Hearing Research xxx (2017) 1–11

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Review Article

Advances in translational inner ear stem cell research

Athanasia Warnecke [a, c], Adam J. Mellott [b], Ariane Römer [a, c], Thomas Lenarz [a, c], Hinrich Staecker [d, *]

[a] Department of Otorhinolaryngology, Head and Neck Surgery, Hannover Medical School, Carl Neuberg-Str. 1, 30625, Hannover, Germany
[b] Department of Plastic Surgery, University of Kansas School of Medicine, Kansas City, KS, USA
[c] Cluster of Excellence "Hearing4all" of the German Research Foundation, Germany
[d] Department of Otolaryngology Head and Neck Surgery, University of Kansas School of Medicine, Kansas City, KS, USA

ARTICLE INFO

Article history:
Received 5 March 2017
Received in revised form
1 May 2017
Accepted 23 May 2017
Available online xxx

ABSTRACT

Stem cell research is expanding our understanding of developmental biology as well as promising the development of new therapies for a range of different diseases. Within hearing research, the use of stem cells has focused mainly on cell replacement. Stem cells however have a broad range of other potential applications that are just beginning to be explored in the ear. Mesenchymal stem cells are an adult derived stem cell population that have been shown to produce growth factors, modulate the immune system and can differentiate into a wide variety of tissue types. Potential advantages of mesenchymal/adult stem cells are that they have no ethical constraints on their use. However, appropriate regulatory oversight seems necessary in order to protect patients from side effects. Disadvantages may be the lack of efficacy in many preclinical studies. But if proven safe and efficacious, they are easily translatable to clinical trials. The current review will focus on the potential application on mesenchymal stem cells for the treatment of inner ear disorders.

Contents

1. Introduction 00
2. Classification of stem and progenitor cells 00
   2.1. Endogenous stem cells in the ear 00
   2.2. Embryonic stem cells 00
   2.3. Induced pluripotent stem cells 00
   2.4. Adult stem and progenitor cells 00
3. Application of stem cells in inner ear disease models 00
   3.1. Delivery routes to the inner ear 00
   3.2. Survival, engraftment and differentiation of stem cells transplanted to the inner ear 00
   3.3. Use of stem cells in animal models of inner ear disease 00
   3.4. Genetic modification of stem cells 00
4. Potential for stem cell therapy in cochlear implantation 00
   4.1. Immunomodulation, neuroprotection and regeneration 00
   4.2. Safety of autologous stem cells in human cochlear implantation 00
5. Conclusion 00
   References 00

1. Introduction

Research and application of mesenchymal stem cell technology

* Corresponding author.
E-mail address: Hstaecker@kumc.edu (H. Staecker).

http://dx.doi.org/10.1016/j.heares.2017.05.011
0378-5955/

has rapidly emerged in most areas of medicine (Bianco et al., 2013). Despite this rapid progress in other fields, only few publications concentrate on the use of mesenchymal stem cells in the inner ear (Lee et al., 2012; Kasagi et al., 2013; Tan et al., 2014; Zhou et al., 2011; Choi et al., 2012). Mesenchymal stem cells are a readily available population of cells that can be used both for cell replacement strategies but also for modulation of inflammatory injury and production of growth factors. They have the potential for rapid translation into clinical applications since for the most part these cells can be autologously obtained from adipose tissue or bone marrow prior to transplantation. This review will give an overview on mesenchymal stem cells and their potential application in otology. Application of stem cells for regenerative treatment and cell replacement has been previously reviewed (Pettingill et al., 2007; Shi and Edge, 2013; Almeida-Branco et al., 2015; Santaolalla et al., 2013; Hu et al., 2009; Kohrman and Raphael, 2013; Rubel et al., 2013; Mallick et al., 2012; Gillespie et al., 2014; Müller and Barr-Gillespie, 2015; Devarajan et al., 2011; Richardson et al., 2008; Martinez-Monedero and Edge, 2007; Pauley et al., 2008; Okano and Kelley, 2012; Géléoc and Holt, 2014).

2. Classification of stem and progenitor cells

Stem cells are characterized by their ability to proliferate extensively (self-renewal capacity), by the fact that they usually arise from a single cell (clonality) and by their potency, i.e., their ability to differentiate into different cell types (Kolios and Moodley, 2013) (Table 1). Based on their potency to differentiate, they can be further subdivided into toti- or omnipotent (Condic, 2014), pluripotent (Tesar, 2016), multipotent, oligopotent and unipotent cells. Toti- or omnipotent cells are able to differentiate into embryonic and extraembryonic tissue (Kolios and Moodley, 2013). Thus, they are able to give rise to a complete organism (Condic, 2014). Only the zygote and the cells after the first division are totipotent, i.e., they possess the ability to produce an orchestrated developmental sequence being reflected in the development of the embryo and the placenta (Condic, 2014). Pluripotent stem cells are able to differentiate into cells arising from the ectoderm, endoderm, and mesoderm (Tesar, 2016) a feature that is unique for embryonic stem cells derived from the inner cell mass of the blastocyst (Condic, 2014). However, pluripotency can be induced in somatic cells by reprogramming (Takahashi and Yamanaka, 2006). These cells are termed induced pluripotent stem cells (iPSCs) and have revolutionized the field of regenerative medicine (Zomer et al., 2015).

By contrast, multipotent stem cells are found in most tissues and differentiate into cells from a single germ layer (Kolios and Moodley, 2013). The best defined example of this category is the mesenchymal stem cell (Krampera et al., 2007). Initially isolated only from the bone marrow, these cells are now known to be present in various tissue types such as adipose tissue, bone, Wharton's jelly, umbilical cord and peripheral blood, amnion, skin, hair follicles and dental tissues. They are characterized by their adhesion to cell culture dishes and by the presence of specific surface markers (Dominici et al., 2006). These cells have the capacity to differentiate into adipose tissue, bone, cartilage, and muscle, however, they are also able to transdifferentiate into cell types from other germ layers, such as neuronal tissue (ectoderm) (Chang et al., 2013).

Oligopotent stem cells retain their self-renewal capacity and are able to differentiate into at least two or more cell types within a specific tissue (Kolios and Moodley, 2013). Such cells have been identified on the ocular surface (Majo et al., 2008). Another example of oligopotent stem cells are hematopoietic stem cells since they typically differentiate into myeloid and lymphoid cells (Marone et al., 2002). Although unipotent stem cells can self-renew, they differentiate into only one specific cell type and form a single lineage such as the satellite cells that reside in the muscle (Dumont et al., 2015). They also have been identified in the skin, maintaining the Merkel cell population (Wright et al., 2015). Based on their self-renewal capacity and their differentiation ability, stem cells should be distinguished from progenitor cells. Whereas stem cells retain an unlimited capacity for self-renewal, this capacity is limited in progenitor cells.

2.1. Endogenous stem cells in the ear

Endogenous adult stem cells reside all tissues, and are important for tissue homeostasis and remodelling processes (Kolios and Moodley, 2013; Klimczak and Kozlowska, 2016). They originate during ontogenesis and remain in a quiescent state until local stimuli activate their proliferation, differentiation or migration (Marone et al., 2002). Usually, they reside in a stem cell niche under specific environmental conditions (Kiefer, 2011). The function of tissue-resident stem cells depends on intrinsic and extrinsic signals from their microenvironment (Dumont et al., 2015). During injury, they proliferate in order to induce reparative processes (Kolios and Moodley, 2013; Dumont et al., 2015). In the inner ear, stem or progenitor cells can be isolated from neonatal tissue. Advanced lineage tracing techniques have suggested that supporting cells can proliferate and expand after injury to promote repair (Wang et al., 2015).

Sphere generating cells from the inner ear were first identified by Li et al. (2003). These endogenous progenitor cells have been isolated successfully from neonatal tissue (Coleman et al., 2007). Once formed, cells within spheres show mitosis, apoptosis, necrosis and phagocytosis (Rak et al., 2011; Bez et al., 2003). With sphere generating cells isolated from the utricular epithelium, Li et al. generated hair cell-like cells (Li et al., 2003) which may to be able to repair tissue after inner ear trauma *in vivo* (Li et al., 2004). Rask-Anderson et al. expanded this method and identified progenitor cells in human cochleae (Rask-Andersen et al., 2005). Mouse cochlear stem cells have the ability to transform into inner ear hair cell-like cells (Li et al., 2003; Diensthuber et al., 2009; Yerukhimovich et al., 2007; Savary et al., 2008) as well as glia-like cells (Yerukhimovich et al., 2007). The utricular macula and

Table 1
Classification of stem cells.

Stem Cell Type	Characteristics	Applications
Embryonic (ESC)	Pluripotent, can form all tissue types	Replacement of tissue, disease modelling
Induced pluripotent (iPSC)	Same characteristics as embryonic stem cells but induced from differentiated cells such as fibroblasts	Disease modelling, drug screening, investigation of epigenetics
Endogenous stem cells	Present in all tissues with capacity to replace tissue in which they reside to different degrees	Potential modulation of repair within a tissue
Mesenchymal Stem Cells (MSC)	Multipotent, present in most tissue; easily isolated	Tissue replacement, modulation of inflammation, modulation of apoptosis, induction of angiogenesis

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011

the organ of Corti contain the majority of the inner ear progenitors (Breuskin et al., 2008). Other cells expressing the stem cell marker nestin can be found in spiral limbus, Reissner's membrane, the stria vascularis and the basilar membrane (Carricondo et al., 2010). Cochlear stem cells exhibit long-term survival *in vitro* preserving their inner ear specific surface markers (Savary et al., 2008) without the addition of growth factors and show increased spontaneous differentiation capacity that may also indicate a possible teratogenic potency (Carricondo et al., 2010) supporting previous findings (Knoepfler, 2009).

2.2. Embryonic stem cells

Embryonic stem cells (ESCs) can be isolated from inner cell mass of the blastocyst and express characteristic cell surface markers such as stage-specific embryonic antigen-3 (SSEA-3), SSEA- 4, tumor rejection antigen-1-60 (TRA-1-60), TRA-1-81, and alkaline phosphatase (Girlovanu et al., 2015). For culturing, ESC require a layer of feeder cells or adherent substrates (Turner et al., 2015). Leukemia inhibitory factor-containing medium also allows the ESC cultivation (Desbaillets et al., 2000). In addition, ESC can form embryonic bodies *in vitro*, presenting an excellent model for embryogenesis (Desbaillets et al., 2000). The regenerative capacity of these cells is very promising and ESC differentiated into oligodendrocytes are currently used in an on-going phase 1 clinical trial for the treatment of spinal cord injuries (Goel, 2016). Furthermore, retinal pigmented epithelium obtained from human ESC for the treatment of wet and dry age-related macular degeneration is currently being analysed in safety and tolerability studies (Song et al., 2015). However, risk of teratoma formation as well as ethical considerations still limit their clinical translation. A technique for the non-embryo-destructive extraction of ESC from the inner cell mass has been introduced, potentially making the use of ESC more acceptable (Dittrich et al., 2015).

