Elucidating the Relationship Between ADC Measures of Cellularity and [^{18}F]FLT-PET Indications of Cellular Proliferation in a Multimodal Imaging Study of Treatment Response

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Purpose: In developing tumors, cellular and molecular changes such as alterations in cellularity or proliferation may occur before morphological or other physical transformations are detectable by anatomical imaging techniques. These events are of considerable interest as potential imaging biomarkers of the response of tumors to treatments, but a better understanding of how these measures are related to tumor characteristics is still needed. We have begun to compare and correlate the relationships between imaging biomarkers from different modalities. Here we describe the relationship between the apparent diffusion coefficient (ADC) of tumors and the uptake of the positron emission tomography (PET) radiotracer 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT), an indicator of cellular proliferation.

Materials and Methods:

Animal Model Athymic nude mice bearing human colorectal cancer (DiFi) xenografts were imaged pre-treatment and one week post-treatment with an epidermal growth factor receptor (EGFR)-directed therapeutic monoclonal antibody (cetuximab; 40 mg/kg *ip* on days 1, 4).

Magnetic Resonance Imaging Mice were imaged on a Varian 4.7T Inova scanner using a spin echo diffusion-weighted sequence: diffusion weighting in all directions, TR_{eff} = 2s, TE = 28ms, b = 25, 309, 544, 771, 993 s/mm^2.

Positron Emission Tomography Mice were administered 150-250 μCi [^{18}F]FLT *via* a single retroorbital (*iv*) injection. Following a 40-minute uptake period, mice were imaged for 20 minutes on a Concorde Microsystems microPET Focus 220. Images were reconstructed using 3D ordered subset expectation maximization (OSEM3D) followed by maximum a posteriori (MAP) reconstruction.

Computed Tomography Following [^{18}F]FLT-PET, each mouse was transferred on the same bed to an Imtek MicroCAT II or a Bioscan NanoSPECT/CT system for anatomical CT data acquisition.

Data Analysis Coregistrations were performed by transforming all of the images into CT space: First the MR and PET images were manually initialized to match the CT orientation and were then registered to the CT images through optimization of the mutual information similarity metric.

Results: In a preliminary study of four mice, we observed a significant 25% decrease in overall tumor [^{18}F]FLT uptake (p=0.045) and a 34% increase in ADC values following cetuximab treatment in the entire population (p=0.081; Fig 1). One animal's tumor [^{18}F]FLT uptake remained approximately the same pre- and post-treatment, while in a different sample the tumor showed a decreased ADC post-treatment (Fig 2). To further elucidate this relationship, additional animals are being evaluated and voxel-by-voxel comparisons between modalities and histological sections are being performed using accurate co-registration (ex. in Fig 3).

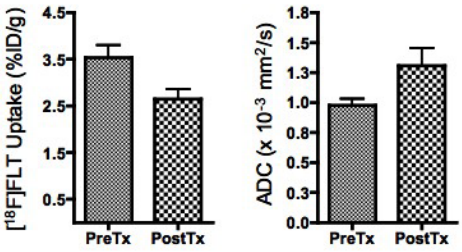

Fig 1. Post-treatment with cetuximab there is a significant 25% decrease in the overall tumor [^{18}F]FLT uptake and a 34% increase in ADC in a preliminary study of four DiFi tumor-bearing mice.

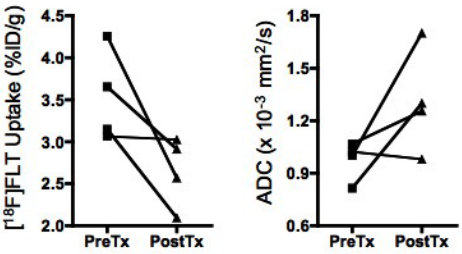

Fig 2. Analysis of individual mice reveals one tumor that did not demonstrate a change in [^{18}F]FLT uptake, while a separate tumor demonstrated a decreased ADC post-treatment.

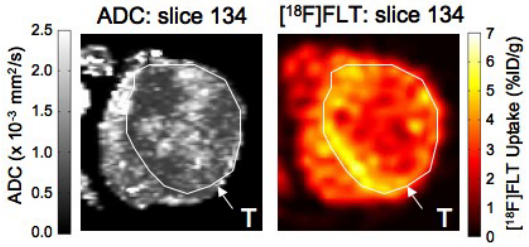

Fig 3. An example of a coregistered ADC map and [^{18}F]FLT image from the center slice of a tumor (T), which both demonstrate distinct regions of heterogeneity. These preliminary coregistration studies suggest that there may be an inverse correlation between [^{18}F]FLT uptake and ADC values, particularly in highly heterogeneous tumor regions. Ongoing work is aimed at unraveling and quantifying this relationship.

Discussion: Here, we demonstrate the ability to follow tumor progression with a multi-modal imaging approach to provide a more thorough profile of treatment response. In addition, we demonstrate preliminary coregistration studies to enable voxel-by-voxel correlation analyses for further elucidation of the relationship, correlation and/or disparity between the biological parameters described by ADC and [^{18}F]FLT uptake by PET. These studies will allow quantitative comparisons of the relative sensitivities of these different imaging biomarkers, and shed light on their interpretations.

References: [1] Paran Y *et al.* NMR Biomed 2004; 17:170. [2] Lee KC *et al.* Clin Cancer Res 2007; 13:443. [3] Yankeelov TE *et al.* MRI 2007; 25:1. [4] Leyton J *et al.* Cancer Res 2006; 66:7621; [5] Manning HC *et al.* Clin Cancer Res 2008; 14(2).

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