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Can histone deacetylase inhibitors uncover novel therapeutic agents for inherited retinal dystrophies

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***Introduction*:** Inherited retinal dystrophies (iRDs) affect 1 in 3000 people worldwide and effective treatment options are not widely available due to the genetic and clinical heterogeneity. Recently, histone deacetylase inhibitors (HDACi) have gained attention as a potential therapeutic option based on their neuroprotective effects within the retina[1]. However, the benefits of HDACi remains highly controversial[2-3], and their downstream mechanism of action are yet to be thoroughly elucidated. Preliminary data from studies conducted has shown that treatment of zebrafish retinal mutant with HDACi, trichostatin A (TSA), could rescue visual capacity and retinal morphology[4]. The current study is designed to address the suitability of HDACi as therapeutic options for iRDs using zebrafish models.

***Methods*:** A zebrafish retinal mutant model, *raifteirí* (*raf*) was selected for the present study and was subjected to treatment with two different HDACi, namely tubastatin A (TST) and TSA. Progeny from incross of two heterozygous parents were treated at 3 days post fertilization (dpf) with either 100 µM TST or 1 µM TSA for a period of two days. At the end of the treatment period, the larvae were subjected to behavioral assays (OKR and VMR), to determine the effect of drug treatment on the visual capacity. Retinal morphology was also analyzed by light microscopy. Each experiment was performed in triplicates with n = 12 per treatment condition, and Student's T-test was used for data analysis.

***Results*:** Preliminary data obtained from treatment of *raf* mutants with TST, showed that visual function was significantly improved in the treated *raf*$^{-/-}$, with an average of 2 saccades/minute compared to untreated mutants, which had on average 0.2 saccades/minute. VMR analysis additionally revealed that the Max On response to light exposure was increased in the treated larvae as well. Contrarily, 1 µM TSA treatment proved to be highly toxic, resulting in adverse effects in the *raf* line.

***Conclusion*:** Further experiments are needed to determine the maximum tolerated dose, the safety and efficacy profile and the mechanism of action of these drugs. From this pilot study, HDACi have proved to be suitable candidates with potential to uncover additional therapeutic targets for iRDs, though this still needs to be thoroughly investigated.

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