Imaging Growth And Anti-Cancer Activity in Orthotopic Patient Derived Tumors

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Background
Preclinical models that more closely mimic the clinical setting are being sought using patient-derived tumors (PDX). Utilization of PDX material in an orthotopic (OT) setting provides a preclinical model in a disease-relevant location. Here we describe the growth and treatment response data of OT pancreas, lung (NSCLC) and breast PDX tumors obtained using both conventional, and non-invasive imaging techniques.

Materials & Methods
PDX tumors were obtained via collaboration with Oncotest GmbH (Freiburg, Germany). SCID Beige mice (Harlan) were used with the appropriate material surgically implanted into the pancreas, directly injected into the left lung or directly injected into the mammary fat pad. All dosing was shown as dosed in the Figures. Imaging protocols applied are shown in the table below:

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<td>Agilent 7 Tesla MRI</td>
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Fig. 1 – Orthotopic PDX
Pancreatic tumor uptake of FMT probe

MRI Control D50 MRI Treated D50

Fig. 2 – Orthotopic Pancreas Analysis

Figure 2: Orthotopic pancreas tumor progression as followed by imaging. A) FMT imaging shows treatment with docetaxel significantly inhibits tumor progression. B) High correlation was seen between FMT and MRI which results in C) similar endpoint results with both technologies. D) Representative H&E image of tumor.

Fig. 3 – Orthotopic Lung (NSCLC)

Figure 3: A) Test of orthotopic lung PDX proves to be FDG avid. B) CT is used to quantify tumor burden longitudinally in the lung. C) Bevacizumab was not shown to have a significant effect on tumor burden. D) No effect on lifespan was observed with treatment.

Fig. 4 – Orthotopic Breast

Figure 4: A) Breast Orthotopic PDX has proven to be 18F-FDG PET avid. B) Strong response was observed with Cytoxan. Tumor volume doubling time -8 days. D) mediansurvival -75 days.

Results & Conclusions
PANCREAS: OT implantation of pancreatic PDX material resulted in robust disease establishment with a near 100% take rate. We utilized MRI and Fluorescence Molecular Tomography (FMT) imaging to non-invasively track tumor progression. We found that different FMT probes had different capabilities for detecting tumor burden (data not shown). Both MRI and FMT showed that this model was highly sensitive to treatment with docetaxel, where a significant number of mice had complete response and increased overall survival when compared to controls. NSCLC OT implantation showed near 100% take rates as determined by CT evaluation. By CT we found a minor bevacizumab response, as is consistent with this drug not being an optimal VEGFR inhibitor in the mouse. PET imaging was performed and demonstrated FDG avidity. However, no drug response was observed.

BREAST: Treatment with cyclophosphamide resulted in a robust response with approximately 1/5 of mice having no measurable tumors on Day 77. In this setting, FDG PET and FMT imaging were utilized to determine metabolic activity and avidity. FMT reflected the decrease in tumor burden with treatment. At the time of imaging, no difference in FDG SUV values was observed with treatment. In all models, disease latency and tumor volume doubling times were consistent with expectations based on known subcutaneous data. We have shown the establishment of OT PDX pancreas, lung and breast models. The use of multi-modality imaging non-invasively tracked tumor burden over time and provided useful readouts of disease progression and drug treatment response in these more disease-relevant models. Future work continues to investigate the metastatic potential of OT PDX material and non-invasive imaging to track this.

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