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Treating nonsense may be a cure for the blinding disease Choroideremia

Choroideremia (CHM) is a blinding genetic eye disease, where male children as early as 5 years old develop night-blindness, followed by loss of their peripheral field of vision in adolescence, culminating in complete blindness in late adulthood. In over 30% of patients, the disease is caused by a nonsense mutation, which introduces an abnormal stop signal in the CHM gene that blocks normal protein production. As yet, no effective treatment exists for patients so they face a future of inevitable blindness.

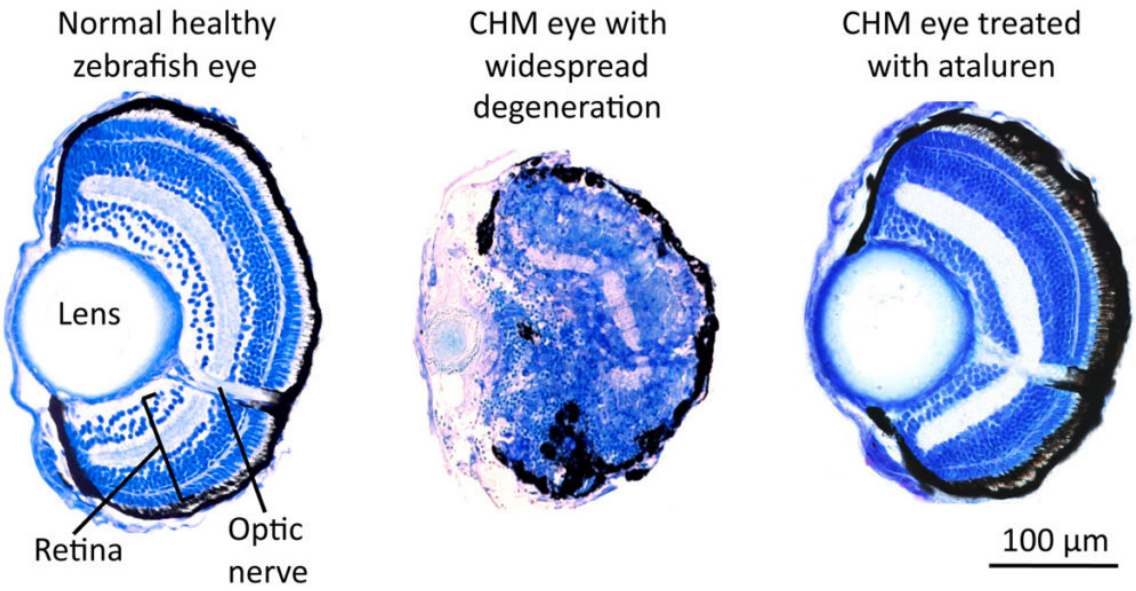
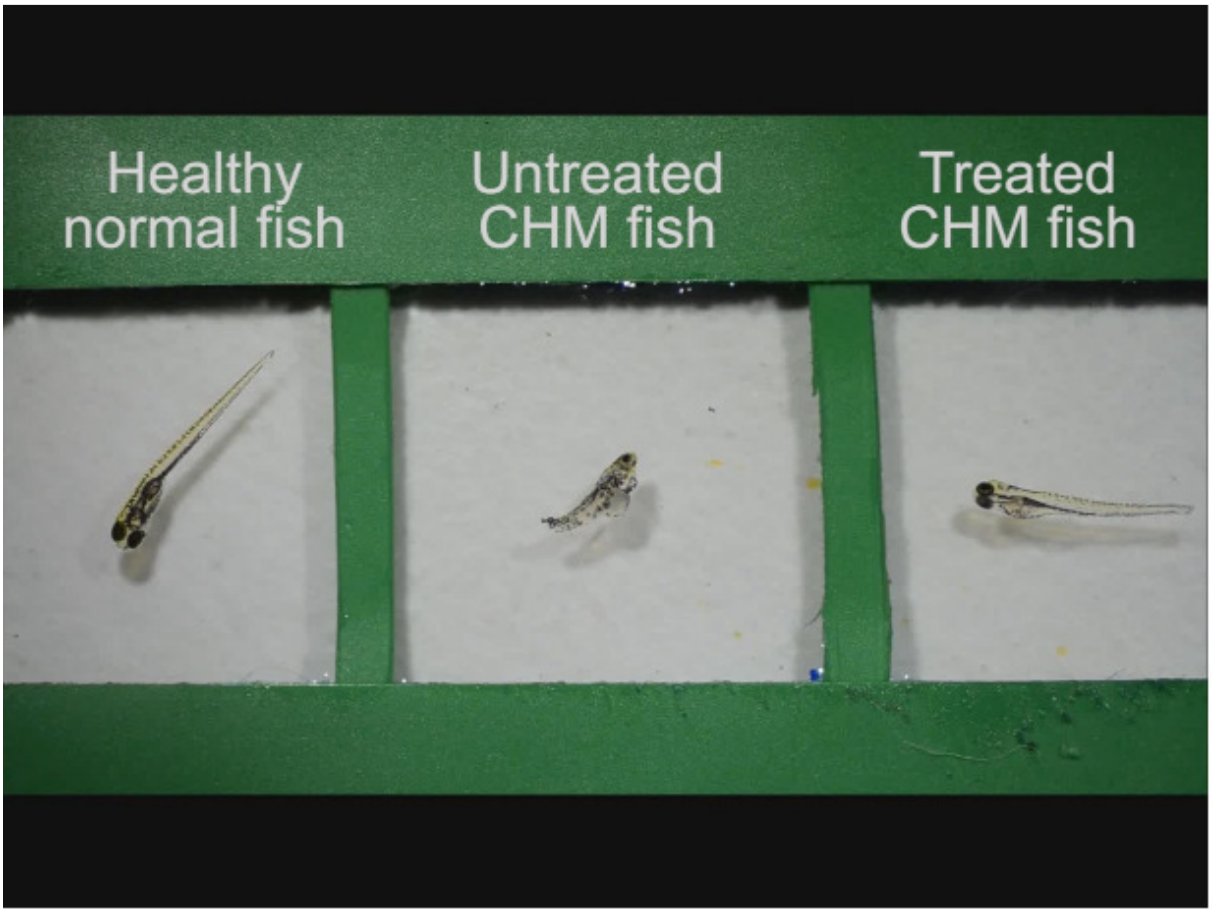


