^{131}I-CLR1404 and CLR1404: Broad Spectrum, Cancer-Targeted Molecular Radio- and Chemotherapeutic Phospholipid Ether Analogs

Abstract #3831

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(related abstracts: #3495, #5740)

Background

The effectiveness of current approaches to cancer therapy is often limited by off-target toxicity or, if relatively selective, by 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 cancer cells/cancer stem cells compared to normal cells/stem cells, in vitro and in vivo. 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), 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 efficacy of CLR1404 as a molecular radiotherapeutic (^{131}I-CLR1404) and, at a 100-fold higher mass dose, as a chemotherapeutic.

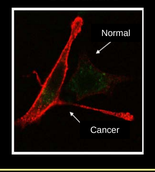
Lipid Raft-Based Cancer Targeting

Lipid Raft Staining

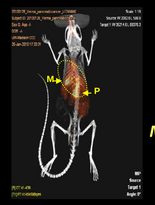
Normal *(hu fibroblast)*

Cancer *(hu NSCLC)*

Co-culture



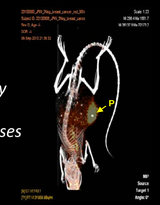
^{124}I-CLR1404 PET/CT Imaging in Human Tumor Xenografts *(48h)*



Pancreatic xenograft

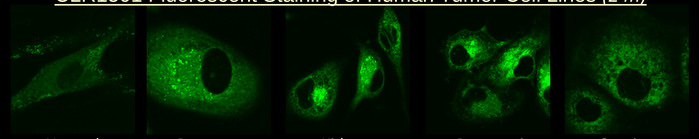
P *= primary tumor*

M *= metastases*



Triple-negative breast xenograft

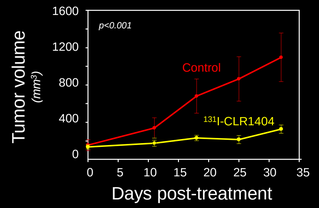
CLR1501 Fluorescent Staining of Human Tumor Cell Lines *(24h)*

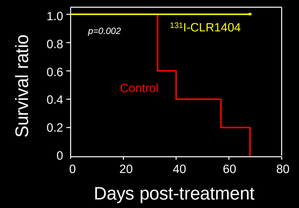


Normal Prostate Kidney Pancreatic Ovarian

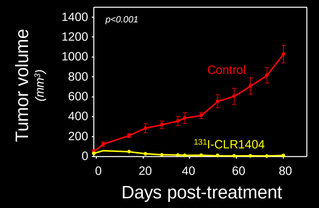
Single Dose ^{131}I-CLR1404 Suppresses Tumor Growth and Increases Survival in Human Tumor Xenograft Models

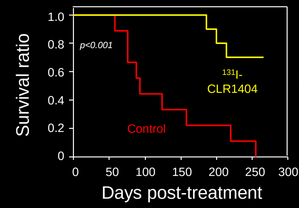
Ovarian Carcinoma ***(Ovcar-3; n=5):***





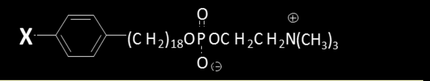
Triple negative mammary gland adenocarcinoma (*MDA-MB-231; n=9):*





^{131}I-CLR1404 (100 µCi, 3.8 µg/mouse) i.v. Day 0; Control = 3.8 µg CLR1404

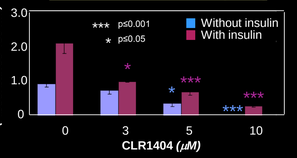
Similar results were obtained in renal (Caki-2), colorectal (HCT-116), prostate (PC-3) & pancreatic (Mia Paca-2) models. A single dose radiotoxicology study in normal rats did not find significant radiation toxicity below 5 mCi .



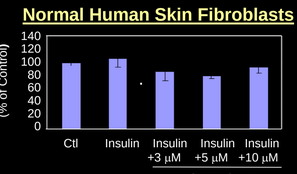
CLR1404	X = ^{127}I	*non-radioactive isostere; chemotherapeutic*
^{131}I-CLR1404	X = ^{131}I	*radioisostere; molecular radiotherapeutic*
^{124}I-CLR1404	X = ^{124}I	*radioisostere; PET imaging*
CLR1501	X=	*fluorescent analog*

CLR1404 Inhibits Akt and Proliferation in Cancer Cells

Prostate Carcinoma ***(PC-3)***



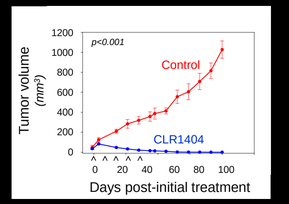
Normal Human Skin Fibroblasts

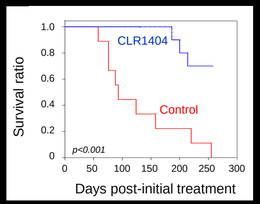


Cell Line	IC50 (µM; 24 hr)
Normal human fibroblast	*51.4*
Prostate *(PC-3)*	**3.2**
Ovarian *(Ovcar-3)*	**3.5**
Triple-negative breast *(MDA-MB-231 and MDA-MB-468)*	**4.3, 2.0**
Pancreatic *(Panc-01)*	**2.7**
NSCLC *(A549)*	**4.8**

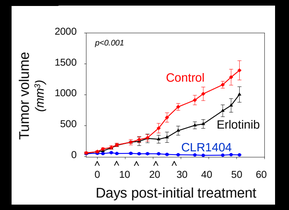
CLR1404 Suppresses Tumor Growth and Increases Survival in Human Tumor Xenograft Models

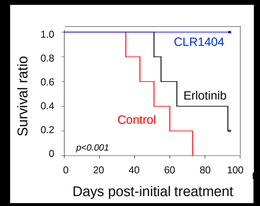
Triple negative mammary gland adenocarcinoma (*MDA-MB-231; n=8):*





Non-small cell lung cancer ***(A549; n=5):***





CLR1404 dosed weekly x 5 wks, i.v. injection , 380 µg/mouse indicated by ∧ ; Control = saline; Erlotinib dose = 12.5 mg/kg daily x 25 days

CONCLUSIONS

- ^{131}I-CLR1404 and CLR1404 each combine wide-ranging, cancer cell-selective targeting with cytotoxicity mechanisms known be broadly effective (intracellular radiation or Akt inhibition, respectively).
- Both agents have the potential to provide effective, well-tolerated therapy across numerous cancer types.