FEATURED PUBLICATION

Nano-enabled Pancreas Cancer Immunotherapy Using Immunogenic Cell Death and Reversing Immunosuppression

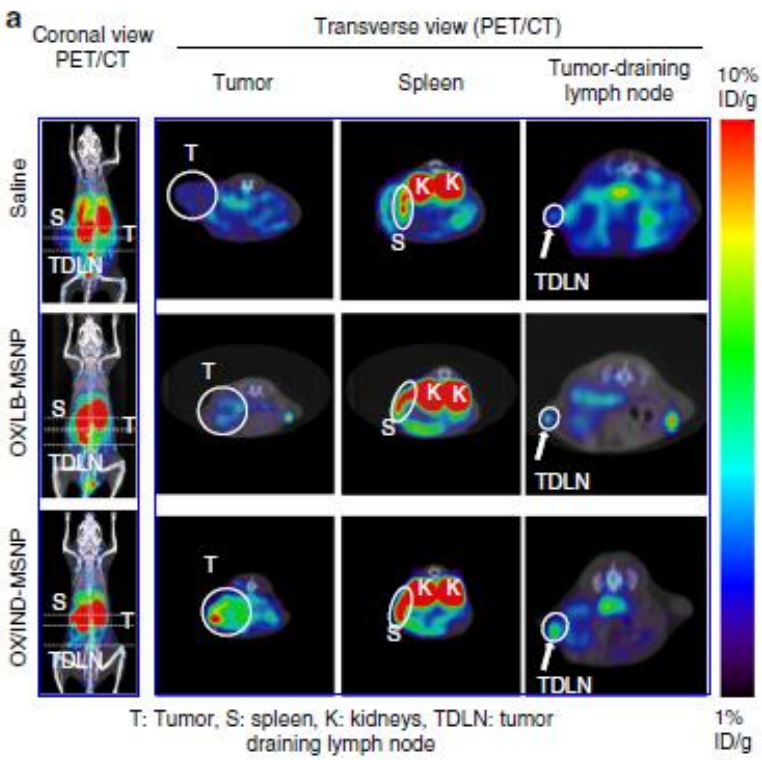
Lu, J and Nel, A. et al.
David Geffen School of Medicine, California NanoSystems Institute and Jonsson Comprehensive Cancer Center, University of California, Los Angeles, 90095 CA, USA.

Nanocarrier delivery of chemotherapy has resulted in some improved survival for patients with pancreatic ductal adenocarcinoma (PDAC). However, survival could potentially be increased with the additional engagement of the patient's immune system. This work demonstrated the use of a nano-enabled approach to achieve anti-PDAC immunity in syngeneic mice through the induction of immunogenic cell death (ICD) as well as interference of the immunosuppressive indoleamine 2,3-dioxygenase (IDO) pathway. This was accomplished by:

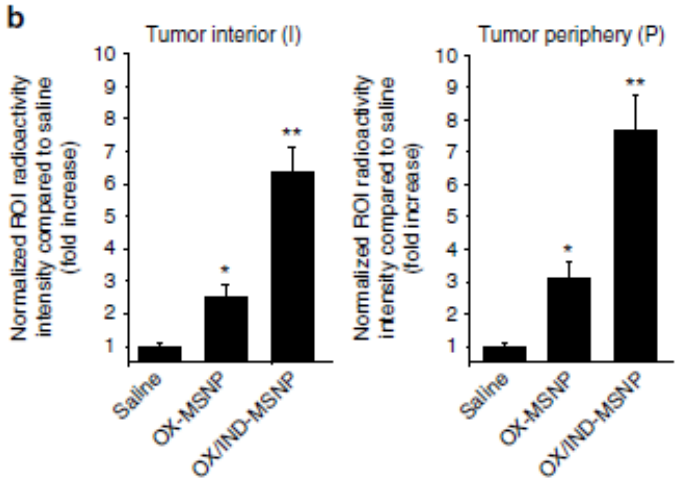
- Conjugating a phospholipid that allows prodrug self-assembly into nanovesicles or incorporation into a lipid bilayer that encapsulates mesoporous silica nanoparticles (MSNP) to the IDO inhibitor, indoximod (IND). The porous MSNP interior allows contemporaneous delivery of the ICD-inducing chemotherapeutic agent, oxaliplatin (OX).

- Immuno-PET imaging was used to demonstrate the induction of the systemic immune response by OX/IND-MSNP administration to animals carrying orthotopic KPC tumors. This non-invasive imaging technique enables the assessment of immunotherapy success before the treatment impact at the tumor site can be determined. To validate tumor-infiltration and systemic activation of CD8+ T cells, a ^{89}Zr-desferrioxamine-labeled anti-CD8 cys-diabody (^{89}Zr-malDFO-169 cDb) was used for monitoring.

- The nanovesicles plus free OX or OX/IND-MSNP were found to induce effective innate and adaptive anti-PDAC immunity when used in a vaccination approach, direct tumor injection or intravenous biodistribution to an orthotopic PDAC site.



Preclinical imaging using the G8 PET/CT system validated the capabilities of nano-enabled pancreas cancer immunotherapy by detecting the activation of CD8+ T cells, an early biomarker of therapeutic efficacy in turning on the innate immune system.



- In **figure (a)** animals with established orthotopic tumors (n = 3/group) were IV injected with saline, OX/LB-MSNP (5 mg/kg OX), and OX/ IND-MSNP (5 mg/kg OX and 50 mg/kg IND on days 10, 14, 18, and 22 post KPC cell implantation into the pancreas. At day 26, 100 µL doses containing 1.07–2.33 MBq (29–63 µCi, 2.3–5.3 µCi/µg) 89Zr radiolabeled cDb in saline was IV injected to the same animals. 20 h later, microPET and CT scans were acquired by a G8 PET/CT scanner (PerkinElmer, Waltham, MA). OX/IND-MSNP-treated mice showed significantly increased radioactivity in the tumor, spleen, and TDLN, corresponding to the induction and infiltration of CD8+ T cells.

- **Figure (b)** shows a 6.2- and 7.5-fold increase in the signal intensity in the tumor interior and periphery, respectively, during OX/IND-MSNP compared to saline treatment. The results are expressed as mean ± SEM. *$p < 0.05$; **$p < 0.01$, (ANOVA)

Lu et al. Nano-enabled pancreas cancer immunotherapy using immunogenic cell death and reversing immunosuppression. Nature Communications, 8:1811 (2017);

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