Imaging for Target Engagement in Oncology

Peter Choyke, MD

Molecular Imaging Program, NCI

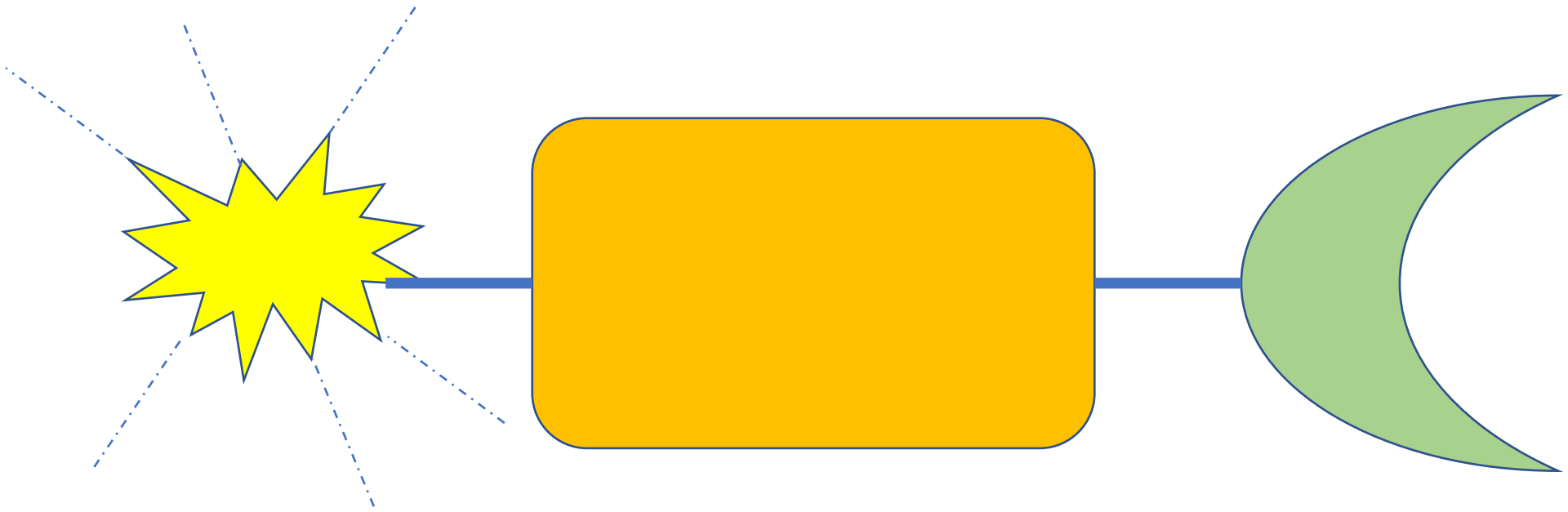
Disclosures (None relevant to lecture)

- Patents: unrelated to lecture content
  - MR-US fusion biopsy system
  - Computer aided diagnosis
  - Photoimmunotherapy
  - Various devices for measuring radioactivity
  - Method to measure GFR with Gadolinium chelates
- Cooperative Research Agreements:
  - Philips, Aspyrian, General Electric, Scan Med

Imaging for Target Engagement in Oncology

- Past mistakes and lessons learned (Antibodies)
- Current use of molecular imaging (FDG)
- Leading edge developments (Small Molecules)
- Opportunities and Challenges
- Kidney as a target for molecular imaging

