PET Imaging of Cancer Biomarkers

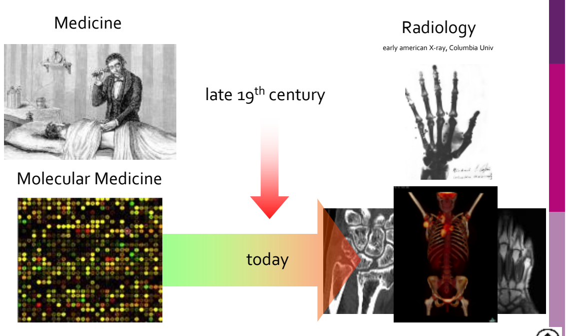
Professor Jason S. Lewis, PhD
Emily Tow Jackson Chair in Oncology
Memorial Sloan Kettering Cancer Center

Disclosure

No relevant financial relationships with commercial interests.

Jason S. Lewis, Ph.D.
Memorial Sloan Kettering Cancer Center

Evolution of Radiology



Radiosynthesis of ^{11}C compounds ($T_{1/2}$ = 20.4 min)

?

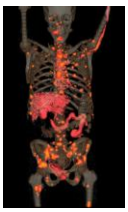
~1975 - ^{11}C-glucose was prepared by photosynthesis using Swiss chard leaves. Mashed up, extracted and a "green solution" injected into humans

2012 - ^{11}C-glucose is prepared by a "black box" automated versatile synthesizer producing drugs ready for human use

Targeted Imaging – Frontiers of Diagnosis

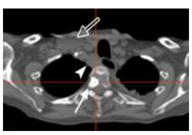
^{99}Tc – Bone Scan

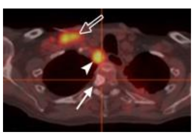
^{18}F-FDG PET/CT
Glycolysis



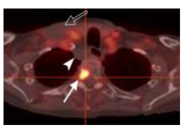
^{18}F-FDHT PET/CT
Androgen Receptor

Prostate Cancer: Revealing Heterogeneous Biology of Tumor Metastasis





^{18}F-FDG PET/CT



^{18}F-FDHT PET/CT

S. Larson, J. Fox, M. Morris et al.,

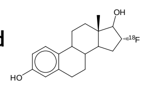
^{18}F-FDHT PET/CT: Predictive and Targeted Response Biomarker

^{18}F-FDHT PET/CT
Baseline

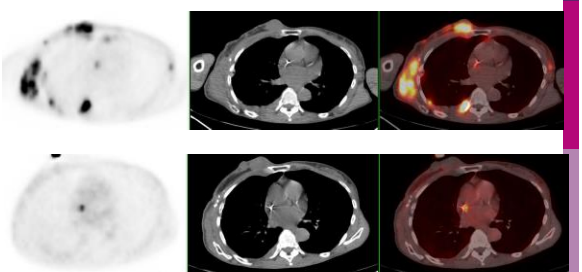
^{18}F-FDHT PET/CT
4 wks after MDV3100

Hricak, Radiology 2010

^{18}F-FES PET/CT: Predictive and Targeted Response Biomarker ER+ breast cancer patients?



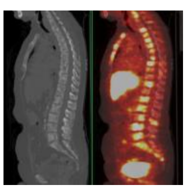
^{18}F-FES
Imaging of Estrogen Receptors

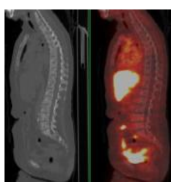


Pre-treatment

Post-treatment

Confirmed full target occupancy ~20 hours post dose





Courtesy of Drs. Dickler, Ulaner et al.,

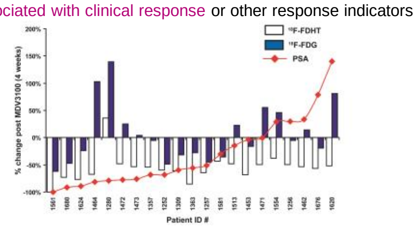
^{18}F-FDHT PET/CT: Predictive and Targeted Response Biomarker

