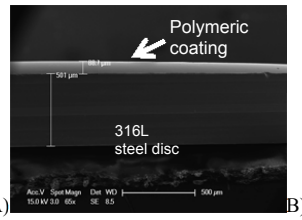
Design of a Drug Eluting Stent for treatment of pancreatic malignancy

Laura Indolfi [1], Matteo Ligorio[2], David Ting[2], Cristina R Ferrone[2], Jeffrey W Clark[2], Robert Langer [1,3], Elazer R. Edelman [1].
[1] Harvard-MIT Division of Health Science and Technology, Massachusetts Institute of Technology, Cambridge, MA, USA
[2] Massachusetts General Hospital (MGH), Department of Surgery and Cancer Center, Boston, MA. USA
[3] Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA

Statement of Purpose: Pancreatic ductal adenocarcinoma is a highly chemorefractory malignancy - in large part from impaired drug delivery caused by hypovascularity and significant desmoplastic stromal response. These factors cannot be overcome by systemic therapies because of dose limiting toxicities. However, there is evidence that modification of these drug delivery barriers can sensitize pancreatic primary tumor cells to standard doses of cytotoxic therapies. The aim of our work is to bypass these therapeutic obstacles by developing a chemotherapy-eluting pancreatobiliary stent that can locally deliver high levels of conventional chemotherapies for effective tumor cell cytotoxicity and minimal bystander toxicity. Drug-eluting stent technology has been well characterized in vascular biology and has successfully translated into routine clinical practice in cardiovascular disease. Application of this technology to the pancreatobiliary ductal system will require design of appropriate drug eluting stents for this system, characterization of malignant epithelial ductal structures, and pre-clinical testing of this device in animal models.

Methods: Poly(D,L-lactide-co-glycolide) (50:50) (PLGA) (Resomer®RG502) was dissolved in acetone at several concentrations (w/v). Solutions containing 250µg of Paclitaxel (Invitrogen) were coated on a AISI 316L stainless steel 6mm disc. The surface chemical characterization was carried out by analysis in dispersion of energy (EDAX, Oxford mod. INCA 200) using scanner electron microcopy (SEM, Leica 420). For release study a ratio 1:250 of fluorescent drug was added to the solution, the disc put in PBS and incubated at 37C. At selected time point aliquot of supernatant was analyzed and replaced by fresh media. Six newly established pancreatic adenocarcinoma cell lines (PDAC 1-6) were generated from metastatic ascites in patients enrolled in an IRB approved protocol at MGH. Cell lines were orthotopically injected in NOD/SCID/γc immunodeficient mice to identify the optimal xenograft tumor model system for testing the drug eluting polymer scaffold.

Results: The coating film, obtained by spin coating of reported solutions on the metallic surface, ensues optimal for the clinical purpose. The thickness of the film layer may be, particularly, modulated through an opportune selection of the polymer concentration. As an instance, homogeneous coating, with an uniform thickness spanning between 50 and 100µm could be achieved as shown in Figure 1A.



A)

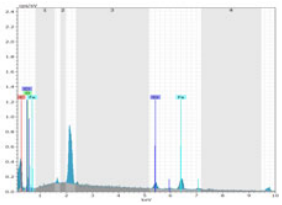

B)

Figure 1. A) Scanning electron microscopic photogram of PLGA-coated disc; B) EDS graph of atomic constituents.

Electron microscopy analysis showed an homogeneous, smooth, non porous PLGA layer coating the metallic surface; EDS characterization indicated the presence of polymeric constituents on steel surface (atomic%, C: 65.76%, O: 18.09%) (Figure 1B). All orthotopic pancreatic xenografts formed tumors in mice with varying histologies. Cell line PDAC-6 (Figure 2) developed the most desmoplastic response compared to other cell lines *in vivo*.

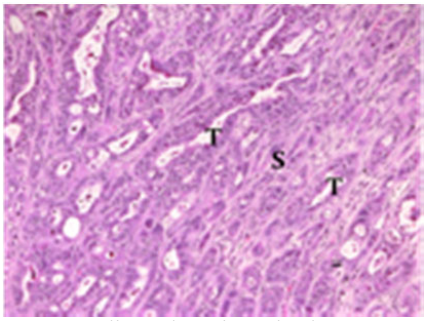


Figure 2. Hematoxylin and Eosin stained PDAC-6 orthotopic xenograft highlighting epithelial tumor cells (T) surround by desmoplastic stromal response (S)

Preliminary release studies, carried out with the higher polymeric concentration, show a delayed onset of the kinetics and a sustained ongoing release after ten days.

Conclusions: The present study shows the possibility to achieve polymeric coating on metallic stents and to optimize the interface properties. By changing processing conditions it is possible to modulate thickness of the film layer. The proposed system allows, besides, the possibility to release suitable drugs from the coating. Preliminary studies in this direction are in progress. Upon identification of the ideal controlled release formulation a cohort of mice with PDAC-6 xenografts will be evaluated for adjunctive treatment based on optimal tumor/normal tissue toxicity that may enhance local therapy delivery. These initial studies will provide the foundation for the development of viable local delivery platforms to treat pancreatic cancer.

Acknowledgment: The present study is supported by *The Bridge Project grant* (Dana Farber/Harvard Cancer Center and Koch Institute collaboration)