3THp: THE POTENTIAL OF STEM CELLS FOR AUDITORY NEURON GENERATION AND REPLACEMENT IN THE DEAF COCHLEA

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Cochlear implants function by electrically stimulating auditory neurons in the absence of hair cells, to enable hearing in severe to profoundly deaf individuals. The efficacy of this device therefore depends on a critical number of surviving auditory neurons. Stem cell transplantation therapy is emerging as a potential strategy for auditory nerve rehabilitation, as differentiated stem cells may provide a source of replacement neurons to the deaf cochlea. The successful engraftment of stem cells into the cochlea will require both the directed growth of new processes and the formation of functional connections with existing structures, and we are investigating these questions using both *in vitro* and *in vivo* models.

Specifically, we have developed an *in vitro* assay to differentiate human stem cells into sensory neural precursors (neural crest), which we have co-cultured with early post-natal cochlear explants. After 11 days in culture, we observe stem cell-derived processes growing toward the hair cells along the peripheral processes in the explant. Both the migratory phenotype and molecular profile of these differentiated stem cells (including expression of HNK1, Sox10, peripherin and NF-H) suggests that they are sensory neural progenitors and may be suitable for auditory neuron replacement. The potential to differentiate human stem cells into auditory neurons for transplantation, including the incorporation of new induced pluripotent stem cell technology, will be discussed.

We have also examined the engraftment of stem cells into the deafened mammalian cochlea using various surgical approaches. Our transplantation studies were designed with the primary intention of investigating whether stem cells could be applied in a clinical manner that would eventually allow combined therapy with a cochlear implant. Collectively, these studies have shown that stem cells can survive and differentiate into neural cells in the deafened cochlear environment, however, their long term survival, neurite outgrowth and functional connectivity needs further investigation. Our research illustrates the potential of, and future considerations for, combined stem cell therapy with cochlear implantation.

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