intratumoral delivery CD40 agonist antibody

**Background** Pancreatic adenocarcinoma (PDAC) is associated with extremely poor prognosis and a 5-year survival rate of 10% and remains a lethal malignancy. Surgical resection and combination with chemoradiotherapy are the current standard-of-care options, may improve long-term survival in localized disease; however, the majority of patients are diagnosed at advanced stage. The incorporation of immunotherapy in the treatment algorithm convenes a new era for PDAC treatment.

**Methods** To sensitize the TME in response to immunotherapy, we developed an implantable intratumoral delivery device, Nanofluidic Drug-Eluting Seed (NDES) can be injected via a minimally invasive trocar system that feasible for the clinical setting. NDES has shown efficiently delivered immunotherapy to murine breast cancer model and reduced tumor burden and showed low liver inflammation compared to the intraperitoneal delivery approach in the previous study. Here, we utilized NDES for the sustained intratumoral delivery of the CD40 antibody. We compared the efficacy of NDES against intraperitoneal and intratumoral administration, which mimics conventional systemic treatment. Tumor growth was investigated for treatment efficacy. Local and systemic immune responses were assessed via flow cytometry.

**Results** NDES delivered CD40 significantly reduced tumor burden, some even achieved tumor clearance. Local NDES CD40 delivery approach showed a systemic increase of CD8+ and CD4+ T cells in the tumor-draining lymph node and spleen by flow cytometry. Furthermore, NDES CD40 treated mice showed an increase of CD8+ and CD4+ central memory T cells locally and systemically. We also investigated the combination with radiotherapy, no significant difference in tumor burden was observed when compared to single-agent CD40 antibody. The results indicated CD40 promotes TME response and improved treatment efficacy.

**Conclusions** These immunological responses demonstrate ‘cold’ to ‘hot’ tumor transformation, which translated to tumor burden reduction. Overall, NDES delivery strategy offers promise for enhancing therapeutic index and transforming the landscape of PDAC tumor therapy.

**REFERENCES**


one healthy control (figure 1). When TAA responses were pooled together, 83.3% of responders were patients (n=5) and 100% of non-responders were healthy controls (n=2).

Conclusions The presence of circulating T cells responding to CEA in all 5 patients, but also to MUC-1 and hTERT in 3 patients suggests that these TAAs may be good targets for immunotherapy in CRC. Our findings also provide a rationale to investigate the prognostic value of CEA-, MUC-1- and hTERT-specific T cells in the peripheral blood of CRC patients to consider vaccination with these antigens to boost or induce responses to control residual tumor post-surgery.

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Dot plot of one representative healthy control (#3) and one representative patient (#2) showing IFN-γ production by CD8 T cells in response to (A) MUC-1, hTERT, NY-ESO-1 and CEA stimulations or without any restimulation (negative control) and (B) positive controls (CEF and PMA/ionomycin). Percentages of IFN-γ+ CD8+ T cells are displayed in each plot. C. Frequency of MUC-1-, hTERT-, NY-ESO-1-, CEA- and pooled TAA-specific CD8+ T cell responses in patients (grey) and healthy controls (black). Fisher exact test, * p=0.0179; ns=not significant.

Development of an Implantable Artificial Lymph Node as a Therapeutic Cancer Vaccine

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Background Personalized therapeutic cancer vaccines aim to target and reprogram the host immune system to achieve cancer eradication in situ. Cancer vaccines deliver two main components: immunostimulants (S) and tumor antigens to reduce tumor burden with a robust T cell response; however, none have reached broad clinical success due to difficulty in vaccine administration, ex vivo cellular manipulation, low clinical efficacy and broad administrative barriers. While most efforts to date have focused on repeated bolus administrations, biomaterial-based vaccine strategies have led to promising clinical translation.

Methods In light of these challenges, we have designed a clinically-viable platform-based vaccine strategy, termed the NanoLymph, to provide spatiotemporal elution of immunostimulants and tumor antigens locally to recruit and activate antitumor immunity for cancer eradication. Here, we aim to target the release of granulocyte macrophage colony stimulating factor (GM-CSF) and TLR-7/8 agonist Resiquimod (R848) to promote recruitment and activation of dendritic cells (DCs), a key player in antitumor cytotoxicity.

Results We demonstrate the NanoLymph as a structurally stable and biocompatible immunostimulatory niche for durable DC-driven tumor specific T-cell mediated cytotoxicity. Additionally, we demonstrate the NanoLymph’s ability to recruit and activate immune cells of interest, activating antitumor immunity against model antigen. Thus, we have provided the framework necessary to develop a personalized therapeutic cancer vaccine for tumor-specific T-cell mediated responses necessary to generate immunological memory.

Conclusions Future studies will evaluate immunostimulant and tumor antigen biodistribution in vivo and further apply the NanoLymph in a tumor bearing model to effect antitumor cytotoxicity. Ultimately, we aim to develop a personalized platform applicable for every patient of any cancer type aimed at direct clinical translation.

Abstracts

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Background Immune checkpoint blockade (ICB) using anti-CTLA-4 and anti-PD-1/PD-L1 has revolutionized the treatment of advanced cancer. However, ICB cures only a fraction of patients, and biomarkers such as PD-L1 expression or CXCL11 have suboptimal sensitivity and specificity. Exposure-response (E-R) relationships have been observed in other therapeutic mAbs. There are many factors that can influence E-R, yet several studies have shown that trough levels of anti-PD-1/PD-L1 correlated with clinical outcomes. Little is known about the potential utility of anti-CTLA-4 levels as a predictive biomarker.

Methods Serum was obtained after doses 2 and 4 from patients with advanced melanoma who received ipilimumab alone (3 mg/kg every 3 weeks for 4 treatments) via an expanded access program. We have successfully established a proteomics assay to measure ipilimumab concentration in serum using a versatile LC-MS/MS-based nano-surface and molecular-orientation limited proteolysis (nSMOL) approach.

Results Serum samples from 38 patients were assessed for the ipilimumab trough levels by the nSMOL assay. The ipilimumab concentrations after dose 2 were ranged between 4.44 and 33.63 ug/ml (median:16.30, IQR: 11.41 – 20.87). We found that patients with lower serum trough levels of ipilimumab concentrations after dose 2 have a better clinical outcome.