# Engineering drug-eluting coatings to design next generation devices for locally treat pancreatic cancer.

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**Aim:** Pancreatic ductal adenocarcinoma (PDAC) is a highly chemorefractory malignancy, due in part to impaired drug delivery caused by hypovascularity and significant desmoplastic stromal response. These factors cannot be overcome by systemic therapies because of dose limiting toxicities. The aim of our work is to bypass these therapeutic obstacles by developing a chemotherapy-eluting pancreatobiliary device that can locally deliver high levels of conventional chemotherapies for effective tumor cell cytotoxicity and minimal bystander toxicity.

**Methods:** Poly(D,L-lactide-co-glycolide) (50:50) (PLGA) was dissolved in ethanol at several concentrations (w/v) and solutions containing Paclitaxel (Invitrogen) were coated on AISI 316L stainless steel 6mm disc. The coating thickness characterization was carried out 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 points, aliquots of supernatant were analyzed and replaced by fresh media. We modeled drug retention in tumor tissue following systemic intravenous administration or local delivery of paclitaxel. Simulations using the finite element package COMSOL 3.5a were compared by contrasting the spatio-temporal dynamics of the apparent concentration of labeled drug in a confined tumor volume. The tissue retention of fluorescent drug and overall anti-tumoral effects of this new paclitaxel-eluting device (PED) were compared to systemic intravenous (IV) dosing of paclitaxel measuring the relative growth of two luciferase-transfected PDAC patient-derived cell lines orthotopically xenografted in NOD/SCID/gamma-c mice. Tumors were monitored by *in vivo* luciferase imaging and values recorded in relative light units (RLU). A multilevel mixed-effect model (two-way anova) was used to determine statistical significance.

**Results:** Coating thickness of PEDs may be modulated through an opportune selection of the polymer concentration optimized for the clinical application proposed. As an instance, homogeneous coating, with uniform thickness spanning between 50 and 100µm could be achieved. This result is critical given the tight relationship of PLGA degradation kinetics, and therefore the elution rate of paclitaxel, as a function of polymer thickness. Release studies, carried out with two different polymeric formulations, show the typical release kinetics from PLGA – a slow onset followed by sustained release for over a month (Figure 1A). Computational modeling predicted markedly improved drug distribution in PED treatment compared to I.V. dosing, with increased local retention (≤45 µM) extended over a prolonged period of time (Figure 1B).

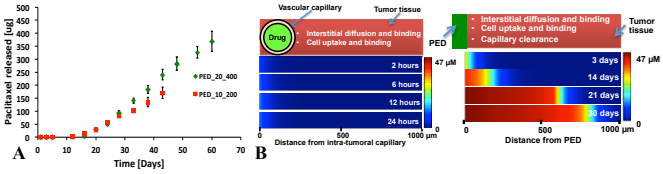


**Figure 1: A**. In-vitro release kinetics of two PED's formulation. **B.** In-silico prediction of drug tissue retention following systemic or local treatment.

All orthotopic pancreatic xenografts formed tumors in mice with varying histologies. Serial sections of fresh frozen tumor were imaged by quantitative confocal microscopy. Paclitaxel tissue retention in the PED group (Figure 2A) was strikingly higher compared to I.V. dosing (Figure 2B), with penetration depth extended over 400 µm from the PED, in accordance with the prediction by the computational model at 14 days, and forty times deeper than I.V. treatment. In vivo analysis of the tumor mass over time confirmed that local application of paclitaxel-releasing device ensures to be successful in slowing tumor progression of 12 times (Figure 2C).

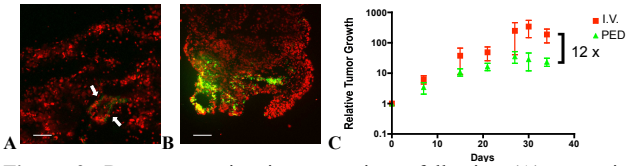


**Figure 2:** Drug penetration in tumor tissue following (**A**) systemic delivery and (**B**) local treatment. (**C**) Relative tumor growth of orthotopic xenograft treated with I.V. or PED.

**Conclusions:** The results constitute a proof-of-principle that effective engineering of coated devices can overcome multiple PDAC chemoresistance mechanisms by local delivery of conventional chemotherapeutic agent. This strategy opens the door for a new therapeutic paradigm of localized drug delivery to treat pancreatic cancer. By building an ad hoc mouse-sized paclitaxel-eluting device, we were able to show its safety and efficacy, and superiority to standard intravenous administration in a pancreatic orthotopic xenograft mouse model. Moreover, we developed a technique to computationally model the differences in drug delivery between I.V. and localized PED therapy, which provides a path to test a variety of novel agents for the platform device *in silico* before full development and utilization. Our approach addresses a major clinical problem and provides mechanistic insights to drive new devices to the clinic safely, effectively and rapidly.