2.3. Induced pluripotent stem cells

Cellular reprogramming was first initiated in 1962 by somatic cell nuclear transfer experiments from a differentiated cell isolated from the mid-intestine of feeding tadpoles into an enucleated xenopus oocyte (GURDON, 1962). Several decades later, nuclear reprogramming of somatic cells became reality by the *in vitro* hybridization with ESC (Tada et al., 2001). Thus, the idea that unfertilized eggs and ESC may contain factors that are able to reprogram somatic cells was born. Indeed, adult somatic cells can be induced to pluripotency by nuclear reprogramming. Successfully initiated in 2006 by Takahashi and Yamanaka, pluripotency was driven in adult murine and human fibroblasts by four factors, i.e., Oct3/4, Sox2, c-Myc, and Klf4, that play a critical role in maintaining the pluripotency of embryonic stem cells (ESC) (Takahashi and Yamanaka, 2006). This nuclear reprogramming resulted in a cell type that resembled all the characteristics of ESC. Development of induced pluripotent stem cells (iPSC) has several advantages: elimination of ethical issues, reduction of rejection after transplantation, and high differentiation capacity and the autologous transplantation. Several obstacles need to be overcome in order to advance iPSC towards clinical application. Reprogramming seems to be a slow process and takes up more than two weeks (Takahashi and Yamanaka, 2006; Romito and Cobellis, 2016). In addition, only a few of the transfected cells become iPSCs (up to 3%) (Takahashi and Yamanaka, 2006; Apostolou and Hochedlinger, 2013), indicating not only the inefficiency of this procedure but also the existence of epigenetic barriers, such as DNA methylation and histone modifications that stabilize the cell identity (Apostolou and Hochedlinger, 2013). The use of retro- or lentiviral vectors for the expression of reprogramming factors may also cause insertional mutagenesis resulting in tumor formation (Romito and Cobellis, 2016; Cefalo et al., 2016). In addition, some of the transcription factors used for the reprogramming may promote tumor formation. Recent strategies for the development of clinically applicable iPSC concentrated on alternative strategies for the delivery of reprogramming factors and on alternative factors to c-Myc since this is associated with an increased risk of tumorigenicity (Rony et al., 2015). Recent experiments have used small molecules in combination with a single gene to efficiently produce iPSC that are less prone to tumor formation (Li et al., 2011). Although initially thought to be unlikely, a immune response to autologous iPSC-derived cells has also been demonstrated (Scheiner et al., 2014). The reasons for the immune response include immaturity of transplanted cells, genetic and epigenetic changes due to reprogramming or culture adaptation, effects of xenogeneic or non-physiological culture reagents, and expression of gene-corrected proteins (Scheiner et al., 2014). Another major concern in the use of iPSC is the fact that they are prone to teratoma formation if they are transplanted in an undifferentiated state (Peterson and Loring, 2014).

By combining iPSC technology with the ability to induce production of hair cells from stem cells, investigators have started to produce hair cells from patients with known genetic disorders. Induced pluripotent stem cells from patients both with myosin VIIa and myosin 15 mutations have been produced and used to investigate the effect of gene therapy on functional recovery in these cells (Tang et al., 2016; Chen et al., 2016). These *in vitro* approaches allow us to model gene therapy in human tissue and can provide early-stage proof of concept studies prior to moving into animal models. Maturation of this technology will allow screening of drugs and therapeutics in human cell systems.

2.4. Adult stem and progenitor cells

A key factor in the development of tissue engineering technologies is the availability and source of donor cells. For clinical applications where cell populations have to be expanded, tissue must be processed by good manufacturing process as defined by the government agencies such as the U.S. Food and Drug Administration. Mesenchymal stem cells (MSC) have an advantage in that they can often be derived autologously and in sufficient, easy to obtain quantities so that no expansion is needed. Two main sources of mesenchymal stem cells are fat and bone marrow. Adipose derived stem cells (ADCs) are easily obtained (in humans) from liposuction or fat grafts. After being morcellized and collagenase digested, a centrifugation step yields a pellet that can be plated in plastic culture flasks. Cells that are adherent to plastic represent the preadipocyte stem cell population. These cells express characteristic surface markers and can be further characterized by immunohistochemistry or flow cytometry (Gimble et al., 2007). These plastic adherent cells can be induced into a wide variety of tissue types including adipocytes, cardiomyocytes, chondrocytes, endothelial cells, neuronal-like cells and osteoblasts (Gimble et al., 2007; Mizuno et al., 2012). Repeated passaging of these cells results in reduction of histocompatibility antigens raising the possibility that these can be used for allogenic transplantation. The euphoria resulting from the ease of isolation and the availability has been dampened by recent reports showing severe adverse effects after transplantation to the eye such as loss of vision (Kuriyan et al., 2017; Marks et al., 2017).

The bone marrow hosts a diverse population of adult mesenchymal stem cells. Their secretome makes them unique and allows for their pleiotropic actions (D'souza et al., 2015; Tran and Damaser, 2014). However, the bone marrow also contains different kinds of cell lineages and the mixture of these cells will be termed bone

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011

marrow-derived mononuclear cells (BM-MNC). They include MSC, hematopoietic stem cells (HSC), epithelial stem cells, common lymphoid and myeloid precursors and their mature forms T and B lymphocytes, NK cells, monocytes, dendritic cells, megakaryocytes, and granulocytes (Sharma et al., 2015a; Pösel et al., 2012; Algoe et al., 2008). An orchestrated interplay of these cells promotes a variety of actions such as angiogenesis, vascular repair, expression of growth factors and cytokines (Pösel et al., 2012) (Fig. 1). BM-MNCs cells have been used in a range of clinical studies over the last year (Assmus et al., 2016; Cai et al., 2015a; Duan et al., 2015; Franz et al., 2015; José et al., 2015; Mann et al., 2015; Mansour, 2016; Martino et al., 2015; Mesentier-Louro et al., 2016; Moniche et al., 2015; Morales et al., 2015; Nemoto et al., 2015; Peeters Weem et al., 2015; Huang et al., 2015; Sharma et al., 2015b; Skora et al., 2015; Tabatabaee et al., 2015; Taguchi et al., 2015; Taylor et al., 2015; Yiou et al., 2015; Zhang et al., 2015), thus ample preclinical and clinical safety data, as well as feasibility and efficacy data exists (Pösel et al., 2012). Potentially transplantation of BM-MNC rather than MSC can be used for a variety of clinical applications since no purification and plastic adherence step is needed. Isolation of MSC by plastic adhesion may alter the natural cell physiology and thus raises several concerns in terms of clinical translation: the differentiation and proliferation capacity as well as their therapeutic properties may be diminished and cells may acquire chromosomal abnormities (Mabuchi et al., 2012).

Stem cells derived from umbilical cords present an alternative source of cells that can be used for allogenic transplantation. The stromal cells in Wharton's jelly have been shown to display similar markers as other stromal stem cells and have been shown to differentiate into bone, cartilage and neural tissue. Wharton's jelly cells (WJCs) also produce a range of different growth factors and are overall well-tolerated by the immune system. WJCs have been tested in a number of different preclinical animal models of human disease and are easy to obtain (Troyer and Weiss, 2008).

3. Application of stem cells in inner ear disease models

Application of stem cells to treat different inner ear diseases will need careful evaluation. The major drawback is the lack of knowledge of the pathophysiology of inner ear diseases such as sudden sensorineural hearing loss or Menières disease. However, by improving diagnostics such information may be available in the future thereby aiding in the identification of suitable therapeutic agents. Although this seems very speculative at the moment, mesenchymal stem cells could be helpful for the treatment of diverse conditions in the inner ear based on what is being done in other areas of medicine. Atrophy of the stria vascularis has been considered to be one of the underlying pathophysiological changes in presbycusis (Peng and Linthicum, 2016; Kurata et al., 2016). Providing the inner ear with vascular endothelial growth factor secreted by different stem cell types might be one putative treatment option. In Menières disease, inflammation and damage of cochlear structures may also be addressed by cell-based therapies. The immunomodulation and release of anti-inflammatory substances of mesenchymal stem cells could be beneficial as adjuvant treatment during cochlear implantation in order to prevent fibrotic tissue formation and foreign body reaction. Another option could be stem cell application for cell replacement therapy. However, the road towards translation is long and the efficacy of cell-based therapies need to be proven. Below, delivery routes as well as preclinical data will be reviewed and discussed, particularly pointing out promising results as well as pitfalls and drawbacks.

3.1. Delivery routes to the inner ear

Cells can be delivered either systemically or locally to the inner ear. Intravenous application makes local manipulation of the inner ear unnecessary. However, the delivered cells would also exert their effects in other tissues that do not require intervention with the risk of systemic side effects. In addition, systemically administered cells may be cleared in other organs such as the lung preventing the accumulation of effective cell numbers in the target organ (Choi et al., 2012; Barbash et al., 2003; Orlic et al., 2002). Thus, injection techniques bypassing the pulmonary circulation may be necessary.

Intense noise or ototoxic injury induces homing of human

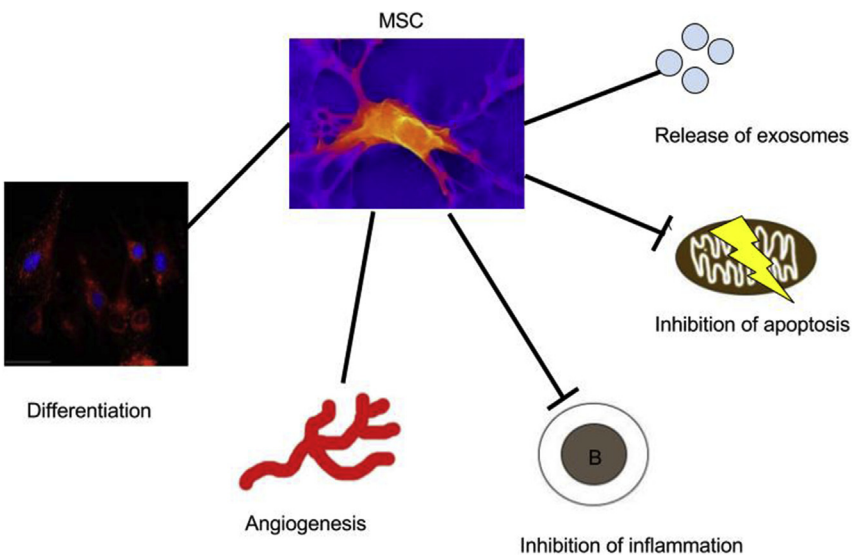

Fig. 1. Effects of transplanted mesenchymal stem cells (MSC). MSCs have been demonstrated to differentiate into a wide variety of different tissue types including neurons, muscle and cartilage. The tissue type produced depends on the origin of the MSC, the culture conditions used to modify it and the tissue that it is transplanted into. MSCs have also been shown to induce angiogenesis, inhibit inflammation including inhibition of B cells, T cells and oligodendrocytes as well as inhibiting apoptosis. Many of these effects may be mediated through the production of exosomes which contain a mix of lipids, proteins and nucleic acids particularly miRNAs. The characterization of the contents and effects of exosomes produced by different cell types are a key frontier in MSC research.