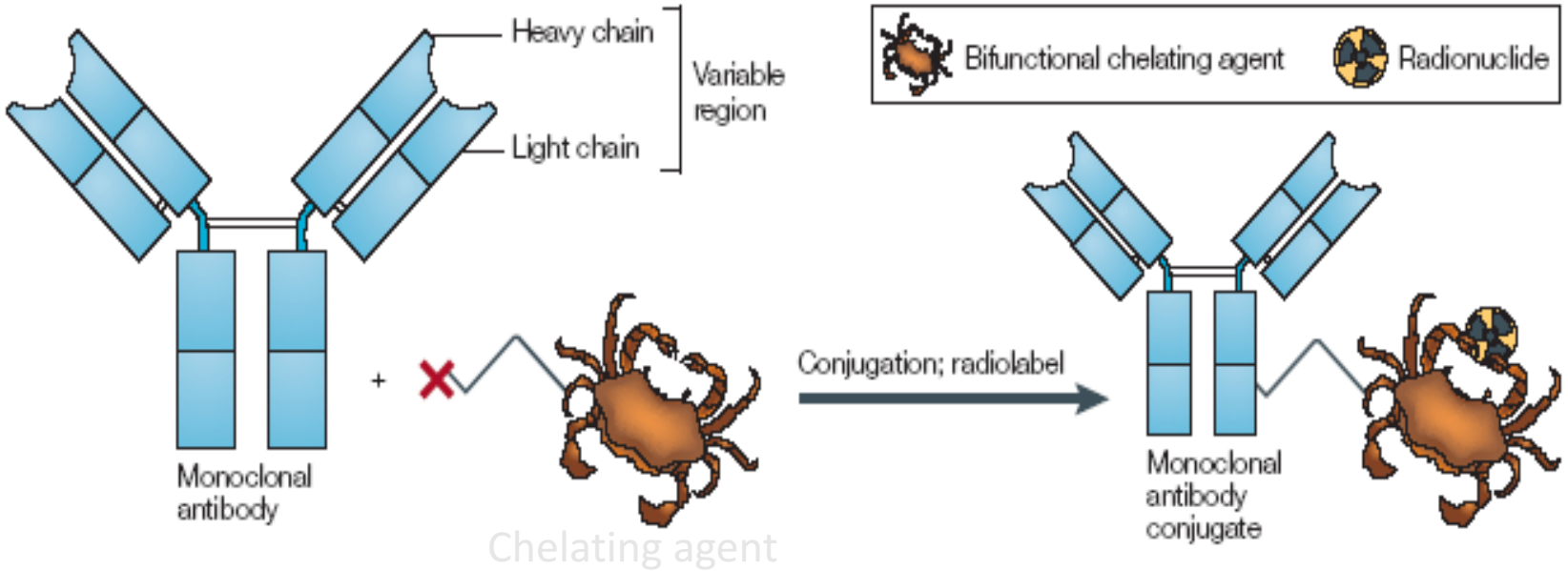
Molecular Imaging PET Agent Anatomy



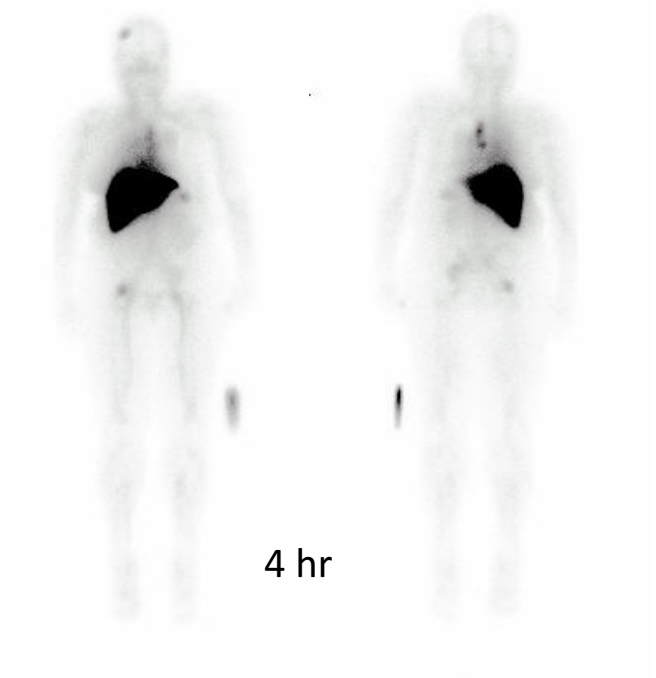
Beacon

Carrier or Bifunctional binder

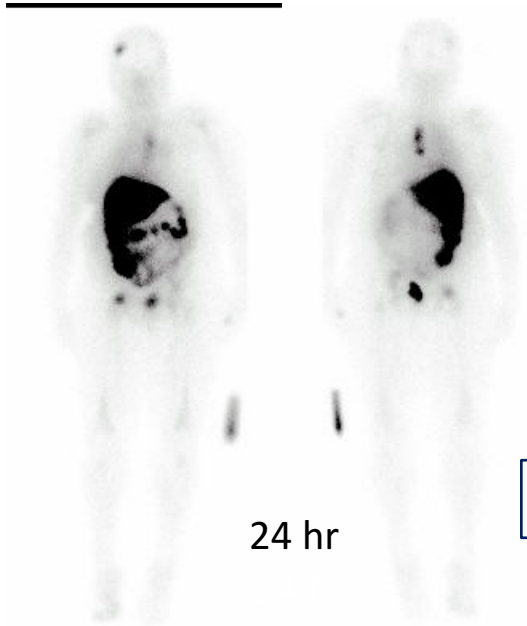
Targeting Moiety



Milenic, Brady, and Brechbiel Nature Rev Drug Disc 2004



4 hr



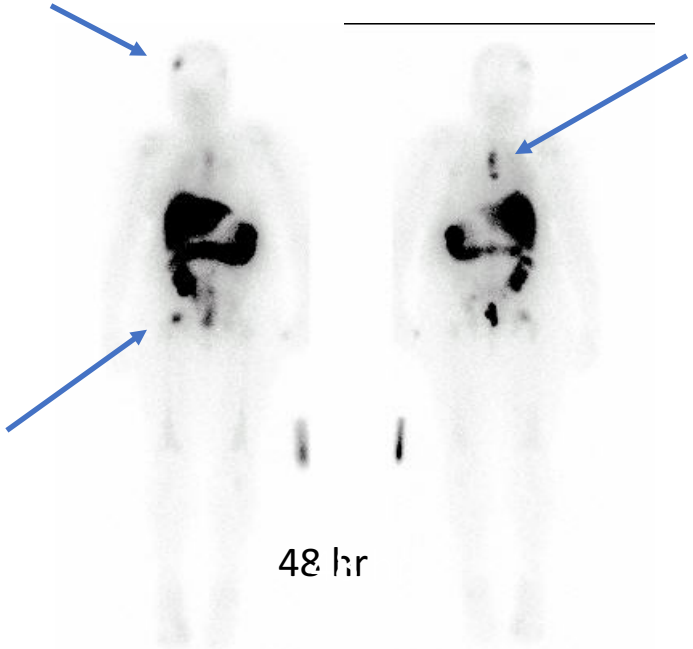
24 hr

^{111}In-Trastuzumab

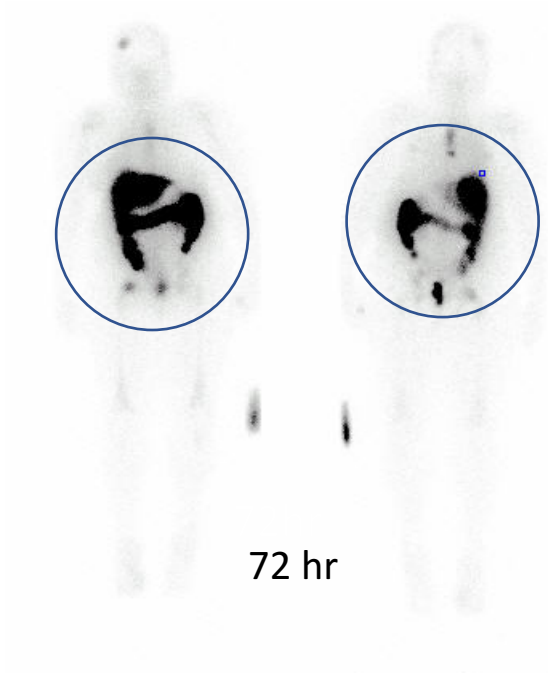
AntiHER2 imaging