^{18}F-FDHT PET/CT
Baseline

^{18}F-FDHT PET/CT
4 wks after MDV3100

Rationale for Developing a Biomarker of AR Pathway Activity

Changes in FDHT binding post MDV3100 are not uniformly associated with clinical response or other response indicators

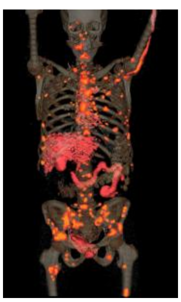


FDHT is a radioligand for AR that measures receptor occupancy by PET

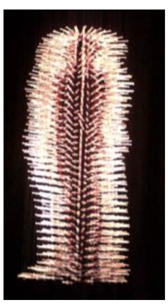
Each bar represents % change in FDHT uptake post MDV3100 for one pt

Scher, Morris, Fox, Larson et al.,

Intra/Inter Tumoral Heterogeneity - Challenge to Precision Medicine: Can we/should we biopsy each and every lesion ?



^{18}F-FDHT PET/CT



Grace Cathedral , San Francisco

Courtesy of H. Hricak

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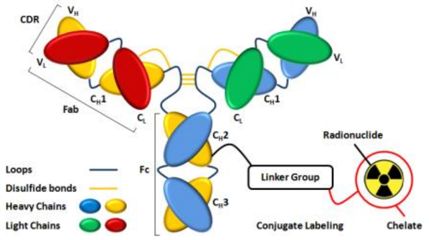
Radiopharmaceuticals

- Agents
  - Small molecules
  - Peptides
  - Monoclonal antibodies



Radiopharmaceutical	Imaging Target	Cancer Site	Human studies
Small Molecules (Imaging)			
[^{18}F]-FLT	tumor cell proliferation	Lymphoma, prostate, H&N, NSCLC	MSKCC IND
[^{18}F]-FES	estrogen receptor status	Breast	MSKCC IND
[^{18}F]-FDHT	androgen receptor	Prostate	MSKCC IND
[^{18}F]-FMISO	tumor oxygenation	Head & Neck, Rectal	MSKCC IND
[^{18}F]-FACBC	amino acid metabolism	Breast, Prostate, Brain	RDRC/ GEMS IND
[^{18}F]-FIAU	gene expression	Prostate	MSKCC IND
[^{18}F]-ML10	imaging apoptosis	Brain, NSCLC, H&N,	Non-MSKCC IND
[^{18}F]-dasatinib	tyrosine kinases	Prostate, Breast	MSKCC IND
[^{18}F]-glutamine	tumor metabolism	All solid malignancies	MSKCC IND
[^{64}Cu]-ATSM	tumor oxygenation	Uterine Cervix, Rectal	ACRIN
[^{124}I]-IAZGP	tumor oxygenation	Rectal	MSKCC IND
[^{124}I]-FIAU	gene expression	Prostate	MSKCC IND
Na-[^{124}I]	Na Iodide Symporter	Thyroid	MSKCC IND
[^{124}I]-PUH71	HSP-90	All solid malignancies and lymphoma	MSKCC IND
Antibodies and Fragments (Imaging)			
[^{68}Ga]- Her2 F(ab')	HER2	Breast	MSKCC IND
^{64}Cu-DOTA-trastuzumab	HER2	Breast	MSKCC IND
[^{124}I]-A33	A33 antigen	Colon	MSKCC IND
[^{124}I]-3F8	disialoganglioside GD2	Neuroblastoma (pediatrics)	MSKCC IND
[^{124}I]-8H9	8H9 antigen	Multiple tumors e.g. Leptomeninges (pediatrics)	MSKCC IND
[^{124}I]-G250	CA9 antigen	Renal	MSKCC IND
[^{89}Zr]-DFO-huJ591	PSMA	Prostate	MSKCC IND
[^{89}Zr]-Trastuzumab	HER2	Breast	MSKCC IND
[^{89}Zr]-DFO-MSTP2109A	PSMA	Prostate	MSKCC IND
^{89}Zr-Df-IAB2M	PSMA	Prostate	ImaginAb/MSKCC IND
^{111}In-DOTA-cG250	CA9 antigen	Renal	LICR IND
Antibodies and Fragments (Therapy)			
^{90}Y-DOTA-cG250	CA9 antigen	Renal	LICR IND
^{131}I-8H9	8H9 antigen	Multiple tumors e.g. Leptomeninges (pediatrics)	MSKCC IND
^{131}I-3F8	disialoganglioside GD2	Neuroblastoma (pediatrics)	MSKCC IND
^{225}Ac-lintuzumab	Anti-CD33	Acute Myeloid Leukemia	MSKCC IND
Nanoparticles (Imaging)			
[^{124}I]-Cdot nanoparticles	$\alpha v\beta 3$	Melanoma	MSKCC IND