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011

mesenchymal stem cells to the cochlea after intravenous administration in rats (Choi et al., 2012). The recruitment of cells to severely injured areas of tissues has been demonstrated in various organs such as the lung (Cai et al., 2015b), the heart (Barbash et al., 2003), the gut (Kavanagh et al., 2015) or the brain (Yu et al., 2015). The complex architecture of the human cochlea offers several compartments for the local delivery of cells. Attempts to transplant cells into the scala tympani (Coleman et al., 2006; Hu et al., 2005a), the scala media (Hildebrand et al., 2005), the auditory nerve or modiolus (Corrales et al., 2006; Hu et al., 2004; Regala et al., 2005; Sekiya et al., 2006), Rosenthal's canal (Coleman et al., 2007) and the semicircular canals (Kamiya, 2015) have been successful. Injecting cells into the scala tympani or the semicircular canals is less invasive but results in increased cell dispersal (Coleman et al., 2006). The scala tympani delivery technique has been shown to be surgically easy to develop and the procedure is in routine clinical use during insertion of cochlear implant electrodes. However, the spiral ganglion neurons are rarely reached since only very few cells migrate from the scala tympani to Rosenthal's canal (Coleman et al., 2006). By contrast, injection into the auditory nerve or directly into the modiolus may be more invasive but results in better integration and less dispersal (Okano et al., 2005). However, when delivering cells via the modiolar approach, a significant loss of spiral ganglion neurons occurs due to the invasiveness of this technique (Backhouse et al., 2008). Approaching the auditory nerve using a translabyrinthine approach leads to a fibrous tissue formation throughout all turns of the cochlea (Backhouse et al., 2008). This is also associated with a significant reduction in neuronal density (Backhouse et al., 2008). Bogaerts and colleagues compared three different injection sites into the mouse cochlea (anterior and posterior cochleostomy and the round window approach) (Bogaerts et al., 2008). Interestingly, fluorescence-labelled immortalized human mammary epithelial cells used as a model were not detected in half of the injected animals, demonstrating a low integration and survival rate that was not dependent from the transplantation site (Bogaerts et al., 2008).

3.2. Survival, engraftment and differentiation of stem cells transplanted to the inner ear

ESCs or neural cells derived from ESCs have been transplanted into the cochlea in multiple experimental settings with varying results and overall limited donor cell survival in the host environment. Survival of small numbers of transplanted ESC was observed for up to 4 weeks although a decrease in the number of surviving cells after 4 weeks was obvious despite their pre-differentiation to neuroectoderm prior to transplantation (Coleman et al., 2006). Approximately 10% of the cells survived 4 weeks following transplantation to the cochlea (Coleman et al., 2006; Hu et al., 2005b; Iguchi et al., 2003). Even transplantation directly into the modiolus along the auditory nerve fibres resulted in a poor survival of embryonic dorsal root ganglion cells and ESC (Hu et al., 2004). However, ESC were able to migrate further centrally when compared to embryonic dorsal root ganglion cells (Hu et al., 2004). Transplantation of ESC after stromal cell-derived neuronal induction into the damaged inner ear appears more promising in terms of engraftment and functional replacement of auditory neurons (Okano et al., 2005).

Whether the cochlear environment hampers survival of transplanted cells or if cells leave the cochlear space remains unclear. Attempts to increase survival and neuronal differentiation of ESC after transplantation into the scala tympani of systemically deafened guinea pigs include the administration of glial derived neurotrophic factor (GDNF) via an osmotic pump over 14 days (Altschuler et al., 2008). An increased percentage of transplanted cells acquiring neuronal phenotype was observed under this regimen (Altschuler et al., 2008). Embryonic dorsal root ganglion cells did show improved survival as well as better integration into the host tissue when compared to ESC (Hu et al., 2004, 2005b; Olivius et al., 2003) and they were able to improve survival and integration of ESC when co-transplanted (Hu et al., 2005b). Thus, an embryonic neuronal microenvironment may favor survival and differentiation of ESC in the adult auditory system (Hu et al., 2005b). The cochlear microenvironment offers important cues for the transplanted cells. For example, after injection into sound-damaged cochlea, neural stem cells obtained from fetal tissue up-regulated site-specific proteins that correspond to the host cells of the regions where the transplanted cells engrafted (Parker et al., 2007). Thus, the mature mammalian cochlea seems, at least after induction of damage, to retain the developmental signals that are necessary to induce differentiation towards a cochlear phenotype (Parker et al., 2007). Ouabain-induced degeneration of spiral ganglion neurons in rats resulted in increased neuronal differentiation of neural stem cells transplanted into the cochela (He et al., 2014). One possible mechanism for the regulation of neuronal differentiation of stem cells could be the activation of the canonical Wnt signaling pathway (He et al., 2014; Cardozo et al., 2011; Kondo et al., 2011) and Wnt-1 seems to be up-regulated in the spiral ganglion after induced damage to the neurons (He et al., 2014). Murine ESC pre-differentiated in otic progenitors prior to transplantation resulted in ectopic position of the cells on the cochlear nerve trunk (Corrales et al., 2006). These cells even extended several branches of β-III tubulin-positive neurites towards the organ of Corti, exiting the modiolus to enter Rosenthal's canal (Corrales et al., 2006). Human ESC behaved in a similar fashion and their transplantation into ouabain deafened gerbils resulted in grafting in the modiolus where they formed ectopic beta-tubulin positive cells (Chen et al., 2012). These cells were also able to restore auditory function in the deafened animals despite xenogenic transplantation (Chen et al., 2012). Efforts to transform the hostile environment of the scala media into one that favours engraftment and survival of transplanted cells such as disruption of the junctions of the auditory epithelium, blocking of the pumps in the stria vascularis and replacement of endolymph with perilymph are ongoing (Park et al., 2014) but give a formidable impression of the obstacles that may occur when considering the transplantation of cells to the inner ear.

Ischemic damage to the cochlea of gerbils resulted in swelling and membrane disruption of the afferent fibres as well as damaged stereocilia of the inner ear (Hakuba et al., 2005). Here, homologous transplantation of embryonic neuronal stem cells (NSC) was sufficient to prevent these damage-associated morphological alterations as well as to reduce changes in ABR threshholds (Hakuba et al., 2005). The transplanted cells survived and were located in the tunnel of Corti, along the inner pillar cells under the inner hair cells (Hakuba et al., 2005). Localization of NSC in the hair cell region has been also observed 11 days after homologous transplantation of murine NSC (Nagy et al., 2007). The migration capacity of murine NSC has been demonstrated by engraftment into the vestibular epithelium after their transplantation to the injured cochlea of deafened mice and rats (Tateya et al., 2003; Zhao et al., 2012). Also, migration to Rosenthal's canal and engraftment and neuronal differentiation of murine NSC after transplantation vial the lateral wall of the cochlea has been shown in rats (Zhang et al., 2013a). Efforts to limit dispersal of transplanted stem cells have concentrated on the use of hydrogels for the encapsulation of the transplanted cells (Nayagam et al., 2012). Most of the grafted NSC differentiated to glial (Iguchi et al., 2003; Tateya et al., 2003) and neuronal phenotype (Tateya et al., 2003) and a similar behavior was observed for this cell type after transplantation to the brain or to the retina (Tateya et al., 2003). After transplantation, embryonic derived NSC

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011

survive up to 4 weeks into the cochlea (Iguchi et al., 2003). Furthermore, the surviving cells labelled positive for brain derived neurotrophic factor (BDNF) and GDNF suggesting the expression of these growth factors from the transplanted cells (Iguchi et al., 2003).

Chronic electrical stimulation (CES) with and without nerve growth factor (NGF) treatment was applied to deafened guinea pigs alongside with the transplantation of embryonic murine dorsal root ganglion cells (Hu et al., 2009). The survival of the transplanted cells was not influenced, neither by CES or NGF or a combination of both (Hu et al., 2009). However, neuritic outgrowth from the implanted neurons was stimulated and enhanced by CES and/or NGF (Hu et al., 2009). Electrically evoked auditory brainstem responses, however, did not show any functional improvement due to this treatment regimen (Hu et al., 2009).

Certain cochlear microenvironments have a negative effect of cell migration and survival. After transplantation of partially differentiated and undifferentiated murine ESC into the scala media of deafened guinea pigs, small amounts of fibrous tissue were observed that surrounded the transplanted cells (Hildebrand et al., 2005). None of the surviving cells were found to integrate into the host tissue and the survival rate of transplanted cells significantly reduced over time (Hildebrand et al., 2005).

Another crucial point is the timing of cell transplantation in regard to the cochlear damage: early after an otic insult, the cochlear environment is in a different metabolic state that offers transplanted cells specific factors that are not present in a healthy cochlea (Parker et al., 2007). Viable clusters of murine ESC survived in the early post-injury period in the cochlea of ouabain-deafened gerbils when compared to the transplantation of cells in the late post-injury period (Lang et al., 2008). Thus, there seems to be an optimal time window for engraftment and survival of ESC.

Epithelial stem cells survive for at least 4 weeks within the cochlea and integrate into tissues lining the perilymphatic compartments (Sullivan et al., 2011) where NSC integration has not been observed upon transplantation (Parker et al., 2007). Thus, cochlear integration sites may be stem cell specific and transplantation of a diversity of stem cell types may be most promising for addressing the different regions of the inner ear.

3.3. Use of stem cells in animal models of inner ear disease

Adult stem cell transplantation to the inner ear is a promising approach with several advantages when compared to the use of embryonic cells: lower ethical concerns, lower risk of teratogenicity and tumor formation, easy accessibility, large cell populations and variety of cells available (Krampera et al., 2007; Sng and Lufkin, 2012; Huang et al., 2010). The differentiation capacity and the risk of tumorigenesis after cochlear transplantation of iPS derived from adult or embryonic cells has been compared (Nishimura et al., 2012). Despite neuronal induction, residual undifferentiated cells were present and the cells preserved their proliferation activity even 4 weeks after transplantation (Nishimura et al., 2012). Even so, after the transplantation of embryonic cells into the cochlea, no tumor formation was observed (Coleman et al., 2006; Hu et al., 2004, 2005a; Corrales et al., 2006; Okano et al., 2005; Hu et al., 2005b; Iguchi et al., 2003; Altschuler et al., 2008; Parker et al., 2007; He et al., 2014; Chen et al., 2012; Hakuba et al., 2005; Nagy et al., 2007; Tateya et al., 2003; Nishimura et al., 2012; Hu and Ulfendahl, 2013; Ogita et al., 2009). In terms of engraftment and survival, transplantation of iPS cells derived from adult fibroblasts resulted in significantly higher cell numbers in transplants than iPS cells derived from embryonic cells (Nishimura et al., 2012).