Breast cancer

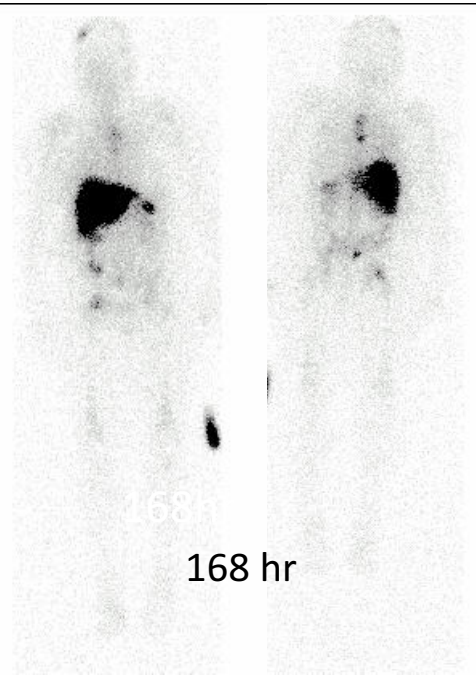
A problem of Target to Background



48 hr



72 hr



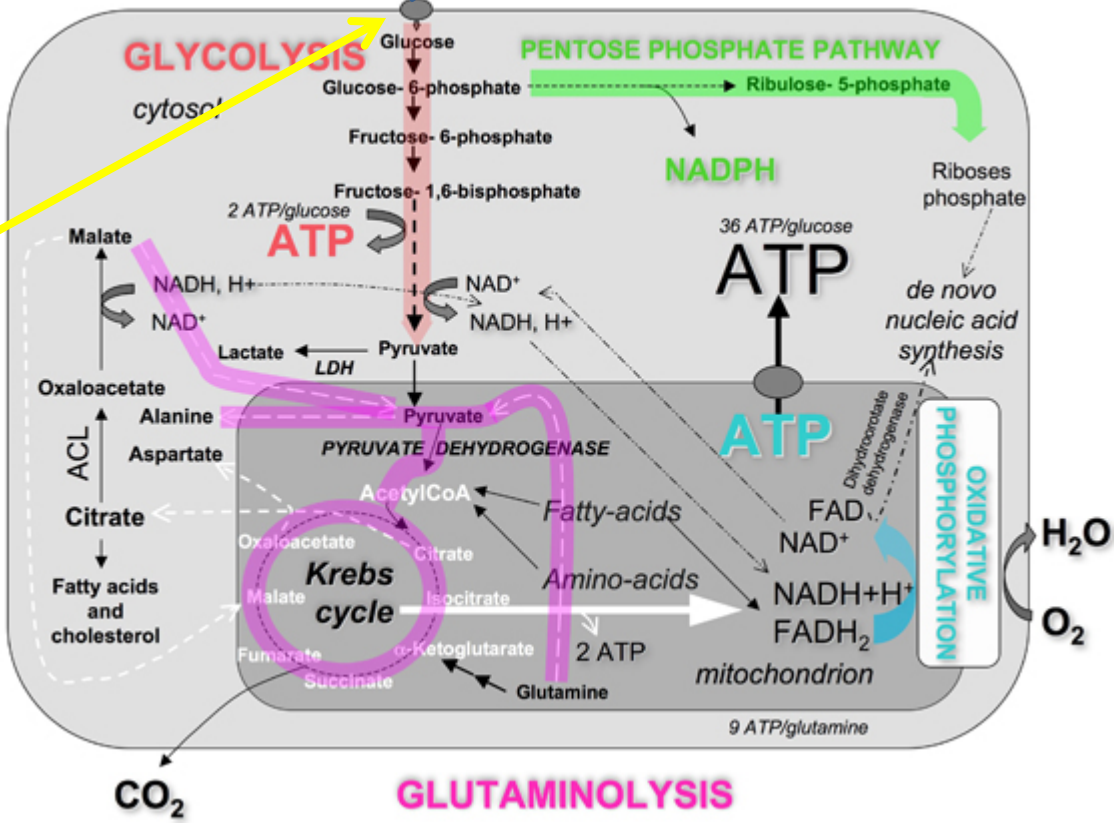
168 hr

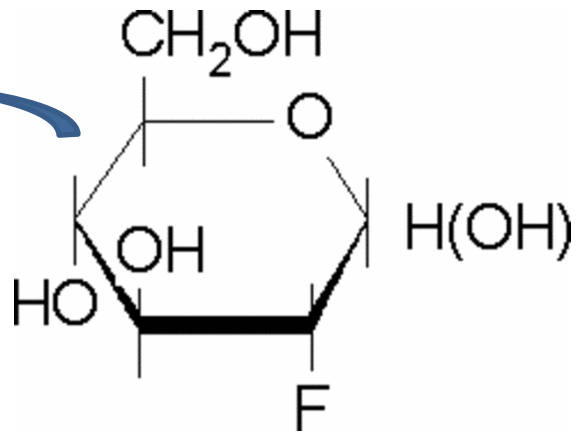
Lessons Learned

- High affinity is not enough
- Target to background ratio is critical (TBR)
- TBR is determined by
  - High affinity
  - Fast clearance
- Affects diagnostic imaging
- Affects therapeutic targeted therapy