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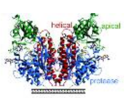
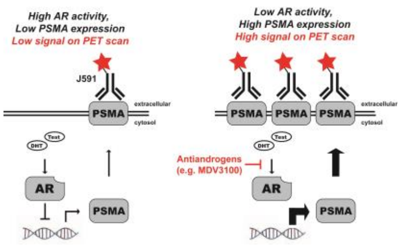
Prostate Specific Membrane Antigen

- Folate hydrolase (FOLH1); 100 kDa
- Type 2 transmembrane glycoprotein, 750 amino acids
- Present in salivary glands and small intestines
- Prostate cancer and non-prostatic solid tumor neovasculature (i.e. bladder, pancreas, lung, kidney)
- FDA-approved ^{111}In-7E11 (intracellular epitope, low sensitivity for viable tumor sites)



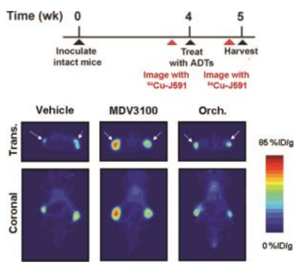
Davis M.I. *et al.* PNAS **2005**;*102*:5981-5986
Haffner, M.C. *Modern Pathology* (2012) **25**, 1079–1085

Evaluating J591 as a Biomarker of Response to AR Pathway Directed Inhibitors in PCa



Evans, MJ et al PNAS (2011) 108, 23:9578-82

Pharmacologically Triggered Elevations in PSMA Expression can be Measured by PET with J591

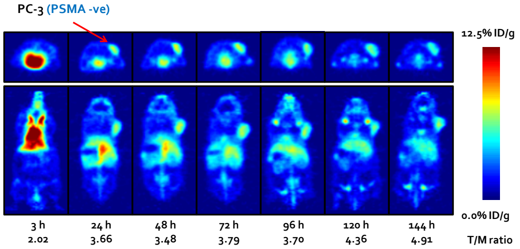


The white arrows indicates the positions of the LNCaP-AR tumors

^{89}Zr-DFO-J591 for ImmunoPET

PET imaging using a PSMA -ve control

PC-3 (PSMA -ve)



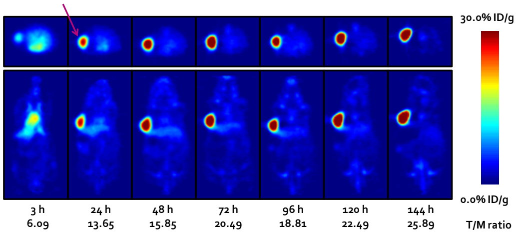
- ImmunoPET images recorded in a male athymic, *nu/nu* mouse with sub-cutaneous PC-3 tumors (70 – 90 mm^3)

Holland *et al.* JNM, 51(8):1293-300, **2010**.