After total bone marrow transplantation from male donors into female recipients, the generation of new neurons containing an X and a Y-chromosome has been shown in post-mortem brain samples (Mezey et al., 2003; Weimann et al., 2003). Although it was not clear if neuronal formation after total bone marrow transplantation occurred by de novo differentiation from stem cells or via cell fusion (Mezey et al., 2003; Weimann et al., 2003), this phenomenon shows the remarkable capacity of bone marrow-derived cells to migrate to the brain, engraft and induce tissue repair and regeneration. Intraveneous injection of human MSC into ototoxically injured cochleae of rats resulted on homing and engraftment of transplanted cells (Choi et al., 2012). By contrast, transplanted cells did not engraft in normal hearing cochleae without any injury (Choi et al., 2012). Thus, significant cochlear injury involving degeneration of inner hair cells and spiral ganglion neurons seems to be required for the successful recruitment of donor cells in the cochlea (Choi et al., 2012). Recruitment of bone marrow cells to ischemic regions in the noise-damaged cochlea is mediated by a inducible nitric oxide synthase and results in the repair of cochlear vessels (Dai et al., 2010). Release of stromal cell-derived factor-1 attracts bone marrow cells (Kamiya, 2015; Dai et al., 2010; Tan et al., 2008) as well as NSC (Zhang et al., 2013b) to local stressed or damaged sites. Via this signaling pathway, peripheral vascularization occurs leading to the to repair of the damaged in the traumatized cochlear blood-labyrinth-barrier (Dai et al., 2010). A short time period after damage may be critical for the homing and engraftment of cells to the areas that are in need for restoration (Tan et al., 2008). Thus, priming of the cochlear environment with homing factors may be an option to increase efficacy of stem cell treatment. In addition, mobilization of endogenous stem cells was achieved by granulocyte colony stimulating factor and this recruitment resulted in the induction of repair processes in aminoglycoside-damaged rat cochleae (Elbana et al., 2015).

Chemically induced changes in the fibrocytes of the lateral wall and spiral limbus of rats without any significant damage to the organ of Corti or spiral ganglion were restored after transplantation of homologous MSC (Kamiya et al., 2007). *In vitro*, MSC were able to stimulate the proliferation of spiral ligament fibrocytes (Sun et al., 2012) and this might be the underlying mechanism for the restoration of the lateral wall (Kamiya et al., 2007). In addition to the generation of new cells by mitosis of cochlear fibrocytes around the injured area (Kamiya et al., 2007), bone marrow-derived cells have the potential to engraft into the lateral wall and differentiate into the cochlear fibrocytes (Lang et al., 2006). Differentiation into fibrocytes was also observed after transplantation of MSC into the mouse cochlea, although this effect was dependent from the age of the recipient and engraftment occurred only in young mice (Kasagi et al., 2013). Experiments with reconstitution after lethal irradiation with bone marrow from GFP-expressing donors showed that bone marrow derived cells regularly reside in the inner ear (Tan et al., 2008) and this phenomenon has been also observed in other studies (Lang et al., 2006; Hirose et al., 2005). In an animal model of autoimmune inner ear disease, IL-4 expressing MSC were identified in the scala tympani and scala vestibuli after their transplantation to the inner and only few cells were found in the organ of Corti, the stria vascularis and the osseous spiral lamina (Tan et al., 2014). Thus, MSC may be used as an alternative to the direct delivery of genes to the inner and cell-based delivery of IL-4 induced recovery from autoimmune-mediated inner ear diseases by anti-inflammation and immunomodulation (Tan et al., 2014). In addition, using another animal model for experimental autoimmune hearing loss, human adipose-derived MSC improved functional recovery and protected hair cells, possibly due to the inhibition of antigen-specific Th1/Th17 cells as well as the production of anti-inflammatory cytokines (Zhou et al., 2011). In follow-up studies, it was demonstrated that infusion of human adipose derived stem cells into the peritoneal cavity of mice with

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011

beta tubulin autoimmune inner ear disease resulted in protection of cochlear structures and maintenance of hearing (Yoo et al., 2015). The authors deduct that this is due to paracrine effects on the host's activated T cell population (Yoo et al., 2015).

Stem cells derived from other tissues also show capacity for homing to damaged areas of the inner ear and effecting a variety of biological effects. For example, the nasal turbinates harbor a significant amount of MSCs that were able to engraft into the lesioned area of the spiral ganglion *in vitro* (Water et al., 2014) and neuronal differentiation was triggered in these cells by activation of the canonical Wnt pathway (Water et al., 2014). Recent studies also evaluated utilization of stem cells to protect against noise-induced hearing loss (Xu et al., 2016). In this study the authors used olfactory epithelium derived stem cells, which are known to secrete a variety of neurotrophins including NGF and NT3 (Xu et al., 2016). Implantation of the cells in a rat model of noise trauma, resulted in protection of hearing (Xu et al., 2016). Again it is assumed that this is a paracrine effect (Xu et al., 2016).

Another potent cell type within the mononuclear cells of the bone marrow are the hematopoietic stem cells (HSC). Intra-scalar transplantation of HSC prevented ischemia-induced damage to the inner hair cells (Yoshida et al., 2007). Whether HSC promoted proliferation of residing cochlear cells and their differentiation into hair cells or if they differentiated to lost host cells after transplantation is not clear (Yoshida et al., 2007). However, another study showed the homing of cells from the bone marrow to the deafened cochlea, but these cells preserved their hematopoietic properties without transdifferentiation to any cochlear cell types after acoustic trauma (Tan et al., 2008).

3.4. Genetic modification of stem cells

The function and applicability of stem cell populations can be altered through gene therapy. Since WJCs have been demonstrated to differentiate into neurons, the potential of these cells to be induced into a hair cell like phenotype was evaluated. WJCs could be transfected with a variety of different adenovectors including vectors based on alternate adenovirus serotypes such as Ad28. Overexpression of math1/atoh1 resulted in production of cells that expressed myosin seven (Devarajan et al., 2013). The efficiency of this process could be enhanced by combination of non-viral delivery of math1 along with siRNA targeting Hes 1 and Hes 5 using nucleofection (Mellott et al., 2015). These studies demonstrate that stem cells could potentially be forced to differentiate into inner ear lineages, thereby allowing the replacement of damaged cell types or potentially utilization of these cells to release bioactive factors within the inner ear.

Even though speculative in the inner ear, there is increasing evidence that MSC chemically modified to produce neurotrophic factors including BDNF (brain-derived neurotrophic factor) can be safely applied in the central nervous system of humans (Marks et al., 2017). Further characterization of cells and target diseases are needed before inner ear related clinical trials are launched.

4. Potential for stem cell therapy in cochlear implantation

4.1. Immunomodulation, neuroprotection and regeneration

A recent experimental data demonstrated early and chronic inflammatory responses characterized by recruitment of leukocytes and expression of pro-inflammatory cytokines due to insertion trauma promoting intracochlear fibrosis, loss of hair cells (HC) and degeneration of auditory neurons in cochlear implantation (Bas et al., 2015). This study highlights the importance of anti-inflammatory treatment in order to protect cochlear structures and prevent loss of residual hearing associated with this procedure. Post-mortem analysis of the temporal bones of a patient who experienced delayed hearing loss - after initially successful preservation of residual hearing with a cochlear implant - did not show any morphological differences in terms of hair cell loss and spiral ganglion neuron degeneration when compared to the non-implanted contralateral side (Quesnel et al., 2015). However, loose fibrous tissue and bone filled the scala tympani and part of the scala vestibuli in the basal turn of the implanted left cochlea and might explain the loss of residual hearing that occurred post implantation (Quesnel et al., 2015). Moreover, fibrosis and new bone formation inside the scala tympani were found (Clark et al., 2014) and growth of fibrous tissue on the implant surface (Somdas et al., 2007). As a consequence to the new tissue formation, a rise in impedance occurs requiring higher electrical stimuli for effective neurostimulation (Xu et al., 1997; Paasche et al., 2006). This, in turn, leads to higher energy consumption and to aberrant spread of current resulting in reduced channel separation (Bierer, 2010). These results suggest that reduction of inflammation and control of immune response to cochlear implantation may not only preserve residual hearing but also improve hearing with a cochlear implant. Immunomodulation and production of trophic factors during cochlear implantation may be achievable using transplantation of stem cells.

4.2. Safety of autologous stem cells in human cochlear implantation

An ideal electrode should thus be able to decrease post implantation trauma and provide support to the residual spiral ganglion population. To achieve this, co-implantation of cells producing and releasing protective factors presents a promising approach. Autologous mononuclear cells can be obtained from bone marrow (BM-MNC). They consist of a variety of cells including a very small percentage of mesenchymal and hematopoietic progenitor cells that possess the innate capacity to induce repair of traumatized tissue and to modulate immunological reactions. In addition, they can be readily isolated in the operating theatre without the need for further *in vitro* expansion prior to transplantation. The neuroprotective effects and immunomodulative secretomes of BM-MNC were demonstrated on co-cultures with spiral ganglion neurons (Roemer et al., 2016). In addition, a simple and effective cell coating procedure for cochlear implant electrodes was developed using fibrin adhesive as a carrier for BM-MNC. This procedure can be utilized on-site in the operating room for the generation of biohybrid electrodes for intracochlear cell-based drug delivery. Finally, a safety study demonstrated the feasibility of autologous progenitor cell transplantation in humans as an adjuvant to cochlear implantation for neurosensory restoration (Roemer et al., 2016). This is the first report of the use of autologous cell transplantation in the inner ear and close follow-up of the patients up to 18 months did not show any adverse effects (unpublished results). For their broad clinical use, however, refinement of clinical outcome measures is as necessary as safety data.

5. Conclusion

1. Transplantation of stem cells is an emerging therapeutic intervention in most areas of medicine.
2. Four main areas of investigation have emerged: replacement of damaged tissue, *in vitro* modelling of diseases, trophic support via release of exosomes and trophic factors and immunomodulation.
3. Early stage animal studies have demonstrated that a variety of different stem cells have the potential to modulate inner ear disease.

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011

4. The source of the stem cell seems of paramount importance in terms of safety.
5. Bone marrow-derived progenitors have been extensively investigated resulting in the availability of human safety data.
6. A first in human study has also established safety of cell transplantation in the human inner ear derived from autologous bone marrow (Roemer et al., 2016).

References

Algoe, S.B., Haidt, J., Gable, S.L., 2008. Beyond reciprocity: gratitude and relationships in everyday life. Emotion 8 (3), 425–429. http://dx.doi.org/10.1037/1528-3542.8.3.425.

Almeida-Branco, M.S., Cabrera, S., Lopez-Escamez, J.A., 2015. Perspectives for the treatment of sensorineural hearing loss by cellular regeneration of the inner ear. Acta Otorrinolaringol. Esp. 66 (5), 286–295. http://dx.doi.org/10.1016/j.otorri.2014.07.009.

Altschuler, R., O'Shea, K., Miller, J., 2008. Stem cell transplantation for auditory nerve replacement. Hear Res. 242 (1–2), 110–116. http://dx.doi.org/10.1016/j.heares.2008.06.004.Stem.

Apostolou, E., Hochedlinger, K., 2013. Chromatin dynamics during cellular reprogramming. Nature 502 (7472), 462–471. http://dx.doi.org/10.1038/nature12749.

Assmus, B., Alakmeh, S., De Rosa, S., et al., 2016. Improved outcome with repeated intracoronary injection of bone marrow-derived cells within a registry: rationale for the randomized outcome trial REPEAT. Eur. Heart J. 37 (21), 1659–1666. http://dx.doi.org/10.1093/eurheartj/ehv559.

