Topical treatment for AMD: Non-invasive delivery and efficacy of ranibizumab and bevacizumab in rabbit and porcine eyes

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Purpose
To investigate cell penetrating peptides (CPP) as novel topical ocular drug delivery vehicles. To use the CPP to replace intravitreal injections that transport anti-VEGF therapeutics, into the posterior segment of rabbit and pig eyes with CPP mediated topical delivery.
Methods
Delivery of ranibizumab and bevacizumab to the posterior segment by the CPP eye drop was determined in rabbit eyes in vivo and porcine eyes ex vivo using ELISA. CPPs were mixed with anti-VEGF and their efficacy was tested using an established model of choridal neovascularization. Animals were then treated with i) CPP+anti-VEGF eye drop, ii) anti-VEGF eye drop, iii) CPP eye drop, v) anti-VEGF intravitreal injection (ivit), vi) saline eye drop. Outcomes were measured using in vivo retinal imaging and immunohistochemistry.
Results
After topical delivery in porcine eyes the CPP+ranibizumab eye drop delivered 1.7±0.4 μg/mL and the CPP+bevacizumab eye drop delivered 1.1±0.3μg/mL all significantly higher levels ($p<0.005$) than CPP, saline, ranibizumab or bevacizumab alone. In rabbits, CPP+bevacizumab eye drop delivered 4.0±2.3 μg/retina at 24 hours significantly higher than controls ($p<0.05$). This increased over 3 days to 83.31±39.72 μg/retina and cleared from the retina over 7 days. Efficacy in disease models was determined in rodents using established models of neovascularization. Animals which had an anti-VEGF ivit and CPP+anti-VEGF eye drop had significantly lower ($p<0.05$) areas of neovascularization than eyes with no treatment, anti-VEGF eye drop, CPP eye drop and PBS eye drop all of which were not significantly different from the untreated eyes.
Conclusions
CPP can be used to deliver both ranibizumab and bevacizumab to the posterior segment of the eye in rabbit and pig eyes. The CPP delivered bevacizumab gave a 7 day clearance pattern in rabbits suggesting a weekly dosing regimen. The CPP delivered anti-VEGF showed efficacy in a disease model of neovascularization with no significant differences between intravitreally injected anti-VEGF and CPP topically delivered anti-VEGF.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.

Neovascular age-related macular degeneration is a leading cause of blindness. While the progression of the disease can be reduced by anti-VEGF therapeutics such as ranibizumab and bevacizumab, delivery of these into the back of the eye is a challenge. Currently the drugs are used successfully in clinic by injecting them into the eye. This causes distress to patients and can have side effects such as retinal tearing.

In this project we use the same drugs currently used in clinic but deliver them as eye drops instead of by injection. In our animal studies, the eye drop system we have developed gives the same outcome as the injected drug. We hope that this can remove the need for injections in patients and give them ownership of their own treatment programme.