Validation of candidate therapeutic targets for Huntington’s disease in *Drosophila*

*Susanna Campesan, Charalambos P. Kyriacou, and Flaviano Giorgini*

Department of Genetics, University of Leicester, Leicester, UK

We recently identified 28 gene deletions that suppress toxicity of a mutant huntingtin (htt) fragment in a yeast model of Huntington’s disease (HD). Here we describe work validating a subset of these loss-of-function suppressors which have human homologs using a *Drosophila* model of HD. In our experiments, we are directing mutant htt exon 1 93Q transgene expression both temporally and spatially via three promoters: 1) *elav* - which directs expression in most neurons; 2) *gmr* - which drives expression in all cells of the eye, including neurons and supporting cells and 3) *tim* – which is expressed in circadian clock neurons. The suppressors are being tested either via known loss-of-function alleles or using RNAi transgenic fly lines from the Vienna *Drosophila* RNAi Center. One of these suppressors being tested encodes the fly homolog of the mammalian enzyme kynurenine 3-monoxygenase (KMO). We have validated our initial yeast work pharmacologically in both mammalian cells and in the R6/2 mouse model of HD, making KMO a promising candidate therapeutic target for this disease. Here we report that a loss-of-function allele of the *Drosophila* Kmo homolog, cinnabar (cn\(^3\)), significantly enhances the number of rhabdomeres (eye photoreceptors) in Htt93Q; \(cn^3\) individuals compared to Htt93Q expressing control flies, which suffer extensive eye degeneration. This work provides the first genetic evidence that inhibition of KMO function is neuroprotective in an animal model of HD, and supports the notion of validating yeast candidate therapeutic targets in *Drosophila*.

In addition to previously used metrics, we are studying behavioural phenotypes in HD model flies, such as circadian locomotor rhythms and visual tracking. We have examined circadian behaviour of the HD model flies that have been aged for several days, in light-dark (LD) cycles and constant darkness (DD). We have observed that pan-neuronal expression of htt using the *elav* promoter led to reduced levels of locomotor behaviour in the flies, and an impaired ability to synchronise to LD cycles. These behavioural characters represent sensitive and novel metrics for assaying suppression of mutant htt-dependent toxicity. We are also measuring visual tracking using the fly’s optomotor responses, a simple measure of the fly’s ability to maintain it’s orientation to a moving visual field. Our initial results suggest that this approach will reinforce and extend that from the anatomical analyses. In summary, we have found novel behavioral phenotypes in HD model flies that will serve as sensitive metrics for validating genetic modifiers of mutant htt toxicity identified in yeast.

Support: HighQ/CHDI Discovery Initiative.