Backhouse, S., Coleman, B., Shepherd, R., 2008. Surgical access to the mammalian cochlea for cell-based therapies. Exp. Neurol. 214 (2), 193–200. http://dx.doi.org/10.1016/j.expneurol.2008.08.002.

Barbash, I.M., Chouraqui, P., Baron, J., et al., 2003. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. Circulation 108 (7), 863–868. http://dx.doi.org/10.1161/01.CIR.0000084828.50310.6A.

Bas, E., Goncalves, S., Adams, M., et al., 2015. Spiral ganglion cells and macrophages initiate neuro-inflammation and scarring following cochlear implantation. Front. Cell Neurosci. 9 (303), 1–16. http://dx.doi.org/10.3389/fncel.2015.00303.

Bez, A., Corsini, E., Curti, D., et al., 2003. Neurosphere and neurosphere-forming cells: morphological and ultrastructural characterization. Brain Res. 993 (1–2), 18–29. http://www.ncbi.nlm.nih.gov/pubmed/14642827.

Bianco, P., Cao, X., Frenette, P.S., et al., 2013. The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine. Nat. Med. 19 (1), 35–42. http://dx.doi.org/10.1038/nm.3028.

Bierer, J.A., 2010. Probing the electrode-neuron interface with focused cochlear implant stimulation. Trends Amplif. 14 (2), 84–95. http://dx.doi.org/10.1177/1084713810375249.

Bogaerts, S., Douglas, S., Corlette, T., et al., 2008. Microsurgical access for cell injection into the mammalian cochlea. J. Neurosci. Methods 168 (1), 156–162.

Breuskin, I., Bodson, M., Thelen, N., et al., 2008. Strategies to regenerate hair cells: identification of progenitors and critical genes. Hear Res. 236 (1–2), 1–10. http://dx.doi.org/10.1016/j.heares.2007.08.007.

Cai, J., Wu, Z., Xu, X., et al., 2015. Umbilical cord mesenchymal stromal cell with autologous bone marrow cell transplantation in established type 1 diabetes: a pilot randomized controlled open-label clinical study to assess safety and impact on insulin secretion. Diabetes Care 39 (January), dc150171. http://dx.doi.org/10.2337/dc15-0171.

Cai, S., Liu, A., Chen, S., et al., 2015. Activation of Wnt/β-catenin signalling promotes mesenchymal stem cells to repair injured alveolar epithelium induced by lipopolysaccharide in mice. Stem Cell Res. Ther. 6 (1), 65. http://dx.doi.org/10.1186/s13287-015-0060-y.

Cardozo, A.J., Gómez, D.E., Argibay, P.F., 2011. Transcriptional characterization of Wnt and Notch signaling pathways in neuronal differentiation of human adipose tissue-derived stem cells. J. Mol. Neurosci. 44 (3), 186–194. http://dx.doi.org/10.1007/s12031-011-9503-9.

Carricondo, F., Iglesias, M.C., Rodr??guez, F., Poch-Broto, J., Gil-Loyzaga, P., 2010. In vitro long-term development of cultured inner ear stem cells of newborn rat. Cell Tissue Res. 342 (1), 13–19. http://dx.doi.org/10.1007/s00441-010-1039-8.

Cefalo, M.G., Carai, A., Miele, E., et al., 2016. Human iPSC for therapeutic approaches to the nervous system: present and future applications. Stem Cells Int. 2016, 4869071. http://dx.doi.org/10.1155/2016/4869071.

Chang, S.L.-Y., Chou, R.-H., Zeng, H.-J., et al., 2013. Downregulation of DAB2IP promotes mesenchymal-to-neuroepithelial transition and neuronal differentiation of human mesenchymal stem cells. PLoS One 8 (9), e75884. http://dx.doi.org/10.1371/journal.pone.0075884.

Chen, W., Jongkamonwiwat, N., Abbas, L., et al., 2012. Restoration of auditory evoked responses by human ES-cell-derived otic progenitors. Nature 490 (7419), 278–282. http://dx.doi.org/10.1038/nature11415.

Chen, J.-R., Tang, Z.-H., Zheng, J., et al., 2016. Effects of genetic correction on the differentiation of hair cell-like cells from iPSCs with MYO15A mutation. Cell Death Differ. 23 (8), 1347–1357. http://dx.doi.org/10.1038/cdd.2016.16.

Choi, B.Y., Song, J.-J., Chang, S.O., Kim, S.U., Oh, S.H., 2012. Intravenous administration of human mesenchymal stem cells after noise- or drug-induced hearing loss in rats. Acta Otolaryngol. 132 http://dx.doi.org/10.3109/00016489.2012.660731. Suppl(January):S94-102.

Clark, G.M., Clark, J., Cardamone, T., et al., 2014. Biomedical studies on temporal bones of the first multi-channel cochlear implant patient at the University of Melbourne. Cochlear Implants Int. 15 (Suppl. 2), S1–S15. http://dx.doi.org/10.1179/1754762814Y.0000000087.

Coleman, B., Hardman, J., Coco, A., et al., 2006. Fate of embryonic stem cells transplanted into the deafened mammalian cochlea. Cell Transpl. 15 (5), 369–380. http://dx.doi.org/10.3727/000000006783981819.

Coleman, B., de Silva, M.G., Shepherd, R.K., 2007. Concise review: the potential of stem cells for auditory neuron generation and replacement. Stem Cells 25 (11), 2685–2694. http://dx.doi.org/10.1634/stemcells.2007-0393.

Condic, M.L., 2014. Totipotency: what it is and what it is not. Stem Cells Dev. 23 (8), 796–812. http://dx.doi.org/10.1089/scd.2013.0364.

Corrales, C.E., Pan, L., Li, H., Liberman, M.C., Heller, S., Edge, A.S.B., 2006. Engraftment and differentiation of embryonic stem cell-derived neural progenitor cells in the cochlear nerve trunk: growth of processes into the organ of Corti. J. Neurobiol. 66 (13), 1489–1500. http://dx.doi.org/10.1002/neu.20310.

Dai, M., Yang, Y., Omelchenko, I., et al., 2010. Bone marrow cell recruitment mediated by inducible nitric oxide synthase/stromal cell-derived factor-1α signaling repairs the acoustically damaged cochlear blood-labyrinth barrier. Am. J. Pathol. 177 (6), 3089–3099. http://dx.doi.org/10.2353/ajpath.2010.100340.

Desbaillets, I., Ziegler, U., Groscurth, P., Gassmann, M., 2000. Embryonic bodies: an in vitro model of mouse embryogenesis. Exp. Physiol. 85 (6), 645–651.

Devarajan, K., Staecker, H., Detamore, M.S., 2011. A review of gene delivery and stem cell based therapies for regenerating inner ear hair cells. J. Funct. Biomater. 2 (3), 249–270. http://dx.doi.org/10.3390/jfb2030249.

Devarajan, K., Forrest, M.L., Detamore, M.S., Staecker, H., 2013. Adenovector-mediated gene delivery to human umbilical cord mesenchymal stromal cells induces inner ear cell phenotype. Cell Reprogr. 15 (1), 43–54. http://dx.doi.org/10.1089/cell.2011.0097.

Diensthuber, M., Oshima, K., Heller, S., 2009. Stem/progenitor cells derived from the cochlear sensory epithelium give rise to spheres with distinct morphologies and features. J. Assoc. Res. Otolaryngol. 10 (2), 173–190. http://dx.doi.org/10.1007/s10162-009-0161-3.

Dittrich, R., Beckmann, M.W., Würfel, W., 2015. Non-embryo-destructive extraction of pluripotent embryonic stem cells: implications for regenerative medicine and reproductive medicine. Geburtshilfe Frauenheilkd 75 (12), 1239–1242. http://dx.doi.org/10.1055/s-0035-1558183.

Dominici, M., Le Blanc, K., Mueller, I., et al., 2006. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8 (4), 315–317. http://dx.doi.org/10.1080/14653240600855905.

Duan, F., Qi, Z., Liu, S., et al., 2015. Effectiveness of bone marrow mononuclear cells delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure: an echocardiographic study of left ventricular remodeling. Med. Ultrason. 17 (2), 160–166. http://dx.doi.org/10.11152/mu.2013.2066.172.effbm.

Dumont, N.A., Wang, Y.X., Rudnicki, M.A., 2015. Intrinsic and extrinsic mechanisms regulating satellite cell function. Development 142 (9), 1572–1581. http://dx.doi.org/10.1242/dev.114223.

D'souza, N., Rossignoli, F., Golinelli, G., et al., 2015. Mesenchymal stem/stromal cells as a delivery platform in cell and gene therapies. BMC Med. 13 (1), 186. http://dx.doi.org/10.1186/s12916-015-0426-0.

Elbana, A.M., Abdel-Salam, S., Morad, G.M., Ibrahim, M., Omran, A.A., 2015. Endogenous bone marrow stem cell mobilization in rats: its potential role in homing and repair of damaged inner ear. Int. J. Stem Cells 8 (2), 146–154. http://dx.doi.org/10.1016/j.ejenta.2013.01.003.

Franz, R.W., Shah, K.J., Pin, R.H., Hankins, T., Hartman, J.F., Wright, M.L., 2015. Autologous bone marrow mononuclear cell implantation therapy is an effective limb salvage strategy for patients with severe peripheral arterial disease. J. Vasc. Surg. 62 (3), 673–680. http://dx.doi.org/10.1016/j.jvs.2015.02.059.

Géléoc, G.S.G., Holt, J.R., 2014. Sound strategies for hearing restoration. Sci. (80-) 344 (6184). http://dx.doi.org/10.1126/science.1241062.Sound.

Gillespie, L.N., Richardson, R.T., Nayagam, B a, Wise, A.K., 2014. Treating hearing disorders with cell and gene therapy. J. Neural Eng. 11 (6), 65001. http://dx.doi.org/10.1088/1741-2560/11/6/065001.

Gimble, J.M., Katz, A.J., Bunnell, B.A., 2007. Adipose-derived stem cells for regenerative medicine. Circ. Res. 100 (9), 1249–1260. http://dx.doi.org/10.1161/01.RES.0000265074.83288.09.

Girlovanu, M., Susman, S., Soritau, O., et al., 2015. Stem cells - biological update and cell therapy progress. Clujul Med. 88 (3), 265–271. http://dx.doi.org/10.15386/cjmed-483.

Goel, A., 2016. Stem cell therapy in spinal cord injury: hollow promise or promising science? J. Craniovertebr Junction Spine 7 (2), 121. http://dx.doi.org/10.4103/0974-8237.181880.

GURDON, J.B., 1962. The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. J. Embryol. Exp. Morphol. 10 (4), 622–640. http://www.ncbi.nlm.nih.gov/pubmed/13951335.

Hakuba, N., Hata, R., Morizane, I., et al., 2005. Neural stem cells suppress the hearing threshold shift caused by cochlear ischemia. Neuroreport 16 (14), 1545–1549. http://www.ncbi.nlm.nih.gov/pubmed/16148742.

He, Y., Zhang, P.Z., Sun, D., et al., 2014. Wnt1 from cochlear schwann cells enhances neuronal differentiation of transplanted neural stem cells in a rat spiral ganglion neuron degeneration model. Cell Transpl. 23 (6), 747–760. http://dx.doi.org/10.3727/096368913X669761.

