and facial recess is filled with similar granulomatous tissue ("+") with lymphocytes (L). The mastoid (M), chorda tympani (CT), facial nerve (FN), tympanic membrane (TM), and external auditory canal (EAC) are marked for reference.

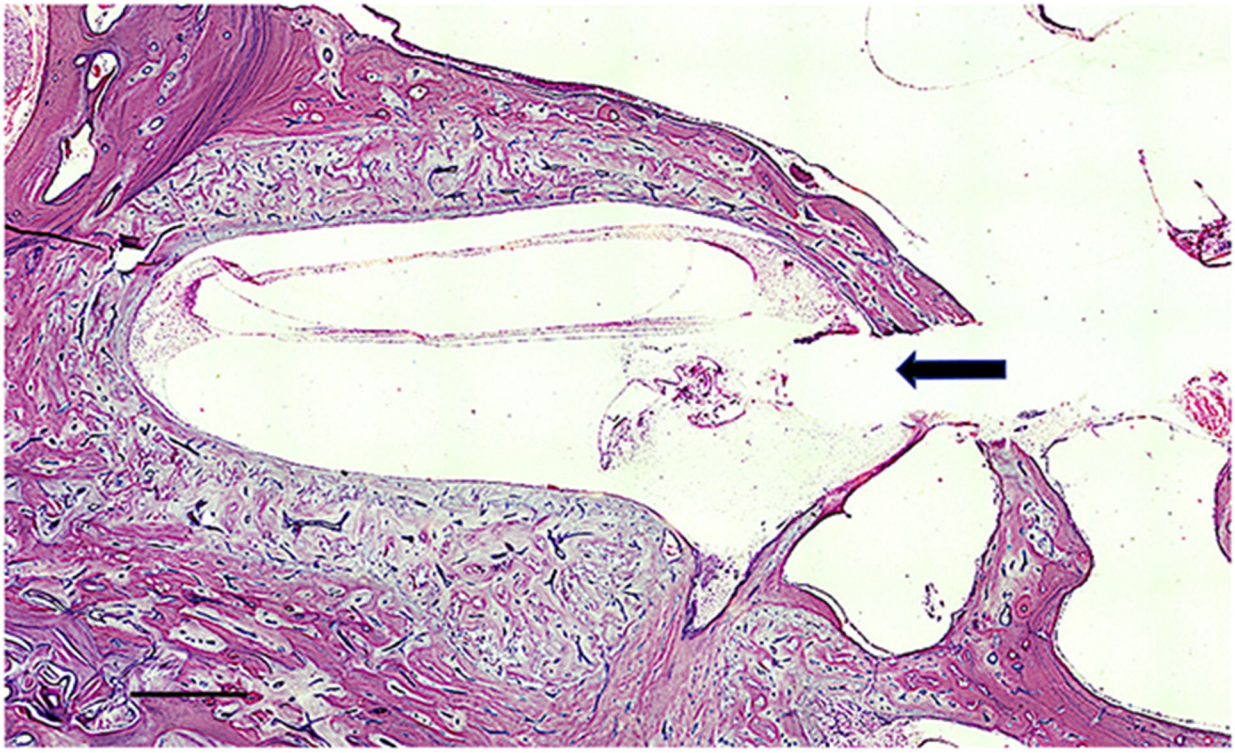

Figure 2. Cochlear implantation with round window insertion using a House/3M 6mm single-channel electrode.

Eighty-year-old male with progressive sensorineural hearing loss underwent cochlear implantation 8 years prior to death. Mild fibrous tissue around insertion site (black arrow) with some loose areolar fibrous tissue in the scala tympani in the inferior basal turn extending only halfway the length of the inferior basal turn is seen. Bar = 500 micron.

