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Ataluren restores function to REP1 in human choroideremia cells and zebrafish

Researchers with funding from Fight for Sight have demonstrated that a new drug treatment for cystic fibrosis and Duchenne muscular dystrophy can override a genetic fault that causes choroideremia – a severe blinding disorder. Treatment with Ataluren restored the function of rab escort protein 1 (REP1) – a protein that is critical for vision – in skin cells from a patient with choroideremia and in a zebrafish model.

Choroideremia is a rare inherited retinal dystrophy caused by any number of faults in the CHM gene which encodes instructions for making REP1. Around 1 in 3 of these faults are nonsense mutations - single letter substitutions that generate a premature instruction for cells to stop assembling the protein.

REP1 is important for cells throughout the body to process protein correctly, but is particularly active in the retina. The loss of function caused by nonsense mutations in CHM damages both the light-detecting photoreceptor cells of the retina and the blood vessel layer (choroid) that supplies them.

Ataluren (PTC Therapeutics) is designed to weaken the cell’s recognition of nonsense mutations. The drug allows cells to misread an abnormal stop instruction, permitting fulllength protein to be made that functions normally.

Dr Mariya Moosajee at UCL Institute of Ophthalmology is first author on the study, which is published in Human Molecular Genetics. She said:

“In this study we have used two independent models of choroideremia. Patient-derived skin cells with absent REP1 function as a model for testing pharmacological therapy with Ataluren and related compounds; and the zebrafish as the only nonsense mutation animal model of choroideremia, enabling study of the whole retina in response to treatment.

“In the zebrafish model, Ataluren prevented the onset of retinal degeneration and significantly reduced oxidative stress and programmed cell death. REP1 production increased by 23% and its biological function was restored from 0% to 98%. Although we did not see a measurable increase in REP1 production in the patient-derived cells, biological function was restored from 0% to 42%, indicating that some quantity of healthy REP1 was produced.”

Dr Dolores M Conroy is Fight for Sight’s Director of Research. She said:

“These results show the potential for this class of drug to rescue retinal function in choroideremia and other inherited retinal dystrophies due to nonsense mutations. The most obvious potential is in the earlier stages when the retina is still functional and able to produce restored protein when treated.

“Ataluren is orally administered and has a demonstrably good safety profile. It has already had some success in clinical trials for other nonsense mutation-based inherited disorders. This could provide an alternative treatment to gene replacement therapy for some choroideremia patients.”

ENDS NOTES TO EDITORS Publication Moosajee, M. et al. Functional rescue of REP1 following treatment with PTC124 and novel derivative PTC-414 in human choroideremia fibroblasts and the nonsense-mediated zebrafish model. Hum. Mol. Genet. (2016). doi:10.1093/hmg/ddw184