Fig. 1. Cross sections through a 6 day old normal healthy zebrafish eye, CHM zebrafish eye and a treated CHM zebrafish eye with ataluren. The CHM zebrafish eye shows widespread degeneration and is smaller than the normal healthy eye. Once treated with ataluren, the CHM eye looks healthier, more akin to the normal healthy zebrafish with correctly developed eye structures and no evidence of degeneration.

Previously, we have taken advantage of the ability of a class of antibiotics called aminoglycosides (including gentamicin and paromomycin) to override nonsense mutations and partially restore full-length, functional protein in the zebrafish model of CHM. Treatment showed remarkable prevention of the retinal degeneration and a 1.7 fold increase in life expectancy of the CHM zebrafish (which normally only survive till 5 days old). However, aminoglycosides were not safe to use long-term in human patients due to serious toxic drug-related side effects affecting the ear and kidneys.

Ataluren (also known as PTC124 or Translarna^{TM}) is a new class of drug designed to be more efficient at overriding abnormal stop signals than aminoglycosides, but with a safer profile. We tested the safety and efficacy of ataluren and its derivative PTC-414 in two different models of CHM both harbouring disease-causing nonsense mutations (i) the zebrafish model and (ii) human cells called fibroblasts taken from a skin

biopsy of a CHM patient. Both drugs were safer than aminoglycosides, ataluren had no significant toxic effects on the zebrafish ear or kidney, however, PTC-414 did affect kidney function. Overall ataluren and PTC-414 successfully prevented the onset of the retinal degeneration in the zebrafish (Fig. 1), and improved general health (follow link to attached video file for live imaging of treated zebrafish) with a 2-fold increase in life expectancy reaching up to 10 days of age. The average amount of normal protein produced increased by 20% in drug treated zebrafish, and this resulted in a gain of 98% (ataluren) and 68% (PTC-414) protein function. In contrast, no protein could be detected in the drug treated patient fibroblast cells, this was thought to be due to the sensitivity limit of the experimental technique to detect low levels of protein. However, when protein function was measured, this showed a 42% (ataluren) and 36% (PTC-414) increase in activity compared to baseline untreated cells.



Video: http://atlasofscience.org/wp-content/uploads/2017/01/MariyaMoosajee-zf-withataluren.mp4

Ataluren has received approval for the treatment of Duchenne Muscular Dystrophy in the European Union, as clinical benefit was noted in the 6-minute walk test in patients when taken orally. It has reached phase III clinical trials in children and adult patients with cystic fibrosis showing improvement in chest symptoms. Ataluren has a good safety profile with few mild and moderate side effects recorded. We are currently conducting a detailed clinical study of CHM to understand the natural history of the disease and identify the most suitable therapeutic

window. Clinical trials with ataluren are forthcoming and may provide a potential treatment for those patients with CHM, but also associated inherited retinal disorders, such as retinitis pigmentosa, Usher syndrome, and Bardet–Biedl syndrome. A molecular therapy that safely targets nonsense mutations, which contribute to over a third of genetic eye disease, could therefore treat a substantial proportion of patients in a disease- and gene-independent manner, making the approach both practical and economical.

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Publication

Functional rescue of REP1 following treatment with PTC124 and novel derivative PTC-414 in human choroideremia fibroblasts and the nonsense-mediated zebrafish model.
Moosajee M, Tracey-White D, Smart M, Weetall M, Torriano S, Kalatzis V, da Cruz L, Coffey P, Webster AR, Welch E
Hum Mol Genet. 2016 Aug 15