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Researchers develop Rx for deafness, impaired balance in mouse model of Usher syndrome

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Jennifer Lentz, PhD, Assistant Professor of Otorhinolaryngology & Biocommunications and a member of the Neuroscience Center of Excellence at LSU Health Sciences Center New Orleans, is the lead author of a paper reporting that hearing and balance can be rescued by a new therapy in a mouse model of Usher syndrome (Usher) that contains the mutation responsible for type 1C Usher. The results provide the first evidence that congenital deafness can be effectively overcome by treatment early in development to correct gene expression. The paper, Rescue of hearing and vestibular function in a mouse model of human deafness, is published online February 4, 2013 in *Nature Medicine*.

Dr. Lentz, along with researchers at Rosalind Franklin University School of Medicine and Science in North Chicago, Illinois and at Isis Pharmaceuticals in Carlsbad, California have developed a novel therapy called an antisense oligonucleotide (ASO) that corrects defective gene expression caused by a mutation in the USH1C gene. Treatment of newborn mice with a single dose of ASOs partially corrects gene and protein expression, and rescues hearing and balance. The results demonstrate the therapeutic potential of ASOs in the treatment of deafness and balance disorders.

Usher syndrome is the leading cause of combined deafness and blindness. Recent estimates suggest that 1 in 6,000 individuals world-wide are affected with Usher. Acadian patients of south Louisiana and

Canada have type 1C Usher, the most severe form of the disease. These patients are born deaf, have impaired balance and, when teenagers, become progressively blind.

"Our study demonstrates that a human disease-causing mutations, modeled in mice, can be effectively corrected to treat deafness and balance dysfunction, and that this treatment may need to occur only once in life, during the critical hair cell developmental period," says Dr. Lentz. "Remarkably, deafness and balance dysfunction are rescued in Usher mice by inducing a relatively small shift in Ush1c gene expression."

Dr. Lentz, who has been studying Usher Syndrome in the Acadian population for the past ten years, led the team of researchers at LSU Health Sciences Center New Orleans which also included Drs. Nicolas G. Bazan, Hamilton E. Farris, and Matthew J. Spalitta. Dr. Michelle L. Hastings, an expert in gene expression and targeting, headed the team at Rosalind Franklin University of Medicine and Science, which includes co-lead authors of the paper, Francine M. Jodelka and Anthony J. Hinrich, along with Kate E. McCaffrey and Dominik M. Duelli. Dr. Frank Rigo at Isis Pharmaceuticals specializes in ASO technology and was key to the success of the project.

"Dr. Jennifer Lentz is an exemplary young scientist," notes Dr. Nicolas Bazan, Director of the Neuroscience Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, and one of the co-authors of the paper. "She succeeded in placing the mutation in the Usher syndrome type 1 gene (USH1C) responsible for Acadian Usher in a mouse, which opened up the possibility for defining how the disease develops and, more importantly, how it can be cured."

"The discovery of an ASO-type drug that can effectively rescue hearing opens the door to developing similar approaches to target and cure other

causes of hearing loss", says Dr. Hastings who will receive a grant from the National Institute of Health to further develop the ASOs for the treatment of deafness with Dr. Lentz and Dr. Duelli.

Provided by Louisiana State University