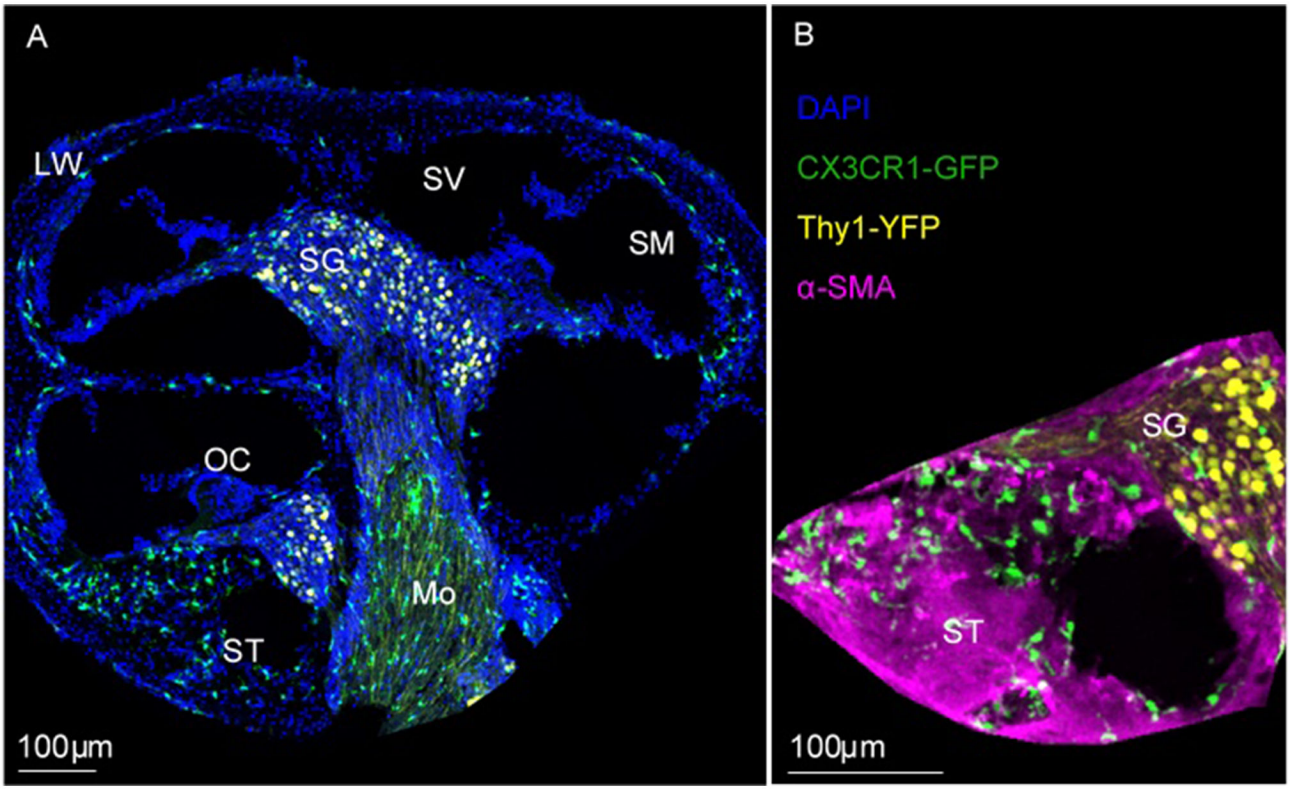

Figure 3: Foreign body response in cochlea following cochlear implantation and electrical stimulation in mouse model

Representative image from a mouse model of cochlear implantation and electrical stimulation. Cochlear implantation was performed in 10-week-old, CX3CR1-GFP/Thy1-YFP C57BL6 mouse with round window electrode array insertion. The CI electrode array consisted of 3 half-banded platinum electrode contacts with a silicone carrier. Electrical stimulation was started 7-day post-implantation and continued for 5 hours, 5 days a week for 3 weeks with the threshold and comfort set at 30 current level below nerve response telemetry threshold. Mice were euthanized 56 days post-implantation. Harvested cochlea was fixed, decalcified, cryopreserved and embedded in OCT. 30 μm thick mid-modiolar sections were labeled with antibody against α-smooth muscle actin (α-SMA) to label myofibroblasts. Nuclei were labeled with DAPI (blue). Confocal images were taken using Leica STELLARIS 5.0 confocal microscope using 20X objective with 0.75 NA. **A**. Mid-modiolar section showing a robust peri-implant foreign body response with cellular infiltration labeled with DAPI including CX3CR1-GFP+ cells (macrophages, green) into the scala tympani of at the base of mouse cochlea. Neurons express YFP (yellow). **B**. Scala tympani of the basal turn of the cochlea showing infiltration of α-SMA+ myofibroblasts (magenta). SM: Scala media, ST: Scala tympani, SV: Scala vestibuli, OC: Organ of Corti, Mo: Modiolus of cochlea, LW: Lateral wall of cochlea