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011

Hildebrand, M.S., Dahl, H.H.M., Hardman, J., Coleman, B., Shepherd, R.K., De Silva, M.G., 2005. Survival of partially differentiated mouse embryonic stem cells in the scala media of the Guinea pig cochlea. JARO - J. Assoc. Res. Otolaryngol. 6 (4), 341–354. http://dx.doi.org/10.1007/s10162-005-0012-9.

Hirose, K., Discolo, C.M., Keasler, J.R., Ransohoff, R., 2005. Mononuclear phagocytes migrate into the murine cochlea after acoustic trauma. J. Comp. Neurol. 489 (2), 180–194. http://dx.doi.org/10.1002/cne.20619.

Hu, Z., Ulfendahl, M., 2013. The potential of stem cells for the restoration of auditory function in humans. Regen. Med. 8 (3), 309–318. http://dx.doi.org/10.2217/rme.13.32.

Hu, Z., Ulfendahl, M., Olivius, N.P., 2004. Central migration of neuronal tissue and embryonic stem cells following transplantation along the adult auditory nerve. Brain Res. 1026 (1), 68–73. http://dx.doi.org/10.1016/j.brainres.2004.08.013.

Hu, Z., Wei, D., Johansson, C.B., et al., 2005. Survival and neural differentiation of adult neural stem cells transplanted into the mature inner ear. Exp. Cell Res. 302 (1), 40–47. http://dx.doi.org/10.1016/j.yexcr.2004.08.023.

Hu, Z., Andäng, M., Ni, D., Ulfendahl, M., 2005. Neural cograft stimulates the survival and differentiation of embryonic stem cells in the adult mammalian auditory system. Brain Res. 1051 (1–2), 137–144. http://dx.doi.org/10.1016/j.brainres.2005.06.016.

Hu, Z., Ulfendahl, M., Prieskorn, D.M., Olivius, P., Miller, J.M., 2009. Functional evaluation of a cell replacement therapy in the inner ear. Otol. Neurotol. 30 (4), 551–558. http://dx.doi.org/10.1097/MAO.0b013e31819fe70a.

Huang, H., Chen, L., Sanberg, P., 2010. Cell therapy from bench to bedside translation in CNS neurorestoratology era. Cell Med. 1 (1), 15–46. http://dx.doi.org/10.3727/215517910X516673.

Huang, R., Yao, K., Sun, A., et al., 2015. Timing for intracoronary administration of bone marrow mononuclear cells after acute ST-elevation myocardial infarction: a pilot study. Stem Cell Res. Ther. 6 (1), 112. http://dx.doi.org/10.1186/s13287-015-0102-5.

Iguchi, F., Nakagawa, T., Tateya, I., et al., 2003. Trophic support of mouse inner ear by neural stem cell transplantation. Neuroreport 14 (1), 77–80. http://dx.doi.org/10.1097/01.wnr.0000050714.17082.9b.

José, R.-L.F., Julia, G., Virginia, I., et al., 2015. Breathing pattern in a phase I clinical trial of intraspinal injection of autologous bone marrow mononuclear cells in patients with amyotrophic lateral sclerosis. Respir. Physiol. Neurobiol. 221, 54–58. http://dx.doi.org/10.1016/j.resp.2015.11.007.

Kamiya, K., 2015. Inner ear cell therapy targeting hereditary deafness by activation of stem cell homing factors. Front. Pharmacol. 6 (January), 2–4. http://dx.doi.org/10.3389/fphar.2015.00002.

Kamiya, K., Fujinami, Y., Hoya, N., et al., 2007. Mesenchymal stem cell transplantation accelerates hearing recovery through the repair of injured cochlear fibrocytes. Am. J. Pathol. 171 (1), 214–226. http://dx.doi.org/10.2353/ajpath.2007.060948.

Kasagi, H., Kuhara, T., Okada, H., Sueyoshi, N., Kurihara, H., 2013. Mesenchymal stem cell transplantation to the mouse cochlea as a treatment for childhood sensorineural hearing loss. Int. J. Pediatr. Otorhinolaryngol. 77 (6), 936–942. http://dx.doi.org/10.1016/j.ijporl.2013.03.011.

Kavanagh, D., Suresh, S., Newsome, P., Frampton, J., Kalia, N., 2015. Pretreatment of mesenchymal stem cells manipulates their vasculoprotective potential while not altering their homing within the injured gut. Stem Cells 33 (9), 2785–2797. http://dx.doi.org/10.1002/stem.2061.

Kiefer, J.C., 2011. Primer and interviews: the dynamic stem cell niche. Dev. Dyn. 240 (3), 737–743. http://dx.doi.org/10.1002/dvdy.22566.

Klimczak, A., Kozlowska, U., 2016. Mesenchymal stromal cells and tissue-specific progenitor cells: their role in tissue homeostasis. Stem Cells Int. http://dx.doi.org/10.1155/2016/4285215.

Knoepfler, P.S., 2009. Deconstructing stem cell tumorigenicity: a roadmap to safe regenerative medicine. Stem Cells 27 (5), 1050–1056. http://dx.doi.org/10.1002/stem.37.

Kohrman, D.C., Raphael, Y., 2013. Gene therapy for deafness. Gene Ther. 20 (12), 1119–1123. http://dx.doi.org/10.1038/gt.2013.39.

Kolios, G., Moodley, Y., 2013. Introduction to stem cells and regenerative medicine. Respiration 85 (1), 3–10. http://dx.doi.org/10.1159/000345615.

Kondo, T., Matsuoka, A.J., Shimomura, A., et al., 2011. Wnt signaling promotes neuronal differentiation from mesenchymal stem cells through activation of Tlx3. Stem Cells 29 (5), 836–846. http://dx.doi.org/10.1002/stem.624.

Krampera, M., Franchini, M., Pizzolo, G., Aprili, G., 2007. Mesenchymal stem cells: from biology to clinical use. Blood Transfus. 5, 120–129. http://dx.doi.org/10.1613/jair.301.

Kurata, N., Schachern, P.A., Paparella, M.M., Cureoglu, S., 2016. Histopathologic evaluation of vascular findings in the cochlea in patients with presbycusis. JAMA Otolaryngol. Head. Neck Surg. 142 (2), 173–178. http://dx.doi.org/10.1001/jamaoto.2015.3163.

Kuriyan, A.E., Albini, T.A., Townsend, J.H., et al., 2017. Vision loss after intravitreal injection of autologous “stem cells” for AMD. N. Engl. J. Med. 376 (11), 1047–1053. http://dx.doi.org/10.1056/NEJMoa1609583.

Lang, H., Ebihara, Y., Schmiedt, R a, et al., 2006. Contribution of bone marrow hematopoietic stem cells to adult mouse inner ear: mesenchymal cells and fibrocytes. J. Comp. Neurol. 496 (2), 187–201. http://dx.doi.org/10.1002/cne.20929.

Lang, H., Schulte, B a, Goddard, J.C., et al., 2008. Transplantation of mouse embryonic stem cells into the cochlea of an auditory-neuropathy animal model: effects of timing after injury. J. Assoc. Res. Otolaryngol. 9 (2), 225–240. http://dx.doi.org/10.1007/s10162-008-0119-x.

Lee, J.-H., Kang, W.K., Seo, J.-H., et al., 2012. Neural differentiation of bone marrow-derived mesenchymal stem cells: applicability for inner ear therapy. Korean J. Audiol. 47–53. http://dx.doi.org/10.7874/kja.2012.16.2.47.

Li, H., Liu, H., Heller, S., 2003. Pluripotent stem cells from the adult mouse inner ear. Nat. Med. 9 (10), 1293–1299. http://dx.doi.org/10.1038/nm925\rnm925 [pii].

Li, H., Corrales, C.E., Edge, A., Heller, S., 2004. Stem cells as therapy for hearing loss. Trends Mol. Med. 10 (7), 309–315. http://dx.doi.org/10.1016/j.molmed.2004.05.008.

Li, Y., Zhang, Q., Yin, X., et al., 2011. Generation of iPSCs from mouse fibroblasts with a single gene, Oct4, and small molecules. Cell Res. 21 (1), 196–204. http://dx.doi.org/10.1038/cr.2010.142.

Mabuchi, Y., Houlihan, D.D., Okano, H., Matsuzaki, Y., 2012. Discovering the true identity and function of mesenchymal stem cells. Inflamm. Regen. 32 (4), 146–151.

Majo, F., Rochat, A., Nicolas, M., Jaoudé, G.A., Barrandon, Y., 2008. Oligopotent stem cells are distributed throughout the mammalian ocular surface. Nature 456 (November), 250–254. http://dx.doi.org/10.1038/nature07406.

Mallick, A.S., Qureishi, A., Pearson, R., O'Donoghue, G., 2012. Neurotrophins and cochlear implants: a solution to sensorineural deafness? Cochlear Implants Int. 0 (0), 1–7. http://dx.doi.org/10.1179/1754762812Y.0000000013.

Mann, I., Rodrigo, S.F., Van Ramshorst, J., et al., 2015. Repeated intramyocardial bone marrow cell injection in previously responding patients with refractory angina again improves myocardial perfusion, anginal complaints, and quality of life. Circ. Cardiovasc Interv. 8 (8), 1–8. http://dx.doi.org/10.1161/CIRCINTERVENTIONS.115.002740.

Mansour, S., 2016. Autologous bone marrow mononuclear stem cells for acute myocardial infarction: is it only about time? Eur. Heart J. 37 (3), 264–266. http://dx.doi.org/10.1093/eurheartj/ehv541.

Marks, P.W., Witten, C.M., Califf, R.M., 2017. Clarifying stem-cell Therapy's benefits and risks. N. Engl. J. Med. 376 (11), 1007–1009. http://dx.doi.org/10.1056/NEJMp1613723.

Marone, M., De Ritis, D., Bonanno, G., et al., 2002. Cell cycle regulation in human hematopoietic stem cells: from isolation to activation. Leuk. Lymphoma 43 (3), 493–501. http://dx.doi.org/10.1080/10428190290011967.

Martinez-Monedero, R., Edge, A.S.B., 2007. Stem cells for the replacement of inner ear neurons and hair cells. Int. J. Dev. Biol. 51 (6–7), 655–661. http://dx.doi.org/10.1387/ijdb.072372rm.

Martino, H., Brofman, P., Greco, O., et al., 2015. Multicentre, randomized, double-blind trial of intracoronary autologous mononuclear bone marrow cell injection in non-ischaemic dilated cardiomyopathy (the dilated cardiomyopathy arm of the MiHeart study). Eur. Heart J. 36 (42) http://dx.doi.org/10.1093/eurheartj/ehv477, 2898.2-2904.

Mellott, A.J., Devarajan, K., Shinogle, H.E., et al., 2015. Nonviral reprogramming of human Wharton's jelly cells reveals differences between ATOH1 homologues. Tissue Eng. Part A 21 (11–12), 1795–1809.

Mesentier-Louro, L.A., Zaverucha-do-Valle, C., Rosado-de-Castro, P.H., et al., 2016. Bone marrow-derived cells as a therapeutic approach to optic nerve diseases. Stem Cells Int. 2016, 1–16. http://dx.doi.org/10.1155/2016/5078619.