Tumors use aerobic glycolysis: Warburg Physiology

Warburg



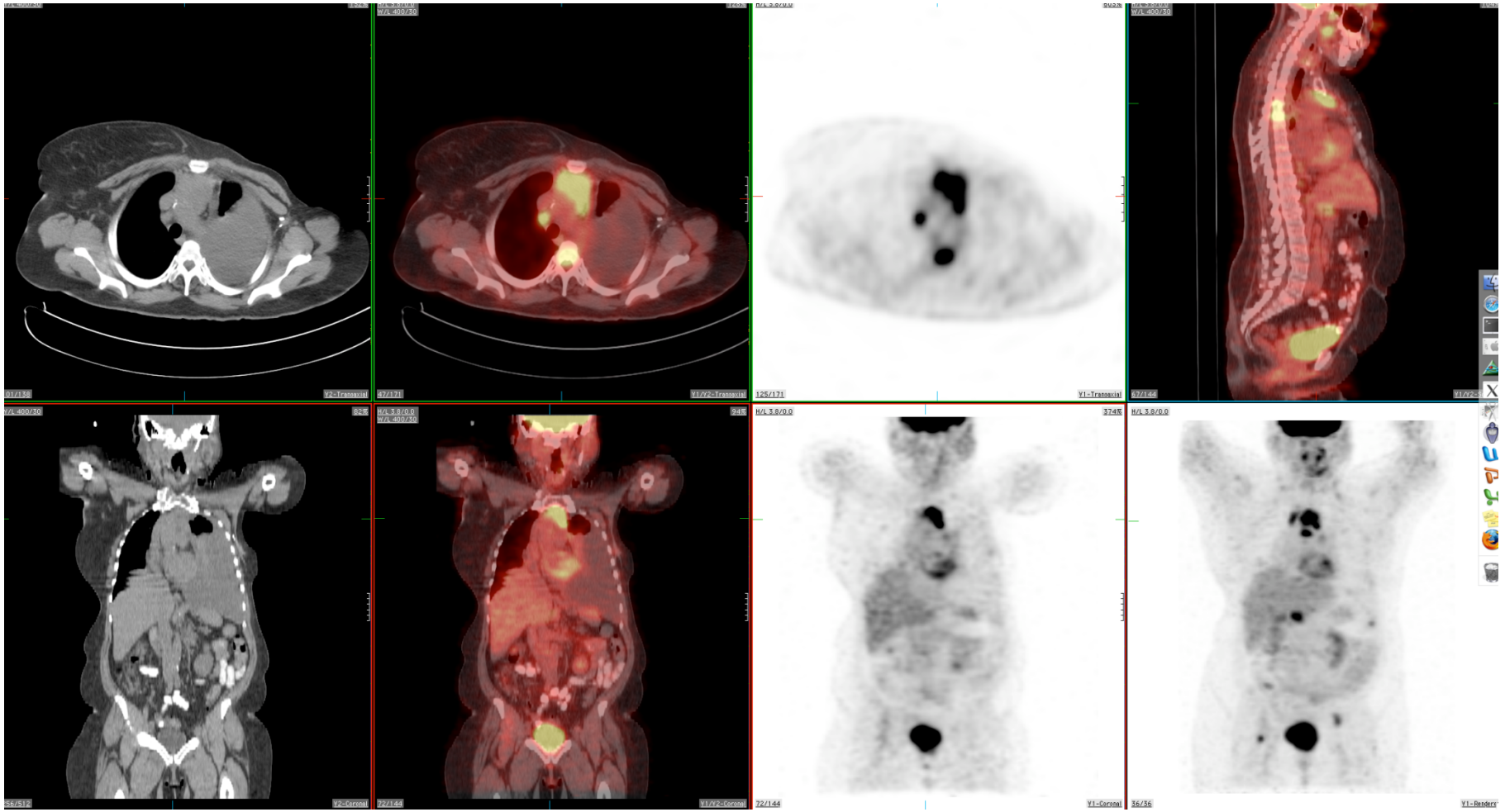


2-deoxyfluoroglucose: FDG

Fatty Acid Synthesis

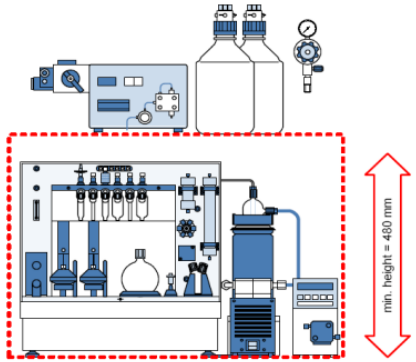
Amino Acid Metabolism

PET/CT Fusion Imaging



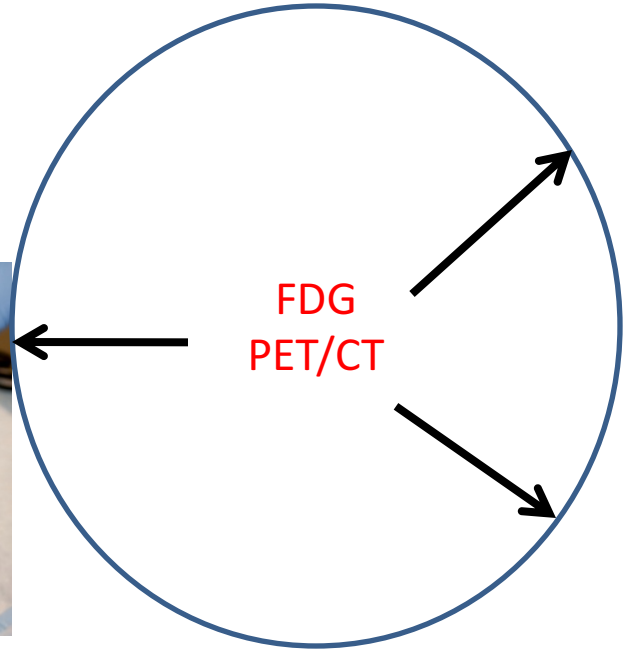
Metastatic Breast Cancer

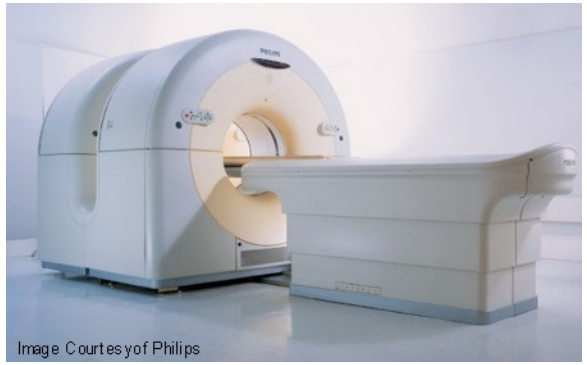
