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# Development of targeted siRNA nanotherapeutics to prevent fibrosis in experimental glaucoma filtration surgery

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Footnotes

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## Abstract

**Purpose** : RNA interference is a promising therapeutic approach as it can be used to silence the expression of pathological genes in a wide range of diseases. We hypothesised that siRNA nanoparticles against the *MRTF-B* gene could be used as a targeted anti-fibrotic therapy in glaucoma filtration surgery.

**Methods** : We tested the effect of 15 liposome-peptide-siRNA nanoparticle formulations on *MRTF-B* gene silencing using real-time quantitative PCR and on cell viability in human conjunctival fibroblasts. Nanoparticle size, zeta potential and morphology were determined by dynamic light scattering, laser Doppler anemometry and transmission electron microscopy, respectively. We validated our results using a randomised, prospective, masked-observer study of 18 New Zealand white female rabbits undergoing glaucoma filtration surgery. The animals received intraoperative 0.2 mg/ml mitomycin-C (MMC) [N=6], or a postoperative subconjunctival injection of 25 µg MRTF-B nanoparticles [N=6] or control nanoparticles [N=6]. Bleb morphology was recorded over 30 days. Tissue sections on day 30 were immunohistochemically assessed. We analysed our results using Kaplan-Meier curve Log-rank test and Student's t-test.

**Results** : *In vitro*, targeted LYR (DOTMA/DOPE-peptide Y-siRNA) formulation was the most efficient (52.7% *MRTF-B* gene silencing) and non-cytotoxic, compared to the non-targeting peptide formulation (23.7% silencing). LYR nanoparticles were spherical particles of 108.3 ± 6.4 (SEM) nm, 56.2 ± 7.2 mV and 0.37 ± 0.01 polydispersity index. Anionic PEGylated formulations had no effect on the *MRTF-B* gene. *In vivo*, bleb survival was increased from 11.0 ± 0.6 (SEM) days for control nanoparticles to 22.0 ± 2.1 days for MRTF-B LYR nanoparticles ($p$=0.005) and 22.5 ± 1.3 days for MMC ($p$=0.001). MRTF-B LYR nanoparticles and MMC reduced conjunctival scarring compared to control nanoparticles using H&E, picrosirius red, Gomori's trichrome and alpha smooth muscle actin staining. MRTF-B LYR nanoparticles were also not toxic and silenced the *MRTF-B* gene by 29.6% ($p$=0.046) in rabbit conjunctival tissues.

**Conclusions** : Receptor-targeted liposome-peptide-siRNA nanoparticles represent a safe and efficient siRNA delivery system that could be used to prolong bleb survival and to prevent conjunctival fibrosis after glaucoma filtration surgery, by targeting the *MRTF-B* gene and potentially other gene targets associated with fibrosis.

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