Mezey, E., Key, S., Vogelsang, G., Szalayova, I., Lange, G.D., Crain, B., 2003. Transplanted bone marrow generates new neurons in human brains. Proc. Natl. Acad. Sci. U. S. A 100 (3), 1364–1369. http://dx.doi.org/10.1073/pnas.0336479100.

Mizuno, H., Tobita, M., Uysal, A.C., 2012. Concise review: adipose-derived stem cells as a novel tool for future regenerative medicine. Stem Cells 30 (5), 804–810. http://dx.doi.org/10.1002/stem.1076.

Moniche, F., Escudero, I., Zapata-Arriaza, E., et al., 2015. Intra-arterial bone marrow mononuclear cells (BM-MNCs) transplantation in acute ischemic stroke (IBIS trial): protocol of a phase II, randomized, dose-finding, controlled multicenter trial. Int. J. Stroke 10 (7), 1149–1152. http://dx.doi.org/10.1111/ijs.12520.

Morales, M.M., Souza, S.A., Loivos, L.P., et al., 2015. Pilot safety study of intrabronchial instillation of bone marrow-derived mononuclear cells in patients with silicosis. BMC Pulm. Med. 15, 66. http://dx.doi.org/10.1186/s12890-015-0061-8.

Müller, U., Barr-Gillespie, P.G., 2015. New treatment options for hearing loss. Nat. Rev. Drug Discov. 14 (5), 346–365. http://dx.doi.org/10.1038/nrd4533.

Nagy, I., Fuchs, S., Monge, A., Huber, A., Bodmer, D., 2007. Transplantation of neural stem cells into the cochlea. HNO 55 (11), 862–870. http://dx.doi.org/10.1007/s00106-007-1538-4.

Nayagam, B.A., Backhouse, S.S., Cimenkaya, C., Shepherd, R.K., 2012. Hydrogel limits stem cell dispersal in the deaf cochlea: implications for cochlear implants. J. Neural Eng. 9 (6), 65001. http://dx.doi.org/10.1088/1741-2560/9/6/065001.Hydrogel.

Nemoto, M., Koyama, H., Nishiyama, A., Shigematsu, K., Miyata, T., Watanabe, T., 2015. Adequate selection of a therapeutic site enables efficient development of collateral vessels in angiogenic treatment with bone marrow mononuclear cells. J. Am. Heart Assoc. 4 (9), e002287. http://dx.doi.org/10.1161/JAHA.115.002287.

Nishimura, K., Nakagawa, T., Sakamoto, T., Ito, J., 2012. Fates of murine pluripotent stem cell-derived neural progenitors following transplantation into mouse cochleae. Cell Transpl. 21 (4), 763–771. http://dx.doi.org/10.3727/096368911X623907.

Ogita, H., Nakagawa, T., Lee, K.Y., et al., 2009. Surgical invasiveness of cell transplantation into the Guinea pig cochlear modiolus. ORL J. Otorhinolaryngol. Relat. Spec. 71 (1), 32–39. http://dx.doi.org/10.1159/000165915.

Okano, T., Kelley, M.W., 2012. Stem cell therapy for the inner ear: recent advances and future directions. Trends Amplif. 16 (1), 4–18. http://dx.doi.org/10.1177/1084713812440336.

Okano, T., Nakagawa, T., Endo, T., et al., 2005. Engraftment of embryonic stem cell-

derived neurons into the cochlear modiolus. Neuroreport 16 (17), 1919–1922. http://dx.doi.org/10.1097/01.wnr.0000187628.38010.5b.
Olivius, P., Alexandrov, L., Miller, J., Ulfendahl, M., Bagger-Sjöbäck, D., Kozlova, E.N., 2003. Allografted fetal dorsal root ganglion neuronal survival in the Guinea pig cochlea. Brain Res. 979 (1–2), 1–6. http://www.ncbi.nlm.nih.gov/pubmed/12850564.
Orlic, D., Hill, J.M., Arai, A.E., 2002. Stem cells for myocardial regeneration. Circ. Res. 91 (12), 1092–1102. http://dx.doi.org/10.1161/01.RES.0000046045.00846.B0.
Paasche, G., Bockel, F., Tasche, C., Lesinski-Schiedat, A., Lenarz, T., 2006. Changes of postoperative impedances in cochlear implant patients: the short-term effects of modified electrode surfaces and intracochlear corticosteroids. Otol. Neurotol. 27 (5), 639–647. http://dx.doi.org/10.1097/01.mao.0000227662.88840.61.
Park, Y.-H., Wilson, K.F., Ueda, Y., et al., 2014. Conditioning the cochlea to facilitate survival and integration of exogenous cells into the auditory epithelium. Mol. Ther. 22 (4), 873–880. http://dx.doi.org/10.1038/mt.2013.292.
Parker, M., Corliss, D., Gray, B., et al., 2007. Neural stem cells injected into the sound-damaged cochlea migrate throughout the cochlea and express markers of hair cells, supporting cells, and spiral ganglion cells. Hear Res. 232 (1–2), 29–43. http://dx.doi.org/10.1016/j.heares.2007.06.007.
Pauley, S., Kopecky, B., Beisel, K., Soukup, G., Fritzsch, B., 2008. Stem cells and molecular strategies to restore hearing. Panminerva Med. 50 (1), 41–53. http://dx.doi.org/10.1097/BRS.0b013e31816c8ab4.
Peeters Weem, S.M.O., Teraa, M., den Ruijter, H.M., de Borst, G.J., Verhaar, M.C., Moll, F.L., 2015. Quality of life after treatment with autologous bone marrow derived cells in No option severe limb ischemia. Eur. J. Vasc. Endovasc. Surg. 51 (1), 83–89. http://dx.doi.org/10.1016/j.ejvs.2015.09.010.
Peng, K.A., Linthicum, F.H., 2016. Atrophy of the stria vascularis. Otol. Neurotol. 37 (2), e9–11. http://dx.doi.org/10.1097/MAO.0000000000000935.
Peterson, S.E., Loring, J.F., 2014. Genomic instability in pluripotent stem cells: implications for clinical applications. J. Biol. Chem. 289 (8), 4578–4584. http://dx.doi.org/10.1074/jbc.R113.516419.
Pettingill, L.N., Richardson, R.T., Wise, A.K., O'Leary, S.J., Shepherd, R.K., 2007. Neurotrophic factors and neural prostheses: potential clinical applications based upon findings in the auditory system. IEEE Trans. Biomed. Eng. 54 (6 Pt 1), 1138–1148. http://dx.doi.org/10.1109/TBME.2007.895375.
Pösel, C., Möller, K., Fröhlich, W., Schulz, I., Boltze, J., Wagner, D.C., 2012. Density gradient centrifugation compromises bone marrow mononuclear cell yield. PLoS One 7 (12), 1–10. http://dx.doi.org/10.1371/journal.pone.0050293.
Quesnel, A., Nakajima, H., Rosowski, J., Hansen, M., Gantz, B., Nadol, J.J., 2015. Delayed loss of hearing after hearing preservation cochlear implantation: human temporal bone pathology and implications for etiology. Hear Res. http://dx.doi.org/10.1016/j.heares pii: S0378–5955(15)00185-9.
Rak, K., Wasielewski, N.V., Radeloff, A., et al., 2011. Isolation and characterization of neural stem cells from the neonatal rat cochlear nucleus. Cell Tissue Res. 343 (3), 499–508. http://dx.doi.org/10.1007/s00441-010-1118-x.
Rask-Andersen, H., Boström, M., Gerdin, B., et al., 2005. Regeneration of human auditory nerve. In vitro/in video demonstration of neural progenitor cells in adult human and Guinea pig spiral ganglion. Hear Res. 203 (1–2), 180–191. http://dx.doi.org/10.1016/j.heares.2004.12.005.
Regala, C., Duan, M., Zou, J., Salminen, M., Olivius, P., 2005. Xenografted fetal dorsal root ganglion, embryonic stem cell and adult neural stem cell survival following implantation into the adult vestibulocochlear nerve. Exp. Neurol. 193 (2), 326–333. http://dx.doi.org/10.1016/j.expneurol.2004.12.027.
Richardson, R.T., Wise, A.K., Andrew, J.K., O'Leary, S.J., 2008. Novel drug delivery systems for inner ear protection and regeneration after hearing loss. Expert Opin. Drug Deliv. 5 (10), 1059–1076. http://dx.doi.org/10.1517/17425247.5.10.1059.
Roemer, A., Köhl, U., Majdani, O., et al., 2016. Biohybrid cochlear implants in human neurosensory restoration. Stem Cell Res. Ther. 7 (1), 148. http://dx.doi.org/10.1186/s13287-016-0408-y.
Romito, A., Cobellis, G., 2016. Pluripotent stem Cells: current understanding and future directions. Stem Cells Int. 2016 (Icm) http://dx.doi.org/10.1155/2016/9451492.
Rony, I.K., Baten, A., Bloomfield, J.A., Islam, M.E., Billah, M.M., Islam, K.D., 2015. Inducing pluripotency in vitro: recent advances and highlights in induced pluripotent stem cells generation and pluripotency reprogramming. Cell Prolif. 48 (2), 140–156. http://dx.doi.org/10.1111/cpr.12162.
Rubel, E.W., Furrer, S a, Stone, J.S., 2013. A brief history of hair cell regeneration research and speculations on the future. Hear Res. 297, 42–51. http://dx.doi.org/10.1016/j.heares.2012.12.014.
Santaolalla, F., Salvador, C., Martínez, A., Sánchez, J.M., Del Rey, A.S., 2013. Inner ear hair cell regeneration: a look from the past to the future. Neural Regen. Res. 8 (24), 2284–2289. http://dx.doi.org/10.3969/j.issn.1673-5374.2013.24.008.
Savary, E., Sabourin, J.C., Santo, J., et al., 2008. Cochlear stem/progenitor cells from a postnatal cochlea respond to Jagged1 and demonstrate that notch signaling promotes sphere formation and sensory potential. Mech. Dev. 125 (8), 674–686. http://dx.doi.org/10.1016/j.mod.2008.05.001.
Scheiner, Z.S., Talib, S., Feigal, E.G., 2014. The potential for immunogenicity of autologous induced pluripotent stem cell-derived therapies. J. Biol. Chem. 289 (8), 4571–4577. http://dx.doi.org/10.1074/jbc.R113.509588.
Sekiya, T., Kojima, K., Matsumoto, M., Kim, T.-S., Tamura, T., Ito, J., 2006. Cell transplantation to the auditory nerve and cochlear duct. Exp. Neurol. 198 (1), 12–24. http://dx.doi.org/10.1016/j.expneurol.2005.11.006.
Sharma, A., Sane, H., Gokulchandran, N., et al., 2015. A clinical study of autologous bone marrow mononuclear cells for cerebral palsy patients: a new frontier. Stem Cells Int. 2015, 905874. http://dx.doi.org/10.1155/2015/905874.
Sharma, A., Sane, H., Kulkarni, P., D'sa, M., Gokulchandran, N., Badhe, P., 2015. Improved quality of Life in A Case of cerebral palsy after bone marrow mononuclear cell transplantation. Cell J. 17 (2), 389–394. http://www.ncbi.nlm.nih.gov/pubmed/26199918.
Shi, F., Edge, A.S.B., 2013. Prospects for replacement of auditory neurons by stem cells. Hear Res. 297, 106–112. http://dx.doi.org/10.1016/j.heares.2013.01.017.
Skora, J., Pupka, A., Janczak, D., et al., 2015. Combined autologous bone marrow mononuclear cell and gene therapy as the last resort for patients with critical limb ischemia. Arch. Med. Sci. 11 (2), 325–331. http://dx.doi.org/10.5114/aoms.2013.39935.
Sng, J., Lufkin, T., 2012. Emerging stem cell therapies: treatment, safety, and biology. Stem Cells Int. 2012, 521343. http://dx.doi.org/10.1155/2012/521343.
Somdas, M.A., Li, P.M., Whiten, D.M., Eddington, D.K., Nadol Jr., J.B., 2007. Quantitative evaluation of new bone and fibrous tissue in the cochlea following cochlear implantation in the human. Audiol. Neurootol 12 (5), 277–284. http://dx.doi.org/10.1159/000103208.
Song, W.K., Park, K.-M., Kim, H.-J., et al., 2015. Treatment of macular degeneration using embryonic stem cell-derived retinal pigment epithelium: preliminary results in asian patients. Stem Cell Rep. 4 (5), 860–872. http://dx.doi.org/10.1016/j.stemcr.2015.04.005.
Sullivan, J.M., Cohen, M a, Pandit, S.R., Sahota, R.S., Borecki, A a, Oleskevich, S., 2011. Effect of epithelial stem cell transplantation on noise-induced hearing loss in adult mice. Neurobiol. Dis. 41 (2), 552–559. http://dx.doi.org/10.1016/j.nbd.2010.11.001.
Sun, G.W., Fujii, M., Matsunaga, T., 2012. Functional interaction between mesenchymal stem cells and spiral ligament fibrocytes. J. Neurosci. Res. 90 (9), 1713–1722. http://dx.doi.org/10.1002/jnr.23067.
Tabatabaee, R.M., Saberi, S., Parvizi, J., Mortazavi, S.M.J., Farzan, M., 2015. Combining concentrated autologous bone marrow stem cells injection with core decompression improves outcome for patients with early-stage osteonecrosis of the femoral head: a comparative study. J. Arthroplasty 30 (9 Suppl. l), 11–15. http://dx.doi.org/10.1016/j.arth.2015.06.022.
Tada, M., Takahama, Y., Abe, K., Nakatsuji, N., Tada, T., 2001. Nuclear reprogramming of somatic cells by in vitro hybridization with ES cells. Curr. Biol. 11 (19), 1553–1558. http://dx.doi.org/10.1016/S0960-9822(01)00459-6.
Taguchi, A., Sakai, C., Soma, T., et al., 2015. Intravenous autologous bone marrow mononuclear cell transplantation for stroke: phase1/2a clinical trial in a homogeneous group of stroke patients. Stem Cells Dev. 24 (19), 2207–2218. http://dx.doi.org/10.1089/scd.2015.0160.
Takahashi, K., Yamanaka, S., 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126 (4), 663–676. http://dx.doi.org/10.1016/j.cell.2006.07.024.
Tan, B.T.G., Lee, M.M.G., Ruan, R., 2008. Bone marrow-derived cells that home to acoustic deafened cochlea preserved their hematopoietic identity. J. Comp. Neurol. 509 (2), 167–179. http://dx.doi.org/10.1002/cne.21729.
Tan, C., Gao, X., Guo, L., Huang, H., 2014. Exogenous IL-4-expressing bone marrow mesenchymal stem cells for the treatment of autoimmune sensorineural hearing loss in a Guinea pig model. Biomed. Res. Int. 2014 http://dx.doi.org/10.1155/2014/856019.
Tang, Z.-H., Chen, J.-R., Zheng, J., et al., 2016. Genetic correction of induced pluripotent stem cells from a deaf patient with MYO7A mutation results in morphologic and functional recovery of the derived hair cell-like cells. Stem Cells Transl. Med. 5 (5), 561–571. http://dx.doi.org/10.5966/sctm.2015-0252.
Tateya, I., Nakagawa, T., Iguchi, F., et al., 2003. Fate of neural stem cells grafted into injured inner ears of mice. Neuroreport 14 (13), 1677–1681. http://dx.doi.org/10.1097/01.wnr.0000088600.22893.ec.
Taylor, D.A., Perin, E.C., Willerson, J.T., et al., 2015. Identification of bone marrow cell subpopulations associated with improved functional outcomes in patients with chronic left ventricular dysfunction: an embedded cohort evaluation of the FOCUS-CCTRN trial. Cell Transpl. 1–33. http://dx.doi.org/10.3727/096368915X689901.
Tesar, P.J., 2016. Snapshots of pluripotency. Stem Cell Rep. 6, 9–13. http://dx.doi.org/10.1016/j.stemcr.2015.12.011.
Tran, C., Damaser, M.S., 2014. Stem cells as drug delivery methods: application of stem cell secretome for regeneration. Adv. Drug Deliv. Rev. http://dx.doi.org/10.1016/j.addr.2014.10.007.
Troyer, D.L., Weiss, M.L., 2008. Wharton's jelly-derived cells are a primitive stromal cell population. Stem Cells 26 (3), 591–599. http://dx.doi.org/10.1634/stemcells.2007-0439.
Turner, D.A., Baillie-Johnson, P., Martinez Arias, A., 2015. Organoids and the genetically encoded self-assembly of embryonic stem cells. BioEssays 181–191. http://dx.doi.org/10.1002/bies.201500111.
Wang, T., Chai, R., Kim, G.S., et al., 2015. Lgr5+ cells regenerate hair cells via proliferation and direct transdifferentiation in damaged neonatal mouse utricle. Nat. Commun. 6, 6613. http://dx.doi.org/10.1038/ncomms7613.
Water, Bas E., Van De, T., Van De Water, T.R., et al., 2014. Adult human nasal mesenchymal-like stem cells restore cochlear spiral ganglion neurons after experimental lesion. Stem Cells Dev. 23 (5), 502–514. http://dx.doi.org/10.1089/scd.2013.0274.
Weimann, J.M., Charlton, C a, Brazelton, T.R., Hackman, R.C., Blau, H.M., 2003. Contribution of transplanted bone marrow cells to Purkinje neurons in human adult brains. Proc. Natl. Acad. Sci. U. S. A 100 (4), 2088–2093. http://dx.doi.org/10.1073/pnas.0337659100.
Wright, M.C., Reed-Geaghan, E.G., Bolock, A.M., Fujiyama, T., Hoshino, M., Maricich, S.M., 2015. Unipotent, Atoh1+ progenitors maintain the Merkel cell