FDG: Transformationa



Delivery and Distribution

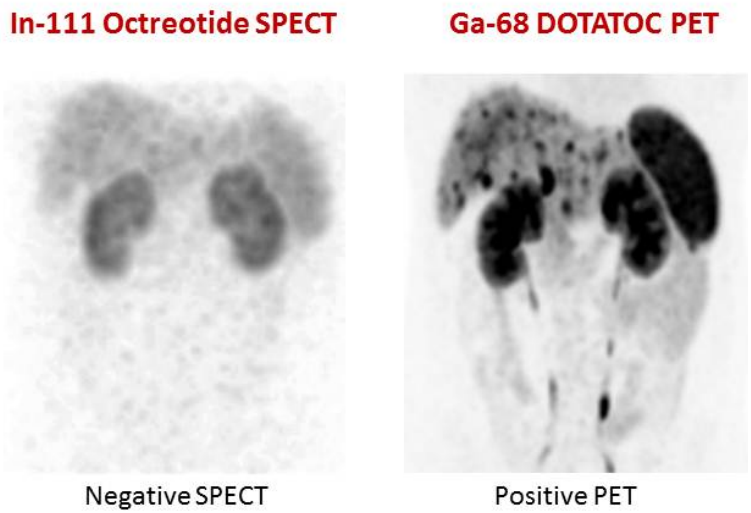
Robotic GMP Synthesis



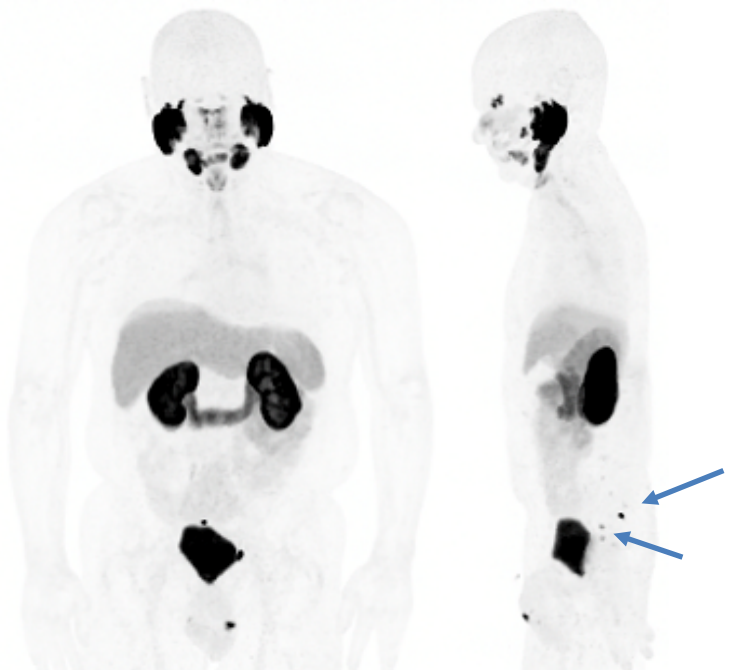


PET/CT Equipment

New Oncologic PET Probes Entering Practice



Metastatic
Carcinoid Ca



Recurrent
Prostate Ca
PSA 0.3ng/ml

PET tagged somatostatin receptor ligands
