Dexamethasone Eluting Polycaprolactone-Poly(lactic-co-glycolic) acid Stent for Treatment of Tracheal Restenosis

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Introduction: Tracheal stenosis is the narrowing of the trachea due to scar tissue formation or malformation of cartilage in the trachea. Long-term intubation, tracheostomy, or trauma are common causes for tracheal stenosis [1]. Tracheal stenosis poses a significant health risk to patients, with reported incidence of post intubation and post tracheostomy stenosis of 10% - 22%, of which 1% -2% result in severe stenosis [2]. When stenotic tissue is removed, there is a risk of recurrence or restenosis. Thus, endotracheal stents such as silicon-based or self-expanding metal stents (SEMS) have been used to counter tracheal restenosis. However, they suffer from several shortcomings including granulation tissue-based airway obstruction, migration, or fracture [3]. Excessive inflammatory reaction and fibrous tissue deposition play significant roles in restenosis. Therefore, mitigation of inflammation locally by eluting an inflammatory agent may be effective for stenosis treatment. We have developed a bioabsorbable polycaprolactone (PCL) based tracheal stent coated with poly (lactic-co-glycolic acid) microparticles (µPLGA) laden with dexamethasone (dex) to effectively manage inflammation and combat restenosis.

Materials and methods: *Stent Fabrication:* Solvent-cast, 180 µm thick PCL sheets were cut into 32 mm x 11 mm rectangles and an array of 0.6 mm diameter holes (0.5 mm spacing) was cut via laser cutter (VLS2.30DT, Universal Laser Systems, Scottsdale, AZ, USA). Stents were heated to 60°C around a 10 mm diameter mandrel to induce curvature (Fig. 1A). The resulting curviplanar stent was rolled, inserted in the trachea, and when released, the stent unfolded circumferentially to lodge within the lumen. PLGA microparticles were fabricated by oil-in-water (o/w) emulsion. The 'oil phase' was comprised of PLGA (10% w/v) in chloroform and dex (1.5% weight of polymer weight). The 'water phase' was PVA in deionized water (2% w/v). Solutions were cooled to 4°C, combined, and stirred (16 hrs, 4°C) to generate dex-µPLGA (Fig. 1B). To adhere the microparticles to the exterior surface of the stent (facing the tracheal wall), 0.125 g of microparticles were mixed with 1 mL of acetic acid-based resin containing PCL (10% w/v), applied over the stent surface, and dried. *Cell Assessment*: RAW 264.7 macrophages were seeded in 6-well plates and a 20 mm diameter PCL+dex-µPLGA-coated cutout was placed into a cell crown well insert. There were four treatment groups: untreated cells (LPS absent-negative control), LPS-activated cells (positive control), LPS-activated cells with dexamethasone directly added to the media, and LPS-activated cells with dex released from PCL-µPLGA. Cells were incubated with cutouts for 48 hours and stained with phalloidin to visualize the cell size increase in macrophages in response to inflammatory activation (Fig 2). *Mechanical Assessments*: Lateral stiffness of PCL-PLGA stents and segments of rabbit trachea were measured and compared. Pull-out force of the deployed stent from the trachea was measured at a rate of 1 mm/s.

Results:

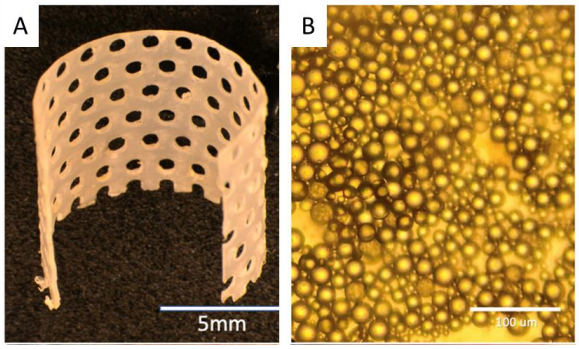

Figure 1. A) Curviplanar PCL stent B) Dexamethasone-PLGA microparticles

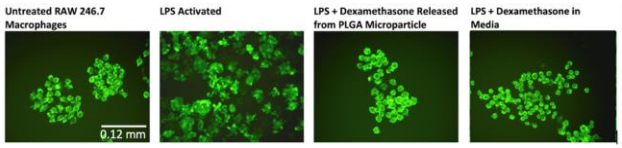

Figure 2. Cell spreading of RAW 264.7 macrophages.

LPS activation resulted in a 4-fold increase in the cellular area compared to inactivated cells. Dex treatment resulted in a 370% reduction ($p > 0.05$) in cell area compared to LPS-induced cells both when added to the medium directly and when released by PCL-µPLGA. Compressive stiffness of the stent was also measured and compared to that of a similarly-sized section of rabbit trachea. Compressive stiffness of the stent (0.156 ± 0.0230 N/mm) and rabbit trachea section (1.420 ± 0.1944 N/mm) were statistically different ($p < 0.05$). The force required to initiate stent pull-out was measured to be 0.425 ± 0.0682 N.

Conclusions: These *in vitro* results suggest the proposed stent concept may be able to deliver effective doses of dex to suppress macrophage response when deployed *in vivo*. Mechanical tests indicate the curved stent was able to lodge in the lumen of trachea securely. In support of this observation, stents with a similar design were deployed in rabbits *in vivo* and stents did not migrate. The stiffness of the stent is about 10% that of the trachea which may be beneficial by countering potential stress shielding based atrophy in the trachea. Overall, results indicate that the concept has feasibility for *in vivo* assessment that will be the next stage for this biomaterial platform.

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