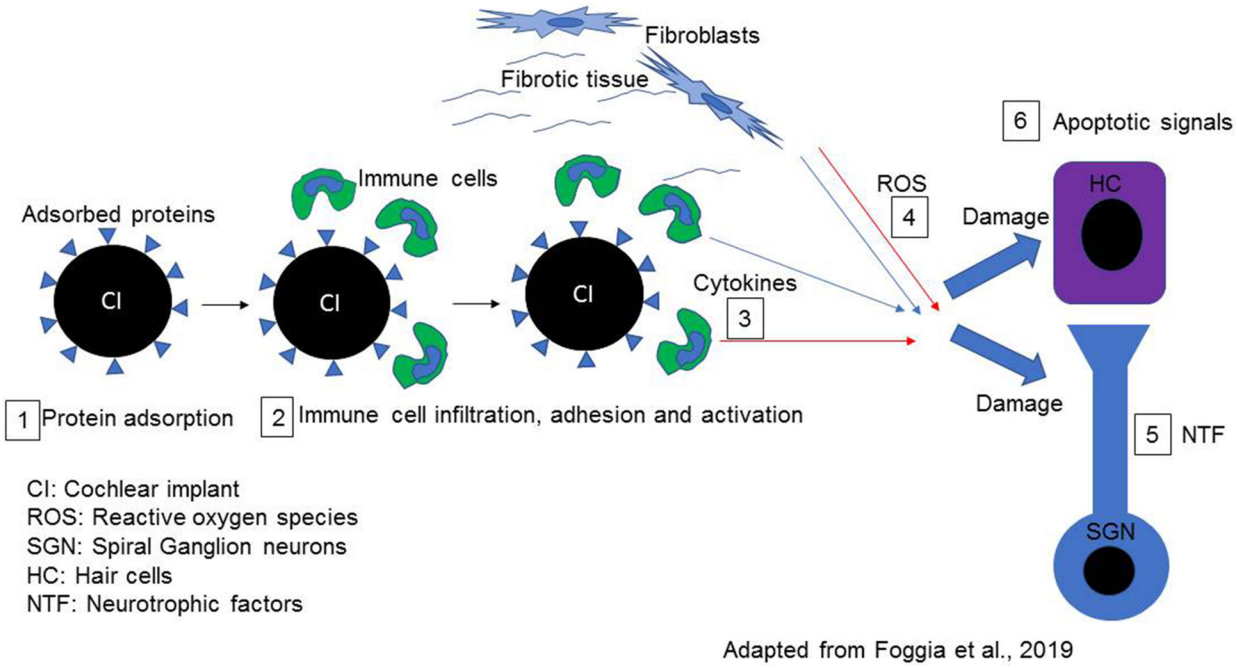

Figure 4:

Schematic representation of the major molecular targets for mitigation of foreign body response (FBR) following cochlear implantation (CI) in *in vitro, in vivo* animal studies, clinical trials, and standard clinical practice. CI results in adsorption of proteins on the CI biomaterials, followed by infiltration of immune cells, adhesion to the adsorbed proteins and CI biomaterials. Immune cells release bioactive cytokines that activate more immune cells, fibroblasts, and many other cell types. Furthermore, inflammatory response results in activation of reactive oxygen species (ROS) and pro-apoptotic signals which might be involved in degeneration of residual hair cells and spiral ganglion neurons (SGNs). The numbered steps (1 to 6) represent major molecular targets for the interventions currently in use in *in vitro, in vivo* animal studies, clinical trials, and standard clinical practice. Additionally, neurotrophic factors (NTFs) have been used to enhance survival of SGNs. A single intervention might have multiple mechanism of actions.

Table 1:

Summary of interventions to mitigate foreign body response (FBR) post-CI with comparison of quantitative effects