for neuroendocrine tumors

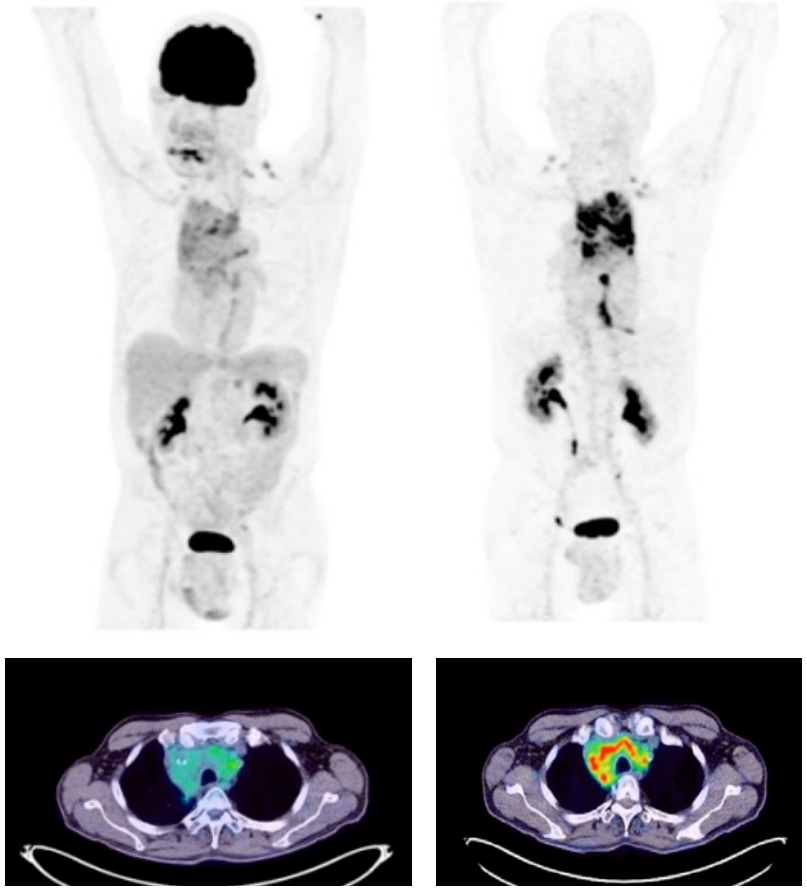
PET tagged PSMA binding ligands
for prostate cancers

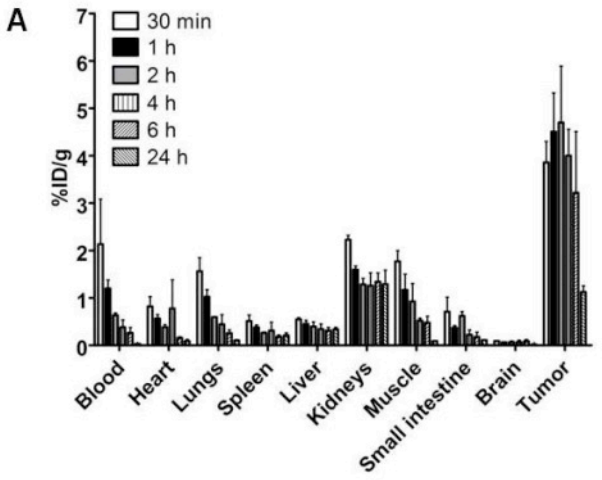
Hallmarks:
High sensitivity and specificity for cancer
Revealing completely new aspects of natural history

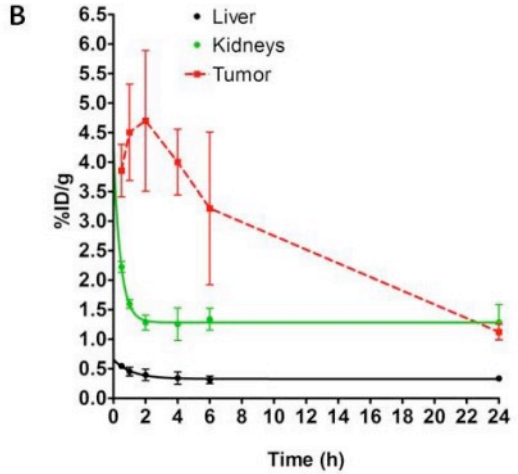
Fibroblast activating protein (FAPI) PET