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011

population in embryonic and adult mice. J. Cell Biol. 208 (3), 367–379. http://dx.doi.org/10.1083/jcb.201407101.
Xu, J., Shepherd, R.K., Millard, R.E., Clark, G.M., 1997. Chronic electrical stimulation of the auditory nerve at high stimulus rates: a physiological and histopathological study. Hear Res. 105 (1–2), 1–29. http://www.ncbi.nlm.nih.gov/pubmed/9083801 (Accessed June 29, 2014).
Xu, Y.-P., Shan, X.-D., Liu, Y.-Y., et al., 2016. Olfactory epithelium neural stem cell implantation restores noise-induced hearing loss in rats. Neurosci. Lett. 616, 19–25. http://dx.doi.org/10.1016/j.neulet.2016.01.016.
Yerukhimovich, M.V., Bai, L., Chen, D.H.C., Miller, R.H., Alagramam, K.N., 2007. Identification and characterization of mouse cochlear stem cells. Dev. Neurosci. 29 (3), 251–260. http://dx.doi.org/10.1159/000096415.
Yiou, R., Hamidou, L., Birebent, B., et al., 2015. Safety of intracavernous bone marrow-mononuclear cells for postradical prostatectomy erectile dysfunction: an open dose-escalation pilot study. Eur. Urol. 2–5. http://dx.doi.org/10.1016/j.eururo.2015.09.026.
Yoo, T.J., Du, X., Zhou, B., 2015. The paracrine effect of mesenchymal human stem cells restored hearing in β-tubulin induced autoimmune sensorineural hearing loss. Hear Res. 330 (Pt A), 57–61. http://dx.doi.org/10.1016/j.heares.2015.07.021.
Yoshida, T., Hakuba, N., Morizane, I., et al., 2007. Hematopoietic stem cells prevent hair cell death after transient cochlear ischemia through paracrine effects. Neuroscience 145, 923–930. http://dx.doi.org/10.1016/j.neuroscience.2006.12.067.
Yu, Q., Liu, L., Lin, J., et al., 2015. SDF-1α/CXCR4 Axis mediates the migration of mesenchymal stem cells to the hypoxic-ischemic brain Lesion in A Rat model. Cell J. 16 (4), 440–447. http://www.ncbi.nlm.nih.gov/pubmed/25685734.
Zhang, P.Z., He, Y., Jiang, X.W., et al., 2013. Stem cell transplantation via the cochlear lateral wall for replacement of degenerated spiral ganglion neurons. Hear Res. 298, 1–9. http://dx.doi.org/10.1016/j.heares.2013.01.022.
Zhang, P., He, Y., Jiang, X., et al., 2013. Up-regulation of stromal cell-derived factor-1 enhances migration of transplanted neural stem cells to injury region following degeneration of spiral ganglion neurons in the adult rat inner ear. Neurosci. Lett. 534 (1), 101–106. http://dx.doi.org/10.1016/j.neulet.2012.11.018.
Zhang, L., Wang, R., Xiao, C.-S., Wu, Y., Gao, C.-Q., 2015. Relationship between perioperative cardiovascular risk factors and bone marrow cells from patients undergoing coronary artery bypass grafting surgery. Genet. Mol. Res. 14 (4), 15233–15241. http://dx.doi.org/10.4238/2015.November.25.11.
Zhao, L.-D., Li, L., Wu, N., et al., 2012. Migration and differentiation of mouse embryonic stem cells transplanted into mature cochlea of rats with aminoglycoside-induced hearing loss. Acta Otolaryngol. 6489 (June 2012), 1–8. http://dx.doi.org/10.3109/00016489.2012.720029.
Zhou, Y., Yuan, J., Zhou, B., et al., 2011. The therapeutic efficacy of human adipose tissue-derived mesenchymal stem cells on experimental autoimmune hearing loss in mice. Immunology 133 (1), 133–140. http://dx.doi.org/10.1111/j.1365-2567.2011.03421.x.
Zomer, H.D., Vidane, A.S., Gonçalves, N.N., Ambrósio, C.E., 2015. Mesenchymal and induced pluripotent stem cells: general insights and clinical perspectives. Stem Cells Cloning 8, 125–134. http://dx.doi.org/10.2147/SCCAA.S88036.

Please cite this article in press as: Warnecke, A., et al., Advances in translational inner ear stem cell research, Hearing Research (2017), http://dx.doi.org/10.1016/j.heares.2017.05.011