A 3D PRINTED MESH-HYDROGEL DRUG-ELUTING DEVICE FOR REDUCING POST-SURGICAL COMPLICATIONS IN GLAUCOMA PATIENTS

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Background: Drainage device insertion or trabeculectomy surgery in late-stage glaucoma patients remains beset by post-operative inflammation and fibrosis. Current approaches rely on the administration of anti-metabolites such as Mitomycin C and an intensive follow-up of patient administered corticosteroid eye drops. These present their own issues, particularly adverse side-effects and poor patient compliance.

Therefore, we describe a modified hyaluronic acid (HyA) drug-device combination that aims to address post-surgical inflammation and remove patient compliance issues.

Methods: A composite device consisting of polycaprolactone (PCL) and hyaluronic acid (HyA)-proteoglycan hydrogels was fabricated using a multi-step process involving 3D printing, chemical crosslinking and freeze-drying. Hydrogels were assessed for percentage crosslinking, swelling speed, degradation and ease of insertion into cadaveric rabbit eyes. Following drug loading, prednisolone drug release over 6 months in PBS was assessed. Immediate *ex-vivo* efficacy was evaluated in a chick embryo model of angiogenesis at day 5. Further evaluation on drug efficacy and safety was undertaken using primary human conjunctival fibroblasts stimulated with Transforming Growth Factor beta (TGF-β).

Results: It was found that HyA hydrogels were capable of rapid swelling with full hydration in <30 min and stability up to 4 weeks minimum. Enzymatic degradation was also shown to be dose dependent and related to cross-linking efficacy. *In vitro* analysis using drug-free, HyA-proteoglycan gels in TGF-β stimulated conjunctival fibroblasts demonstrated a reduction to normal collagen levels at 24 hours.

Release of prednisolone from gel composites was found to exhibit a biphasic release with an initial burst release over 5 days and a more gradual release for a minimum of 12 weeks. Furthermore, drug release was found to be directly influenced by 3D printed dimensions, PCL type and the presence of the HyA hydrogel. Released drug was found to effectively inhibit angiogenesis up to 5 days in the chick embryo model.

Conclusions: This work demonstrates a strong proof of concept validation for a straightforward solution to a long running issue in glaucoma surgery. Future work now focuses on an in-depth pre-clinical study.