^{89}Zr-DFO-J591 for ImmunoPET

PET imaging using a PSMA +ve tumors

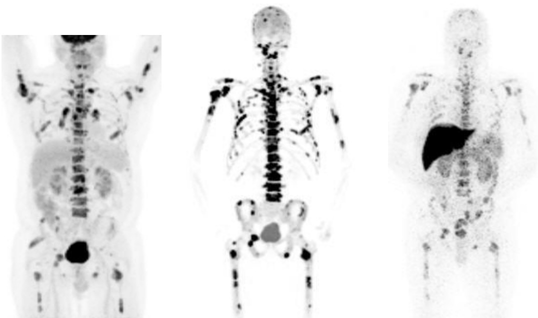
LNCaP (PSMA +ve)



- ImmunoPET images recorded in a male athymic, *nu/nu* mouse with sub-cutaneous LNCaP tumors (50 – 250 mm^3)

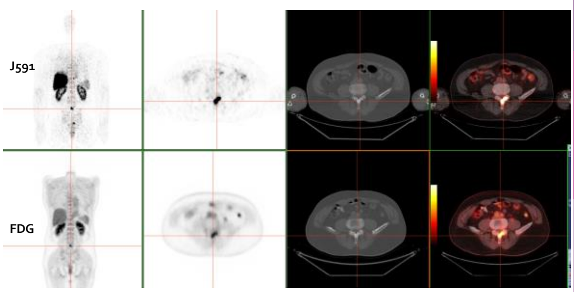
Holland *et al.* JNM, 51(8):1293-300, **2010**.

PET Imaging of Prostate Cancer



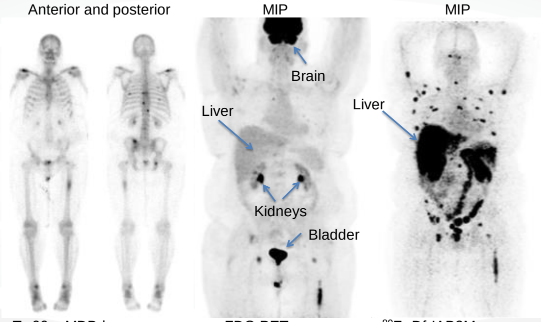
FDG -1d | [F-18] NaF -4d | Zr-89 DFO- J591

Zr-89 J591 @ 7 days pi
Castrate Resistant Prostate Cancer



Coronal WB | Transaxial WB | Transaxial CT | Transaxial Fused

Typical Result (Same Patient)



ImaginAb

Confidential 22

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Imaging Androgen Receptor Signaling with a Radiotracer Targeting Free Prostate Specific Antigen

David Ulmert, Michael J. Evans, Jason P. Holland, Samuel L. Rice, John Wongvipat, Kim Pettersson, Per-Anders Abrahamsson, Peter T. Scardino, Steven M. Larson, Hans Lilja, Jason S. Lewis, and Charles L. Sawyers

Memorial Sloan-Kettering Cancer Center
Howard Hughes Medical Institute
Lund University, Skåne University Hospital, Sweden.
University of Turku, Finland.

Ulmert, D and Evans, MJ et al (2012) Cancer Disc. 2(4): 320-327

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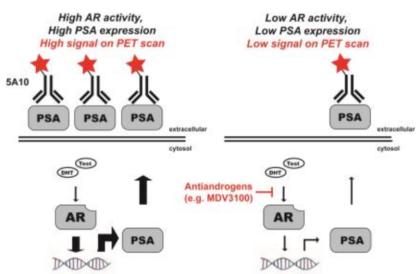
Evaluating 5A10 as a Biomarker of Response to AR Pathway Directed Inhibitors in PCa



Ulmert, D and Evans, MJ et al (2012) Cancer Disc. 2(4): 320-327

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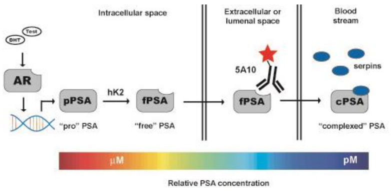
Rationale for the Development of ^{89}Zr-5A10



Our central hypothesis is that targeting a form of PSA more closely related to AR activity may enhance the diagnostic value of PSA expression changes

