

Short Communication

Regenerative Therapy for Sensorineural Hearing Loss: Recent Progress and Future Directions

James Baumgartner^{1*} and Linda Baumgartner²

¹Advent Health Orlando, Department of Paediatric Surgery, University of Central Florida College of Medicine, USA

²Little HEARoes, LLC, USA

Sensorineural Hearing Loss (SNHL) continues to be a significant public health problem with over 270 million affected people worldwide and an incidence that increases with age [1,2]. Some cases of SNHL have a genetic cause, but the majority of SNHL is the result of ototoxic insult [3]. The underlying pathophysiology is related to the loss of sensory hair cells within the organ of Corti. As this structure is post-mitotic at birth, no spontaneous replacement of damaged hair cells is thought to occur. Current therapies (hearing aids and cochlear implants) are designed to augment the function of the damaged organ of Corti [4]. Recently pre-clinical and clinical publications have suggested that hair cell regeneration may be possible in an injured, post-mitotic organ of Corti [5-11].

In addition to damage to the organ of Corti, ototoxic insults can damage structures along the auditory pathways. Modest ototoxic injury can result in Transient Threshold Shifts (TTS) where audiologic testing identifies SNHL which resolves in days to weeks following injury. More severe ototoxic insults cause a Permanent Threshold Shift (PTS) and SNHL that does not improve. Preclinical studies demonstrate that PTS inducing single noise exposure causes apoptosis mediated changes in the dorsal and ventral cochlear nuclei, the central nucleus of the inferior colliculus, the dorsal, ventral and medial subdivisions of the medial geniculate body and layers I-IV of the primary auditory cortex. Even TTS inducing insults create a decreased cell density in the ventral cochlear nucleus [12-14]. Therefore the clinical focus of regenerative therapies for SNHL should not be limited to the organ of Corti but should also include the intracranial auditory processing structures.

***Corresponding author:** James Baumgartner, Advent Health Orlando, Department of Paediatric Surgery, University of Central Florida College of Medicine, USA, E-mail: jim4423@icloud.com

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In their phase 1 trial McLean et al., evaluated epigenetic modification as a treatment for SNHL. They used Histone Deacetylases (HDAC) treatment to allow cochlear stromal support cells to re-enter the mitotic cell cycle and generate new hair cells. HDACs were delivered into the middle ear in a gel preparation. The HDACs diffused into the inner ear reaching the base of the cochlea where higher frequency responsive hair cells were presumably repaired. Treated subjects showed a 10 dB improvement and ABR thresholds at higher frequencies along with improved speech discrimination test scores [10,11]. The study did not measure changes in the CNS auditory pathways.

Baumgartner et al.'s phase 1 trial, which examined intravenous autologous cord blood mononuclear fraction treatment of SNHL, showed a 15 dB improvement in Auditory Brain Stem (ABR) thresholds following treatment. The study also suggested that cord blood treatment might improve the latency of signal transmission along the eighth cranial nerve. In this study 3-Tesla MRI diffusion tensor imaging sequences were used to evaluate Fractional Anisotropy (FA). FA is a measure of white matter tract integrity. FA was shown to improve along the auditory pathways in subjects whose ABR thresholds improved following cord blood treatment. FA improvement was most evident in Heschl's gyrus [9]. Cord blood treatment was thought to act via an immunomodulatory mechanism which has been reviewed elsewhere [15].

These clinical studies are intriguing, and their results support additional phase 2/3 trials to better analyze the effects of epigenetic and immunomodulatory SNHL treatments. In addition, as both studies appear to work through alternate mechanisms, a study combining both approaches might be illuminating.

The above listed preclinical studies evaluate treatments delivered in the acute to near subacute phase following SNHL inducing ototoxic injury. The clinical trials, on the other hand, evaluated treatment administered in a more delayed time frame following SNHL onset. This area of study might benefit from preclinical experiments focusing on a more chronic SNHL model as well as clinical trials where treatment is delivered closer to the time of ototoxic insult.

We support central nervous system imaging and FA analysis in future clinical trials to evaluate the effect of new treatments on auditory pathway white matter tract integrity. As immunomodulation appears to provide some benefit in patients with SNHL, additional immunomodulatory approaches (drugs, polymers, etc.) should be evaluated in the treatment of this disabling condition.

Ongoing research holds great promise in the treatment of SNHL. The quantitative measures available in the evaluation of SNHL make hearing loss a model system to evaluate regenerative medical treatments which cannot be easily analyzed in other conditions. In addition to improving the communication skills of patients with SNHL, continued research in SNHL may result in an improved understanding of broad areas of regenerative medicine.

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