TITLE: Use of PET Imaging to Study Drug Pharmacokinetics and Pharmacodynamics


OBJECTIVE: Investigators are exploring methods to alter tumor vascularity and penetrance using treatment agents and evaluating changes using radiolabeled tracers with positron emission tomography (PET). Liposomes (LP) deliver drug to tumors due to enhanced permeability and retention (EPR). LP labeled with $^{64}$Cu for PET can image tumor localization while drug clearance, delivery and metabolic changes can be imaged with several new tracers. We have shown that Bevacizumab (bev), a VEGF targeted antibody, may modify LP delivery by altering tumor EPR. We have imaged changes in delivery and therapy in a mouse model of colorectal cancer treated with liposomal irinotecan (LP-I) ($^{64}$Cu-LP microPET). We are using the model of pancreatic cancer to see if use of hyaluronidase can improve penetrance and therapy with LP-I ($^{64}$Cu-LP microPET). We are imaging tumor changes in patients with non-small cell lung (NSCLC) treated with dexamethasone (Dex) using the marker of proliferation, fluorothymidine ($^{18}$F-FLT PET). Finally, we are developing studies in patients with neuroendocrine tumors to determine if we can measure teloristat inhibition of tryptophan hydroxylase (TPH) using $\alpha$-$^{11}$C-methyl-L-tryptophan ($^{11}$C-AMT-PET).

1. Utilize $^{64}$Cu-MM-Dx-929 to detect LP uptake following Bev in a mouse model of colorectal adenocarcinoma

HT-29 human colorectal adenocarcinoma tumors were grown subcutaneously in SCID mice. Empty LP MM-DX-929 were labeled with chelated $^{64}$CuCl$_2$ and imaged with microPET. All mice were scanned before and after the treatment period in which half of the mice received anti-vascular treatment with bev for one week. Scans were compared for changes in LP accumulation. Tumor growth following bev treatment, with or without LP-I, was assessed compared to untreated controls.

Results: PET scans of untreated mice showed increased uptake of $^{64}$Cu-MM-DX-929, with a mean change in tumor SUV$_{max}$ of 43.9%±6.6% (n=10) after 7 days. Conversely, images of treated mice showed that liposome delivery did not increase, with changes in SUV$_{max}$ of 7.6%±4.8% (n=12). Changes in tumor SUV$_{max}$ were significantly different between both groups (p=0.0003). Therapeutically, while bev monotherapy, LP-I monotherapy, and treatment with bev followed by LP-I all slowed HT-29 tumor growth compared to controls, combination provided no therapeutic benefit.

2. Hyaluronidase PEGH20 to enhance the efficacy liposomal irinotecan (LP-I) in a mouse model of pancreatic ductal adenocarcinoma

Hyaluronic acid (HA), a glycosaminoglycan is recognized to accumulate around cancer cells inhibiting drug penetrance. PEGH20 is designed to degrade HA to improve the access to tumor cells for chemotherapy. The primary objective is to determine using MicroPET imaging with $^{64}$Cu-MM-DX-929 liposomes if mice with patient derived xenografts treated with PEGH20 demonstrate improved tumor uptake of nanoparticles. We will also compare tumor growth 28 days after implantation in mice receiving LP-I after PEGH20 to those receiving LP-I alone.

3. Utilize $^{18}$F-FLT to detect Dex-mediated S-phase suppression in cell and xenograft models and patients with non-small cell lung cancer (NSCLC)

Pemetrexed (Pem)-based therapies are regularly used to treat NSCLC. Recent work has indicated that dexamethasone (Dex), given to prevent Pem toxicity, is able to protect a subset of NSCLC cells from Pem cytotoxicity by temporarily suppressing of the S-phase of the cell cycle. Therefore, Dex may block treatment efficacy in a subpopulation of patients, and could be contributing to the variable response to PEM. The purpose of this study was to use $^{18}$F-FLT-PET to monitor S-phase suppression by Dex in NSCLC cell models, xenografts, and patients with advanced cancer. We studied the uptake of FLT in vitro and in mice implanted with NSCLC cell lines with varying levels of glucocorticoid receptor alpha and measure the effect of Dex used for 24 hours. A pilot study was also done in 4 patients.

Results: Significant reductions in tracer uptake were observed after 24h Dex treatment in NSCLC cell lines and xenograft models expressing high levels of glucocorticoid receptor alpha. Mice implanted with high-GR A549 tumors demonstrated an average decrease of 50.7% in SUV$_{max}$ after Dex. Coincident
with Pem resistance is the ‘flare’ effect visualized by attenuation and associated with Pem activity. 2/4 patients imaged in a pilot study with $^{18}$F-FLT-PET following Dex treatment demonstrated reductions in tracer uptake from baseline, with variable response between individual tumor lesions. $^{18}$F-FLT-PET presents a useful method for the non-invasive monitoring of Dex-mediated S-phase suppression in NSCLC and could provide a method for the individualization of chemotherapy in patients receiving pemetrexed-based regimens.

4. Monitoring telotristat inhibition of tryptophan hydroxylase (TPH) in patients with neuroendocrine tumors using $\alpha$-[11C]methyl-L-tryptophan (AMT)-PET
The primary objective is to show that telotristat ethyl (Xermelo™, Lexicon Pharmaceuticals, The Woodlands, TX), a recently FDA-approved TPH inhibitor drug, will decrease tumoral AMT uptake and trapping as compared to values measured at baseline before the start of treatment. The use of telotristat ethyl may inhibit tumor proliferation and the image of AMT uptake may provide a predictive marker of this effect. If promising, PET imaging with AMT or an $^{18}$F-labeled analog (with a longer half-life) could be useful to monitor effectiveness of TPH inhibition in future multicenter studies and clinical trials.

CONCLUSIONS:
Ultimately, the imaging approaches used here can be used for the stratification of patient tumors to determine if treatment failure may be the result of poor drug delivery, as we are doing with labeled LP. Imaging can also be used to determine if methods can be developed to improve delivery. Early monitoring of metabolic treatment affects, as demonstrated using Dex in NSCLC, may be used to study variations in treatment response between patients and even within the lesions present in a single patient.