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(54) Title: DUAL RECOMBINANT AAV8 VECTOR SYSTEM ENCODING ISOFORM 5 OF OTOFERLIN AND USES THEREOF

(57) Abstract: The present invention is based on the observation that a dual AAV vector strategy encoding isoform 5 of otoferlin cDNA that has been split into two expression cassettes both packaged in - and delivered by - an AAV8 capsid can efficiently deliver the otoferlin cDNA to the inner hair cell (IHC). Moreover, the inventors highlighted that the use of the CMV promoter in one of the two AAV8 vectors provides a significant expression of otoferlin in these particular cells. As the AAV serotype and the type of promoter used are two key elements that have a significant effect on the transduction efficiency, the development of the vector system of the invention is going to provide optimal therapeutic benefit in patients suffering from DFNB9 deafness. To further improve this therapeutic effect, the inventors finally tested some particular otoferlin-encoding dual vector constructs to identify enhanced transfection rate and a very effective in vitro and in vivo otoferlin expression in mature cochlea of DFNB9 mice models, leading to the restoration of their hearing.