Ulmert, D and Evans, MJ et al (2012) Cancer Disc. 2(4): 320-327

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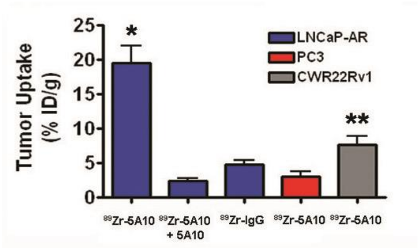
Evaluating 5A10 as a Biomarker of Response to AR Pathway Directed Inhibitors in PCa



- Intact male mice bearing the indicated tumor were treated with ^{89}Zr-5A10
- Tumors were analyzed ex vivo 24 h post injection of radiotracer
- *P<0.01; **P<0.05

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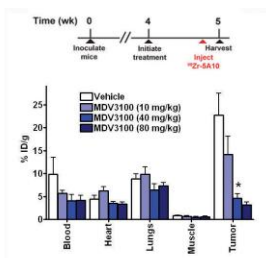
^{89}Zr-5A10 Quantitatively Measures AR Inhibition by an Antiandrogen in PCa xenografts



- Castrate male mice with LNCaP-AR tumors were treated for 7 d with MDV3100
- Tumors were harvested 24 h post injection of ^{89}Zr-5A10

*P<0.01 compared to vehicle

Ulmert, D and Evans, MJ et al (2012) Cancer Disc. 2(4): 320-327

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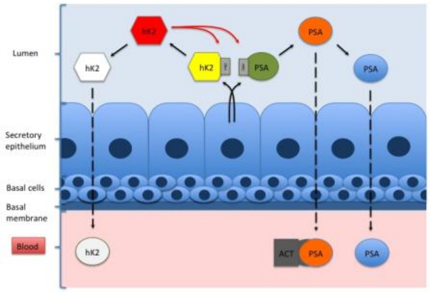
hK2 is an AR-Governed Kallikrein that is Abundantly Expressed in Healthy and Malignantly Transformed Prostatic Tissues



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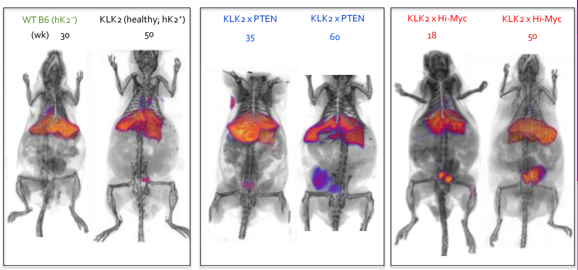
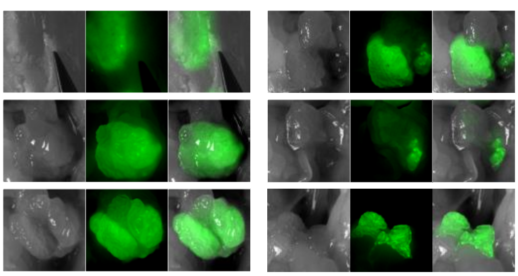
Can ^{89}Zr-11B6 localize and demarcate normal and cancerous prostatic tissue in GEM models?



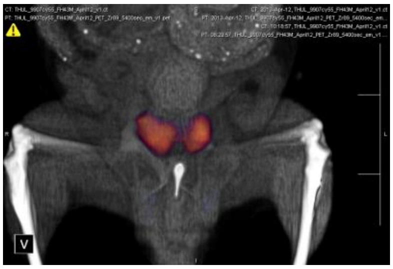
David Ulmert, Daniel Thorek *et al.*,

Memorial Sloan Kettering Cancer Center.

Cy5.5-11B6 Fluorescence Guided Surgery



David Ulmert, Daniel Thorek *et al.*,



Applying PET to Broaden the Diagnostic Utility of the Clinically Validated CA19.9 Serum Biomarker for Oncology

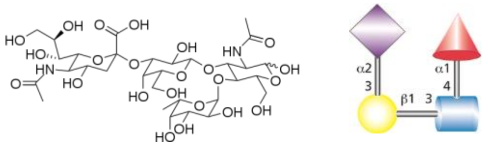
Nerissa Therese Viola-Villegas, Samuel L. Rice, Sean Carlin, Xiaohong Wu, Michael J. Evans, Kuntal Sevak, Marija Drobnjak, Govind Ragupathi, Ritsuko Sawada, Wolfgang W. Scholz, Philip O. Livingston, Jason S. Lewis

Memorial Sloan-Kettering Cancer Center
Mabvax Therapeutics, San Diego, California

Villegas et al., J Nucl Med 2013 54:1876-1882

What is CA19.9?

