^{124}I-CLR1404 and ^{131}I-CLR1404: Broad Spectrum Diapeutic Agents for Cancer Cell-Targeted PET Imaging and Molecular Radiotherapy

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Abstract #5740

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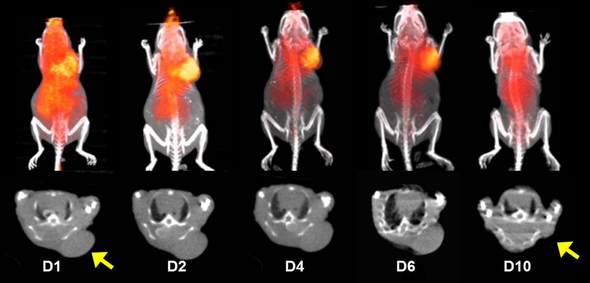
(related abstracts: #3495, #3831)

Background

Current approaches to cancer imaging and therapy are often limited by off-target uptake or lack of drug target expression in tumors. To address these shortcomings, structure-activity relationship studies were undertaken and identified a series of iodophenyl-containing phospholipid ether (PLE) analogs that selectively accumulate in a wide variety of cancer cells compared to normal cells/stem cells, *in vitro* and *in vivo*. These agents also have demonstrated selectivity for glioma stem cells relative to normal astrocytes and neuronal stem cells (abstract #3495). Isosteric iodine substitution in CLR1404 affords either a diagnostic/imaging agent (e.g. using ^{124}I for cancer-selective PET imaging) or a molecular radiotherapeutic agent (e.g. using ^{131}I for cancer-selective cytotoxicity, abstract #3831), both of which are in clinical development. We suggest the term "diapeutic" to describe such drugs which can be used in one form to identify and characterize patients who will benefit from a specific therapy and, in another form, to effect that therapy.

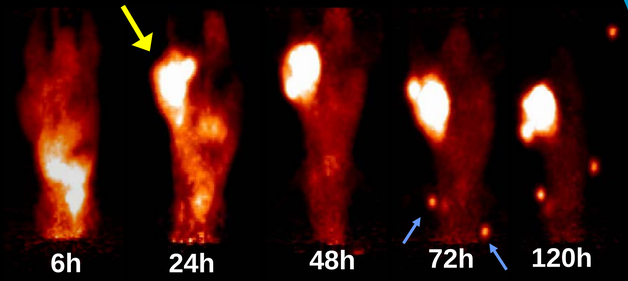
Here we describe the broad scope of tumor selectivity of ^{124}I-CLR1404 as a molecular PET imaging agent and demonstrate its ability to monitor the tumor response afforded by its radiotherapeutic (^{131}I-CLR1404) isostere.

Diapeutics: Anti-tumor Efficacy of ^{131}I-CLR1404 is Clearly Imaged by ^{124}I-CLR1404



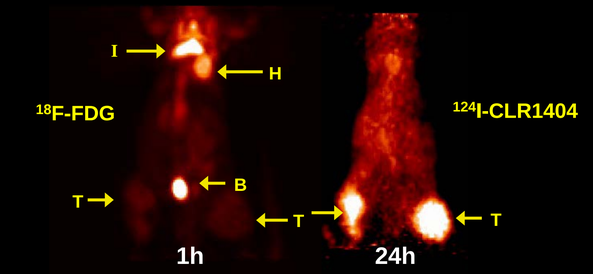
Whole body microPET/CT (top) and axial microCT images (lower) obtained from 1-10 days post injection of both ^{124}I-CLR1404 and ^{131}I-CLR1404 demonstrating significant regression of a colon tumor (LS180) xenograft (arrow) following a single injection of the radiotherapy agent. This study illustrates the diapeutic concept wherein isosteric substitution affords an agent with diagnostic and/or therapeutic properties.

Prolonged Tumor Retention of ^{124}I-CLR1404



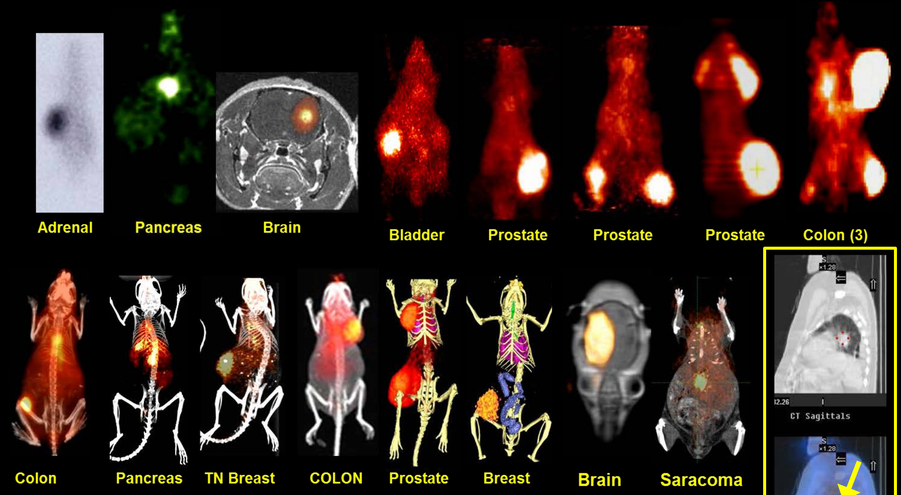
MicroPET scans following iv injection of ^{124}I-CLR1404 into prostate tumor-bearing (PC3) SCID mouse. Strong tumor uptake (yellow arrow) by 24h with continued tumor uptake and body clearance through 120h. Head down/tail up orientation with 3D-projection views. Fiducial markers (blue arrows).

^{124}I-CLR1404 is More Tumor-Specific than FDG



MicroPET comparison of FDG and CLR1404 in the same tumor- and inflammatory lesion-bearing mouse. CLR1404 displays superior tumor uptake and lack of inflammatory lesion uptake relative to FDG. (3D cine projection, I=carrageenan induced inflammatory lesion, H=heart, B=bladder, T=human PC3-prostate tumors, SCID mouse)

Near Universal Tumor Selectivity in Over 50 Tumor Models



^{124}I-CLR1404 displays excellent tumor-selective uptake in a wide variety of human subcutaneous or orthotopic xenograft, spontaneously induced, or transgenic *in vivo* tumor models. Representative nuclear and/or microPET/CT or MRI hybrid images acquired from 24-96h post injection (80-140 µCi) demonstrate excellent primary and metastatic tumor conspicuity in all models shown. Lower right image is a SPECT/CT image obtained in a human colorectal cancer patient with lung metastasis (arrow).

Conclusions

1. ^{124}I-CLR1404 selectively localizes in a very wide variety of both primary and metastatic malignant tumor types regardless of anatomic location.
2. Unlike FDG, CLR1404 avoids uptake in inflammatory and premalignant lesions.
3. CLR1404 undergoes prolonged and selective tumor cell retention which is a critical characteristic for radiotherapeutic efficacy.
4. The I-131/124 isosteric diapeutic concept was demonstrated in a human colon tumor xenograft model (LS180).

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