Intervention	Type of study, Model	Important result(s)	Reference
Dexamethasone eluting cochlear implants	*In vivo, g*uinea pig	Protection of auditory function, hair cells, neural elements, decrease the FBR, fibrosis and bone growth, and decrease electrical impedance. Significant protection of SGN fibers at 120- day post-CI, protection of hearing thresholds, and hair cells t at 3 months post-CI. 6 months post-CI, hearing loss at 16-kHz stimulus frequency is lower in dexamethasone eluting implant group.	(Ahmadi et al., 2019; Bas et al., 2016; Liu et al., 2015; Simoni et al., 2020; Van De Water et al., 2010; Wilk et al., 2016)
Dexamethasone eluting cochlear implants with noise trauma	*In vivo, g*uinea pig	Following noise trauma, animals implanted with dexamethasone eluting implant experienced significantly lower (~10-15 dB) hearing threshold shifts, compared to those implanted with regular implants ($p<0.001$) at 1, 4, 8 and 16 kHz until 30 days post-CI.	(Eshraghi et al., 2019)
Dexamethasone eluting cochlear implants	*In vivo, g*uinea pig	Reduced inflammatory response including fibrocyte, macrophage, and giant cell infiltration (early), reduced infiltration of lymphocyte, macrophage, and capillary formation (late); Mann-Whitney test ($p<0.05$)	(Farhadi et al., 2013)
Etanercept added to artificial perilymph	*In vivo, g*uinea pig	28 days post-CI, significantly lower hearing threshold of 24 dB SPL ± 4.5 dB in etanercept treated in comparison to 52.0 dB SPL ± 4.5 dB in untreated controls (difference of 28.0 dB SPL ± 21.7 dB), ($p = 0.008$)	(Ihler, Pelz, Coors, Matthias, & Canis, 2014)
Intraperitoneal lipoic acid	*In vivo,* Guinea pig	Guinea pigs received intraperitoneal lipoic acid for 4 weeks following insertion of silicone electrode-dummy through the round window. ABR measurements prior to and at 4 days and 1, 2, 3 and 4 weeks after electrode-dummy insertion showed that lipoic acid prevents loss of acoustic hearing at 2kHz.	(Chang et al., 2017)
IGF1	*In vivo, g*uinea pig	Attenuation of implant insertion trauma and loss of low frequency (4kHz) hearing: until 2 weeks after surgery ($p<0.025$)	(Kikkawa et al., 2014) (Yamahara et al., 2018)
tPA	*In vivo, g*uinea pig	Reduction of fibrosis	(Choong et al., 2019)
Laminin-coated electrodes	*In vivo, g*uinea pig	Lower ABR threshold (~7-10dB), higher SGN density in laminin coated group compared to uncoated ($p<0.05$)	(Bas et al., 2019)
JNK signaling inhibitor, AM-111 /brimapitide	*In vivo, g*uinea pig	Protection of acoustic hearing, hair cells, SGNs, and Schwann cells	(Eshraghi et al., 2006; Eshraghi et al., 2010) (Eshraghi et al., 2013).
N-acetylcysteine (NAC)	*In vivo, g*uinea pig	Reduces post-implant chronic inflammation, preserve residual hearing 24–32 kHz 4 weeks post-surgery compared to controls, increased new bone formation	(Eastwood et al., 2010)
Taurodeoxycholic acid (TCDA)	*In vitro,* rat cochlear explant	Hair cell protection: TDCA significantly reduced the loss of HCs in response to electrode insertion trauma (Bertuleit, Groden, Schafer, & Leuwer) in a dose-dependent manner ($p < 0.01$). With 50 μM of TDCA the percentage of total viable HCs 50%, increased to 90% with 100 μM of TDCA, compared to 20% in control.	(Shah et al., 2020)
BDNF-eluting cochlear implant	*In vivo, g*uinea pig	Guinea pig fibroblasts were transduced with an adenovirus with a BDNF gene cassette insert. After confirming that these cells secreted BDNF, BDNF-secreting cells were attached to the cochlear implant electrode via an agarose gel which was then implanted in the scala tympani. BDNF expressing electrodes preserved significantly more SGNs in the basal turns of the cochlea after 48 days post-CI ($p<0.001$), an effect that decreased in the apical cochlear turns.	(Rejali et al., 2007)

Intervention	Type of study, Model	Important result(s)	Reference
BDNF released from the fibroblast cell line NIH3T3	*In vivo, deafened g*uinea pig, *and in vitro*	SGN protection and neurite outgrowth *in vitro,* Increased SGN survival in vivo in coated (6.16 ± 0.43) SGN/10,000 μm^2 compared to uncoated (1.05 ± 0.28) SGN/10,000 μm^2 (mean±SE), $p < 0.001$	(Warnecke et al., 2012)
NT-3 expressed using viral vectors (AAV.Ntf3) injected into the inner ear	*In vivo,* implanted deaf guinea pig	SGNs protection in deafened guinea pigs, amelioration of reduction of ECAP growth function in deafened ears	(Pfingst et al., 2017)
Flexible “electrode” arrays	*In vivo,* guinea pig	Animals implanted with 'soft' arrays had 4.2% less tissue response compared with animals implanted with 'hard' arrays. Immediately following CI, threshold shift ~8 dB higher threshold shift with stiff electrode (33.19 ± 4.57 dB) with soft electrode, (40.84 ± 2.88 dB), (mean±SE) with stiff electrode, p=0.01. Significantly higher threshold shift upto 7-days post-CI with stiff electrode.	(Choong et al., 2019; Giordano et al., 2014; Kopelovich et al., 2015)
CI coated with hydrogels created from hyaluronic acid and gelatin	*In vivo, g*uinea pig skin	Decrease in capsular tissue responses in coated (1030±66) μm comapred to (1335 ± 75) μm in control (Mean±SE), looser collagen distribution, reduced cytokine expression	(Joo et al., 2021)
Laminin coating	*In vitro* rat cochlear explant, *In vivo* in rats	Augment neurite growth in laminin coated (mean, 426 μm) compared to uncoated electrode (mean,165 μm), $p < 0.001$	(Bas et al., 2019)
Systemic methylprednisolone (1 gm, intravenous) for hearing preservation during cochlear implant surgery.	Double blinded placebo-controlled clinical trial	No prevention of loss of residual hearing, no improvement speech perception, no lowering electrode impedances	(O'Leary et al., 2021)
Comparison among 1) standard intravenous dexamethasone (0.1 mg/kg body mass twice a day); (2) intravenous dexamethasone (0.1 mg/kg b.m. twice a day) and oral prednisone (1 mg/kg body mass/24 h), and (3) no steroid therapy.	Clinical trial	Steroids did not protect residual hearing in cochlear implant recipients.	(Skarzynska, Kolodziejak, Gos, & Skarzynski, 2021).
The effect of antioxidant vitamins A, C and E and a vasodilator, Mg, on overall safety and residual hearing preservation in cochlear implant patients.	Randomized, placebo-controlled clinical trial	Perioperative oral administration of these agents is safe and may provide protection of residual hearing in CI patients	(Scheper et al., 2016; Scheper et al., 2020)