- Supports selectin-dependent adhesion
- Carbohydrate antigen 19.9 (aka: sialyl Lewis-a)
  - Up to 200 copies/cell
  - Attached to as many as 50 proteins
- Elevated in several types of cancer, including PDAC (~90%)

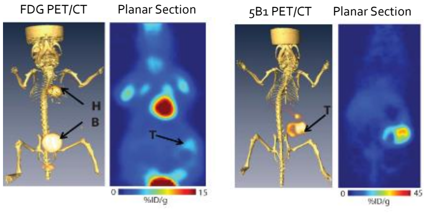


^{89}Zr-labeled Fully Human 5B1 Antibody Targeting SLe^a (CA19.9) Antigen

- SLe^a or CA19.9
  - serum tumor marker
  - present in pancreas, lung and colorectal lesions
  - aids in metastasis through cell adhesion
- Zr-89 5B1
  - Immunoreactivity: ~ 84 %
  - Specific activity: 12 mCi/mg
  - RCY: > 80 %; RCP: > 99 %
- Tumor models:
  1. DMS79 small lung cancer
  2. Colo205-luc colorectal cancer
  3. BxPC3 pancreas cancer

Villegas et al., J Nucl Med 2013 54:1876-1882

^{18}F-FDG vs. ^{89}Zr-5B1 PET



^{89}Zr-5B1 shows better specificity and tumor localization compared to ^{18}F-FDG.

Villegas et al., J Nucl Med 2013 54:1876-1882

Ex vivo CA19.9 Serum Values

Tumor type	Animal #	Tumor volume, mm³	CA19.9, U/ml
Colo205-luc	M1	269.5	3227
Colorectal Cancer	M2	257.3	2957
	M3	281.3	1318
BxPC3	M1	232.38	N.D.*
Pancreatic	M2	320.00	N.D.
Cancer	M3	220.50	N.D.
DMS79	M1	288.0	N.D.
Small Cell Lung	M2	245.0	N.D.
Cancer	M3	232.4	N.D.
Control	M1	–	3
No tumor	M2	–	3
	M3	–	3

* Not detected.

^{89}Zr-5B1 can detect CA19.9 at the tumor site even when the antigen is undetectable in serum.

Villegas et al., J Nucl Med 2013 54:1876-1882

Issues with PDAC xenograft models

- Does not accurately mimic tumor microenvironment
  - PDAC is highly stromal and has low vascular density
    - One of the reasons for poor drug (PET agent?) delivery
  - BxPC3 may not be from primary pancreas tumor
    - Lack of K-ras mutation = almost certainly not
  - Not located in or near pancreas
    - Liver uptake cause for concern with mAB PET agents

New cell line and methods for CA19.9 imaging

- CA19.9 is a human antigen not made naturally by mice
  - Mice lack the enzyme necessary for CA19.9 production
- Collaborating with Dr. David Tuveson (CSHL)
  - Development of mouse model expressing CA19.9
  - First step: develop mouse cell line with CA19.9
    - Dr. Dannielle Engle (Tuveson Lab)
    - Based on KPC mouse
  - Second step: imaging with novel cell line as proof of concept
    - 2.1: xenograft
    - 2.2: orthotopic pancreas model

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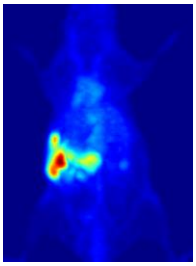
Imaging PDAC (mouse CA19.9 cell line)



MIP -- 24h P.I.
Orthotopic Pancreas Model (14 days)

