Treatment approach to human Usher syndrome: Small molecules ignore stop signals

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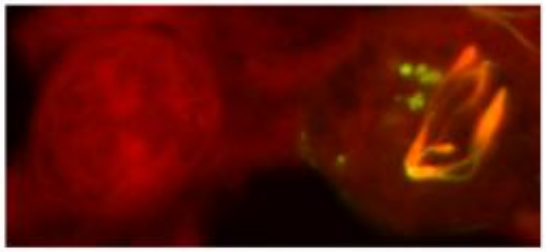

Fluorescence microscopic analyses of cells carrying a nonsense mutation in the USH1C gene. In the left cell, no translational readthrough has occurred. In the right cell, PTC124 mediated translational readthrough of the USH1C nonsense mutation resulted in the restoration of harmonin's (green) capacity for bundling actin filaments (red). Photo: Tobias Goldmann

Usher syndrome is the most common form of combined congenital deaf-blindness in humans and affects 1 in 6,000 of the population. It is a recessive inherited disease that is both clinically and genetically heterogeneous. In the most severe cases, patients are born deaf and begin to suffer from a degeneration of the retina in puberty, ultimately resulting in complete blindness. These patients experience major problems in their day-to-day life. While hearing loss can be compensated for with hearing aids and cochlea implants, it has not proven possible to develop a treatment for the associated sight loss to date. Researchers at Johannes Gutenberg University Mainz (JGU) in Germany have now

developed a new treatment approach to this disease.

In previously conducted research into this subject, the research team headed by Professor Uwe Wolfrum of the Institute of Zoology at Mainz University had already gained insight into of the fundamental molecular processes and mechanisms causing this debilitating syndrome. Using the results of this successful basic research, the Usher treatment team in Mainz headed by Dr Kerstin Nagel-Wolfrum has now evaluated potential ocular treatment options. Their attention was focused on a mutation identified in a specific German family known to develop the most severe form of Usher syndrome. This mutation is a so-called nonsense mutation in the USH1C gene, which leads to the generation of a stop signal in a DNA base, resulting in premature termination of protein synthesis.

The Mainz research team has now published its latest work on pharmacogenetic strategies for the treatment of Usher syndrome patients with nonsense mutations in the May edition of the journal Human Gene Therapy. The researchers were able to show that a small molecule known as PTC124 (Ataluren) causes the stop signal in the mutated USH1C gene to be ignored, thus resulting in continuing protein synthesis and the formation of the functional genetic product in cell and organ cultures. In addition to its ability to cause readthrough of stop signals, the active agent PTC124 has also been demonstrated to be highly compatible with murine and human retina cultures. Moreover, the team managed for the first time to demonstrate readthrough of an eye mutation codon in vivo.

"PTC124 is already being tested in clinical trials for its efficacy in treating other diseases involving nonsense mutations, such as cystic fibrosis and Duchenne muscular dystrophy. We therefore hope that this treatment approach will soon be ready for use in Usher syndrome patients," explains Dr Kerstin Nagel-Wolfrum.

Currently putting the finishing touches on his doctoral thesis, Tobias Goldmann is comparing the efficiency of the readthrough rate and the biocompatibility of other molecules that induce the readthrough of nonsense mutations. The focus is particularly on modified aminoglycosides, i.e. derivatives of commercially available and clinically tested antibiotics. These are being designed and synthesized by an Israeli cooperation partner, Professor Timor Bassov of the Haifa Technicon, and have already been successfully used by researchers in Mainz for readthrough of nonsense mutations in Usher genes. In addition to conducting further preclinical studies of the ocular applications of these new substances, the Usher laboratory in Mainz is planning to use this new method of treating this specific form of Usher syndrome in hospital patients as soon as possible.

More information:

Goldmann T., Overlack N., Wolfrum U., Nagel-Wolfrum K. (2011): PTC124-Mediated Translational Readthrough of a Nonsense Mutation Causing Usher Syndrome Type 1C. *Human Gene Therapy* 22:537-547. DOI: 10.1089/hum.2010.067

Goldmann T., Rebibo-Sabbah A., Overlack N., Nudelman I., Belakhov V., Baasov T., Ben-Yosef T., Wolfrum U., Nagel-Wolfrum K. (2010): Beneficial Read-Through of a USH1C Nonsense Mutation by Designed Aminoglycoside NB30 in the Retina. *Investigative Ophthalmology & Visual Science* 51:6671-80. DOI: 10.1167/iovs.10-5741

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