**A New Era in Gene Therapy for Genetic Hearing Loss**

Genetic hearing loss affects approximately one in every 500 newborns, impacting more than 34 million children worldwide. Additionally, genetic mutations increasingly contribute to hearing impairment in adult populations, including age-related hearing loss. Since the identification of the first deafness genes over three decades ago, significant progress has led to the discovery of more than 150 genes associated with hearing loss in humans. Particularly in the last decade, remarkable advancements have been achieved in developing treatments for genetic hearing loss using mouse models. Innovative technologies, such as adeno-associated virus (AAV)-mediated gene therapy, dual-AAV delivery systems, and genome editing, have recently made possible therapeutic interventions previously considered unattainable.

In this presentation, I will discuss our recent research utilizing genome editing to treat a mouse model of the dominant human genetic hearing disorder DFNA41, caused by mutations in the P2RX2 gene. Our study demonstrates that genome editing can be efficiently and safely applied to adult deaf mice, effectively restoring hearing and vestibular function. The minimal off-target effects and transient nuclease expression observed make this approach highly promising for human clinical applications. Consequently, we are currently conducting a preclinical evaluation of genome-editing therapy for DFNA41.

But how effectively can these animal studies translate to human therapies? In the second part of my talk, I will share insights from the first clinical trial of OTOF gene therapy, which successfully restored hearing and speech capabilities in children with congenital hearing loss. This study also demonstrates the effectiveness of the dual-AAV strategy in overcoming gene size limitations inherent in single-AAV approaches, thus paving the way for treating a broader spectrum of genetic hearing disorders. Finally, I will discuss recent findings regarding long-term outcomes and explore future directions for advancing gene therapy in patients with genetic hearing loss.