FDG FAPI-02

AdenoCa Lung-

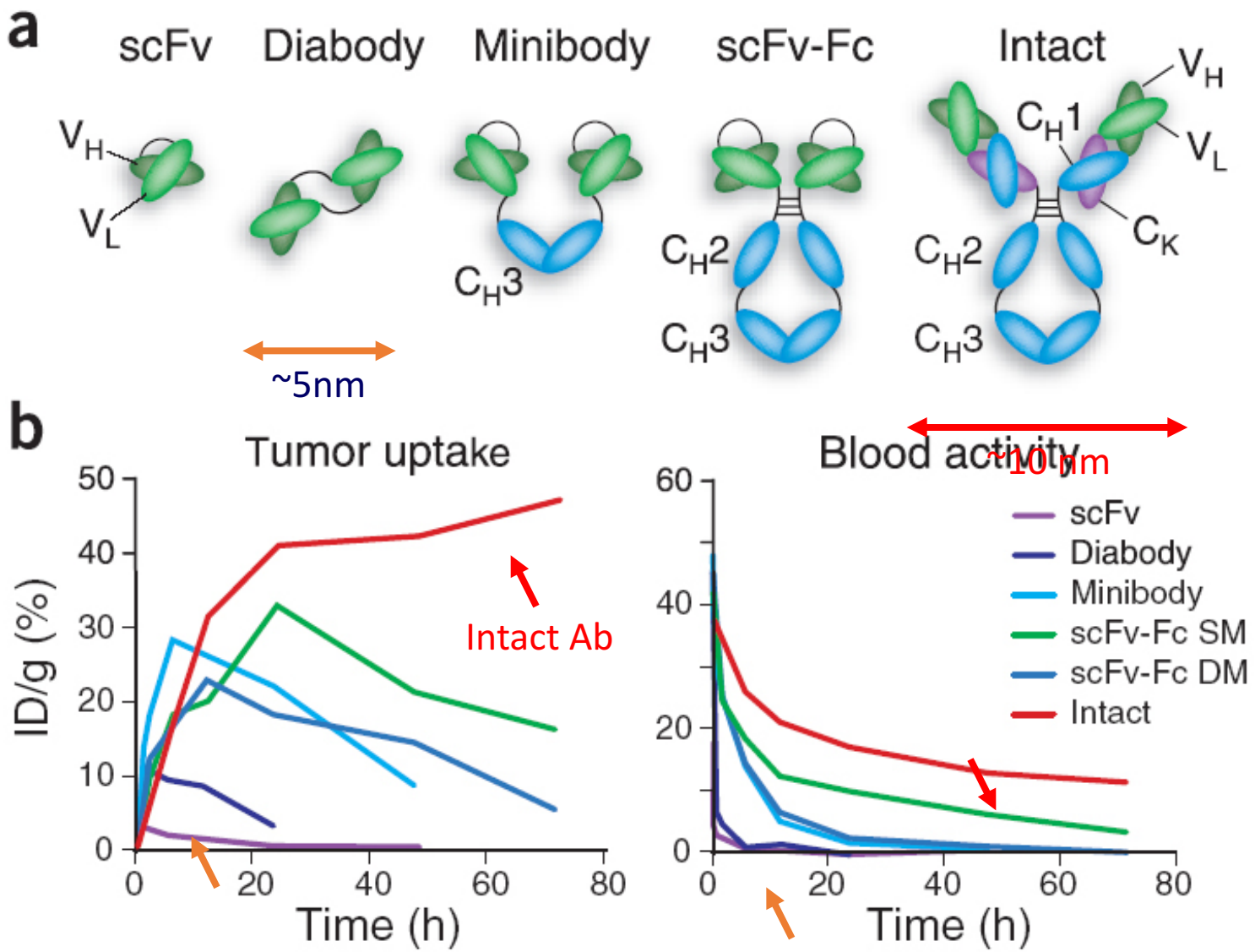






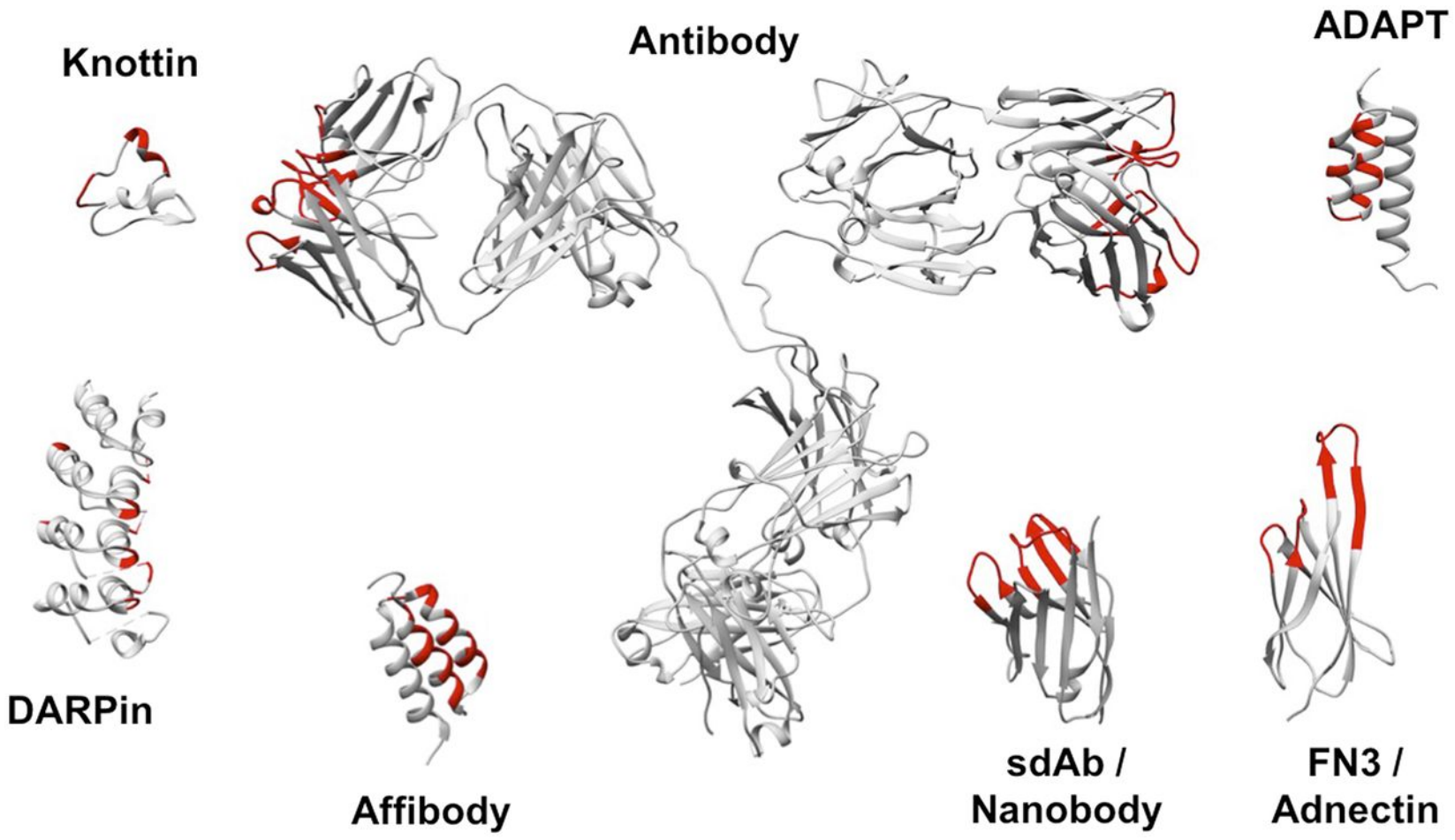
Loktev et al JNM 2018 (Heidelberg)

