Title: Characterisation of a mouse model for testing the efficacy of transplanted human RPE cells

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Introduction: The RCS dystrophic rat has been used to test efficacy of human retinal pigment epithelium (RPE) cells for the treatment of dry age-related macular degeneration (AMD). However, unlike dry AMD, where geographic atrophy denudes Bruch's membrane of RPE, the dysfunctional RPE cells of RCS rats fail to degenerate. An alternative approach uses sodium iodate ($NaIO_3$) to selectively kill the host RPE, a procedure that facilitates survival of polarised human RPE cells along Bruch's membrane in mice (Carido et al., 2014). However, despite RPE phagocytosis of outer segments, no evidence of functional recovery could be found by electroretinography (ERG), possibly due to insufficient delivery of visual chromophore by the grafted cells. Here we characterise the functional and anatomical consequences of administering sodium iodate to mice and test whether the complete restoration of retinal chromophore supply by systemic 9-cis-retinal supplementation can restore retinal function to $NaIO_3$-treated mice.

Methods: Adult C57 mice received a single intravenous injection of $NaIO_3$ (40mg/Kg) and photoreceptor function was then assessed by ERG at 3 days, 7 days and 1-month post-$NaIO_3$ treatment. Mice were dark adapted and received intraperitoneal injections of 9-cis-retinal (1mg/mouse) or saline 16h prior to ERG recordings. Photoreceptor function was also assessed in $NaIO_3$-treated mice by measuring the pupillary light reflex (PLR) at 1 month post-injection. Mice were sacrificed after functional testing and Immunohistochemistry was performed in order to assess RPE ablation and photoreceptor integrity.

Results: In the absence of systemic chromophore, the ERG was flat or negative at all time points studied. Functional recovery of the ERG in $NaIO_3$-treated mice (restoration of A and B waves) could be produced following systemic delivery of 9-cis-retinal. However, this effect only occurred in 50% of animals at 3 days post-$NaIO_3$-treatment and at 7 days post-treatment the ERG was unrecoverable. The sensitivity of the PLR in $NaIO_3$-treated mice was reduced but appeared largely intact at high irradiances. Immunohistochemistry confirmed focal RPE degeneration, disruption to the outer nuclear layer and the persistence of melanopsin expression in $NaIO_3$-treated mice.

Conclusion: The ability of systemic chromophore supplementation to recover ERG function in $NaIO_3$-treated mice is lost between 3 and 7 days post-treatment. This suggests that photoreceptors may be irreversibly damaged by $NaIO_3$-treatment and may help to explain the failure of others to correlate functional improvement by ERG with the presence of grafted human RPE (Carido et al 2014).