PET/CT of the same mouse

Jake Houghton PhD with Tuveson Lab (CSHL)

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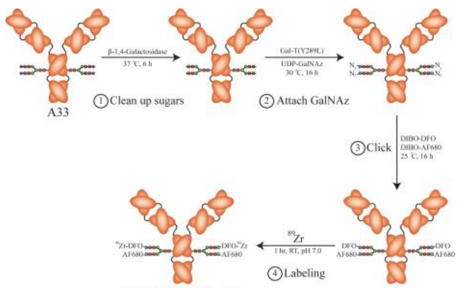
Site-Specific Labeling of Antibodies Multi-Modality Construction?



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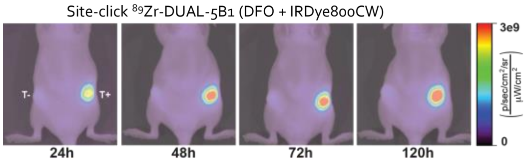
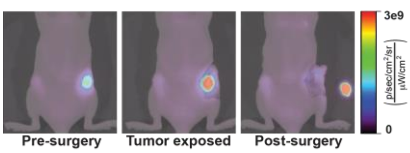
Imaging PDAC – bilateral SubQ nude

Site-click ^{89}Zr-DUAL-5B1 (DFO + IRDye800CW)

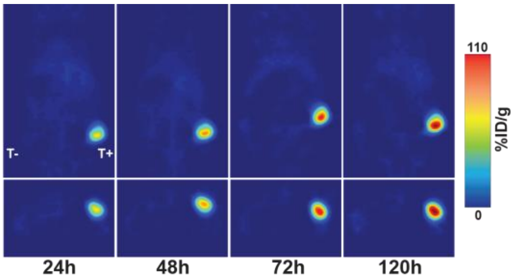




Fluorescence Images (ex. 750, em. 800)
BxPC3 -- Right Flank
MiaPaCa2 -- Left Flank

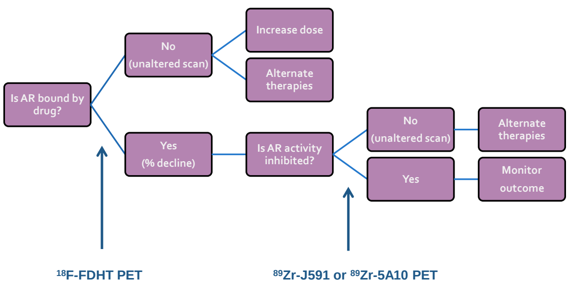
Imaging PDAC – bilateral SubQ nude

Site-click ^{89}Zr-dual-5B1

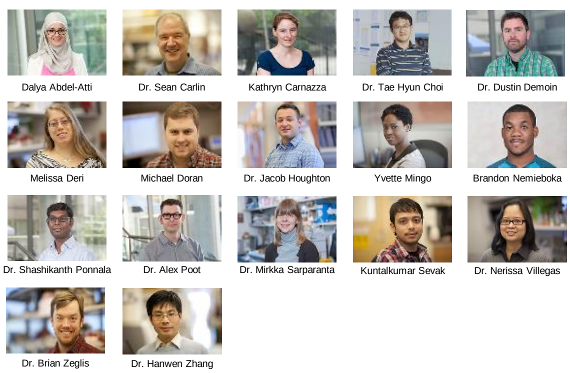


BxPC3 -- Right Flank
MiaPaCa2 -- Left Flank

How Hard are We Hitting the Target?



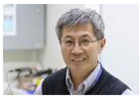
Current Lewis Lab



MSKCC Radiochemistry & Molecular Imaging Probe Core


Dr. Serge Lyashchenko


Mike Trapani


Howard Sheh


Calvin Lom


Ariel Brown


Eva Burnazi


Sam Frackowiak


Jing Qiao


Sherron Hicks


Ryan Kerslake


Lily Wu

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Lewis Group Alumni

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A bottle of wine contains more philosophy than all the books in the world
- Louis Pasteur