Table 2:

Summary of proposed mechanisms of action of experimental interventions to mitigate FBR post-CI

Intervention	Mechanism of action	Reference
Dexamethasone	Ligand-bound glucocorticoid receptor (GR) translocates into the nucleus and elicit changes in gene expression GR can mediate rapid nongenomic signaling, too. Inhibition of phospholipase A_2 is a major mechanism of anti-inflammatory function of steroids.	(Revollo & Cidlowski, 2009) (Flower & Blackwell, 1979)
Etanercept	Etanercept is a biologic inhibitor of tumor necrosis factor (TNF), a soluble inflammatory cytokine. Etanercept is a soluble receptor construct that consists of two p75 TNF receptors fused to the Fc portion of human IgG; this construct binds TNF-alpha and TNF-beta.	(Zalevsky et al., 2007) (Tracey, Klareskog, Sasso, Salfeld, & Tak, 2008)
Lipoic acid	Lipoic acid, a naturally occurring organosulfur compound, synthesized by plants and animals including humans, is known to be anti-inflammatory and 'universal antioxidant'. With a highly negative reduction potential, it increases the expression of antioxidant enzymes, and increases recycling of vitamins C and E.	(Carreau, 1979; Reed, 2001) (Moura, de Andrade, dos Santos, & Goulart, 2015)
Insulin-like growth factor 1 (IGF-1)	IGF1 binds to IGF1R, a membrane-bound receptor tyrosine kinase (RTK), which activates both the mitogen-activated protein (MAP) kinase and PI3K signaling pathways, promoting tissue growth and maturation in almost any tissue, prenatal and early postnatal neurodevelopment, and neural plasticity and remodeling.	(Wrigley, Arafa, & Tropea, 2017)
AM-111 (brimapitide)	A cell-penetrating c-Jun N-terminal Kinase (JNK) inhibitor. JNK pathway plays a central role in stress signaling pathways implicated in gene expression, neuronal plasticity, regeneration, cell death, and regulation of cellular senescence.	(Staecker et al., 2019) (Yarza, Vela, Solas, & Ramirez, 2015)
N acetyl Cysteine	Reduces of disulfide bonds, scavenging reactive oxygen species, a precursor for glutathione biosynthesis, converts into hydrogen sulfide and sulfane sulfur species that scavenge free radicals.	(Pedre, Barayeu, Ezerina, & Dick, 2021)
Tauroursodeoxycholic acid	Neuroprotection with anti-inflammatory, antioxidant and anti-apoptotic functions by inhibiting TNF-α, IL-1β, p-JNK, NF-κB among other targets.	(Daruich, Picard, Boatright, & Behar-Cohen, 2019)
BDNF	BDNF binds to trkB receptor activates proneurotrophic signaling pathways including Ras-MAP and CREB.	(Binder & Scharfman, 2004)
NT-3	Binds to trkC receptor that activates proneurotrophic signaling pathways including Ras-MAP, CREB	(Binder & Scharfman, 2004)
Laminin	α, β, and γ chain subunits of laminin self-assemble, bind to other matrix macromolecules, interacts with cells mediated by integrins, dystroglycan, and other receptors. Laminin critically contributes to cell differentiation, cell shape and movement.	(Colognato & Yurchenco, 2000)