The Development of Lubricated Drug-Eluting Composite Coatings for Endotracheal Tubes

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Statement of Purpose: Prolonged intubation, with large diameter endotracheal tubes (ETTs), puts adults at risk of long-term breathing, voice, and swallowing complications and results in acute laryngeal injury, including tracheal stenosis. In this study, we developed a novel composite coating based on electrospun poly caprolactone (PCL) fibers embedded in a four-arm poly ethylene glycol acrylate matrix (4APEGA) to transform the ETTs from functional, mechanical devices to a dual-purpose device capable of delivering therapeutics and minimizing damage to the local microenvironment. The composite (PCL-4APEGA) coating system is capable of sustained delivery of dexamethasone and therapeutic delivery of targeted *smad3* silencing siRNA to achieve immediate reduction in pro-fibrotic signaling in the upper airway and suppressing long-term sequelae of prolonged intubation.

Methods: To fabricate dexamethasone loaded polycaprolactone (PCL) fibers (at dexamethasone: PCL w/w ratios of 2.5, 5, and 10:100) were prepared using electrospinning. 4APEGA with varying molecular weight (5k, 10k, and 20k) was mixed with the photoinitiator and then, the 4APEGA hydrogels were cast on top of the electrospun fiber coated ETTs and polymerized for 5 minutes under UV (**Fig 1**). Various Polyethylenimine /nucleic acid ratios were prepared and the resulting polyplex aliquot was mixed with 4APEGA solution followed by UV polymerization for 5 minutes. Dexamethasone release (24 days) and siRNA release over 24 hours and their post release efficacy were measured.

Results: Coatings with good interfacial continuity and strength were observed (**Fig 1**) and constant drug release over the first 21 days was observed with greater release from smaller fiber diameters (**Fig 2**). Polyplex release was greater at higher 4APEGA matrix molecular weights **(Fig 3**). Targeted gene silencing was observed, with only downstream targets of *smad3* (i.e. *col1a1*) being downregulated (**Fig 4**). Increase in ETT surface lubrication and reduced surface stiffness due to the hydrogel-based composite coating maintained epithelial mucus production (**Fig 5**, **6**), while reducing epithelial adhesion, and epithelial layer abrasion.

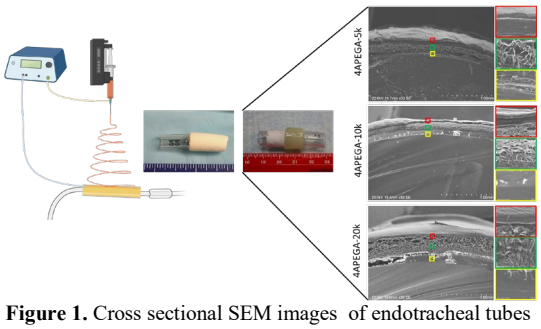

Figure 1. Cross sectional SEM images of endotracheal tubes (ETT) coated with PCL-4APEG composites of different MW

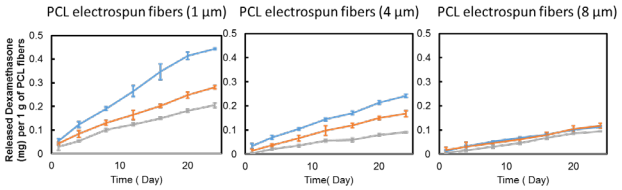

Figure 2. Dexamethasone release from PCL fibers of various diameters.

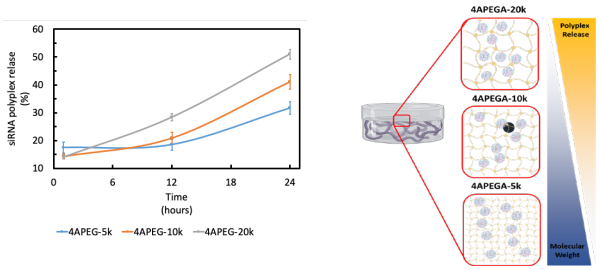

Figure 3. Release profile the loaded siRNA polyplex from different MW hydrogels.

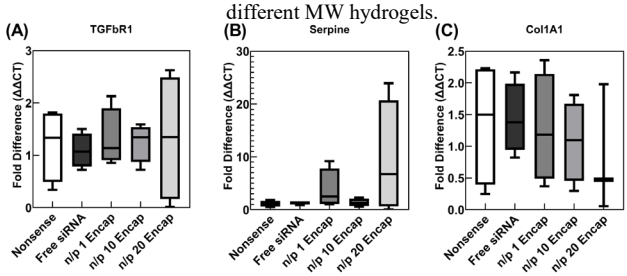

Figure 4. siRNA polyplex transfection and gene silencing efficacy.

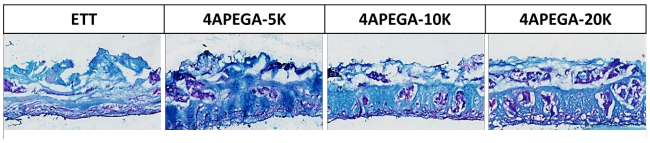

Figure 5. Histological Micrographs of the inner lining of trachea after simulated mucosal abrasive damage with various coated ETTs.

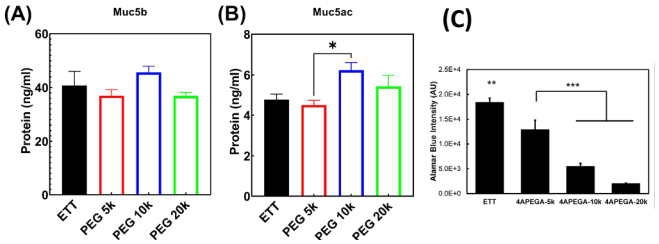

Figure 6. **(A,B)** Mucin production after tracheal mucosal abrasion **(C)** Epithelial Adhesion to 4APEGA composites vs bare ETTs.

Conclusions: The novel PCL-4APEGA coated endotracheal tubes are a promising biocompatible platform technology to minimize focal airway damage during intubation and modulate the inflammatory and fibrotic sequelae through multimodal, controlled, local drug delivery of corticosteroids and targeted siRNA.

Acknowledgements: This effort was supported in part by the Lutcher Brown Chair endowment, the UTSA graduate school, NSF (#1847103) and US Air Force 59th MDW.