Size of Probe



(Wu AM, Nature Biotech. 2005)

New Small Molecule Platforms



JNM The Journal of NUCLEAR MEDICINE

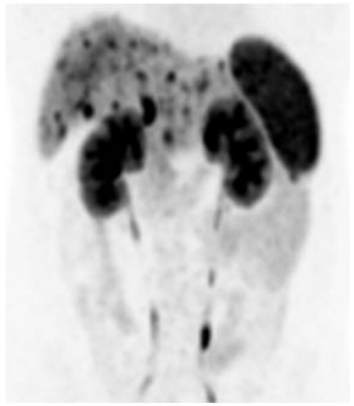
. Ahmet Krasniqi et al. J Nucl Med 2018;59:885-891

Molecular Imaging: Opportunities in the field

In-111 Octreotide SPECT

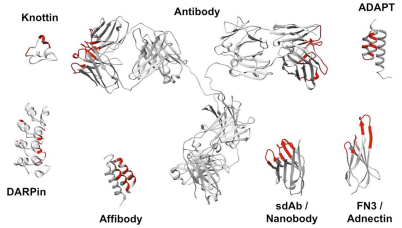
Negative SPECT

Ga-68 DOTATOC PET

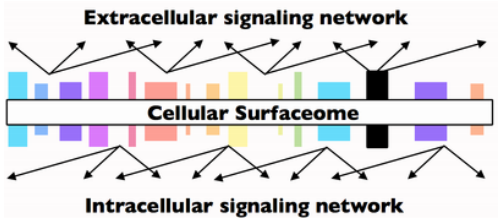


Positive PET

Small Molecule Platforms

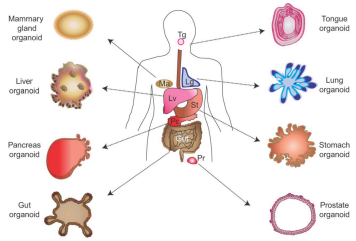


The Surfaceome-targets

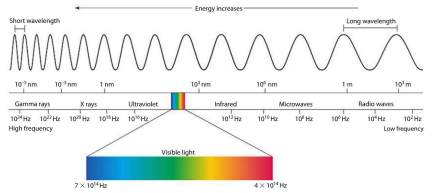


Novel Molecular Imaging Agents

Animal Models and Organoids



Expanded use of EM Spectrum



A few words about MI of the kidney

- Challenge: Most small molecules are excreted thru the kidney so TBR will be a problem.
  - By tweaking PK, one can get small molecules to be hepatically excreted.
- Challenge: Kidney is a high blood flow, dynamic organ, subject to changes in hydration, cardiovascular status etc.
  - Careful control of imaging conditions will be necessary
- Huge opportunities for developing MI for the kidney:
  - Need to solve an important and actionable problem
  - Good cell surface or interstitial targets (high abundance, accessible target)
  - Modify excretory route

Conclusions

- Molecular Imaging in Oncology is poised to make dramatic gains in the next decade
  - Rewrite the natural history of many cancers
  - and lead to earlier interventions
- The major breakthrough is in small molecule chemistry where
  - High affinity ligands with high clearance rates lead to high TBR
  - New platform technologies exist to further this effort
- Huge opportunities in Nephrology
  - Need to find viable targets with meaningful endpoints
  - Same strategy of small molecules but tweak the excretory route

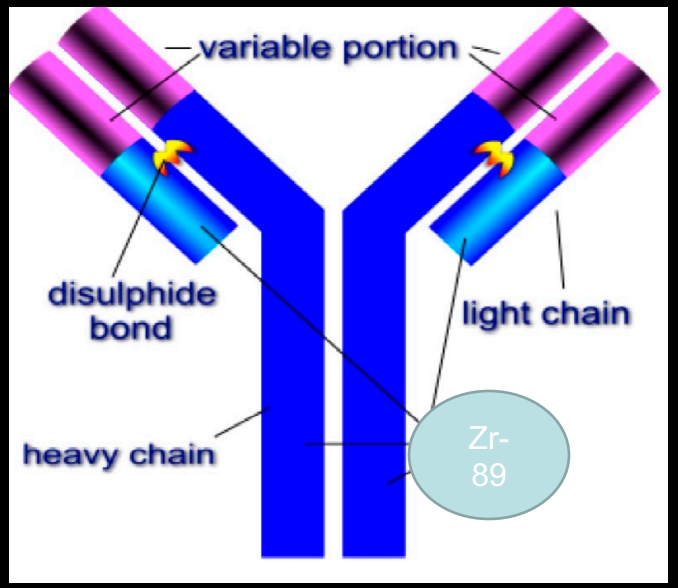
How to Screen All These People?

Imaging or Blood-Urine testing?

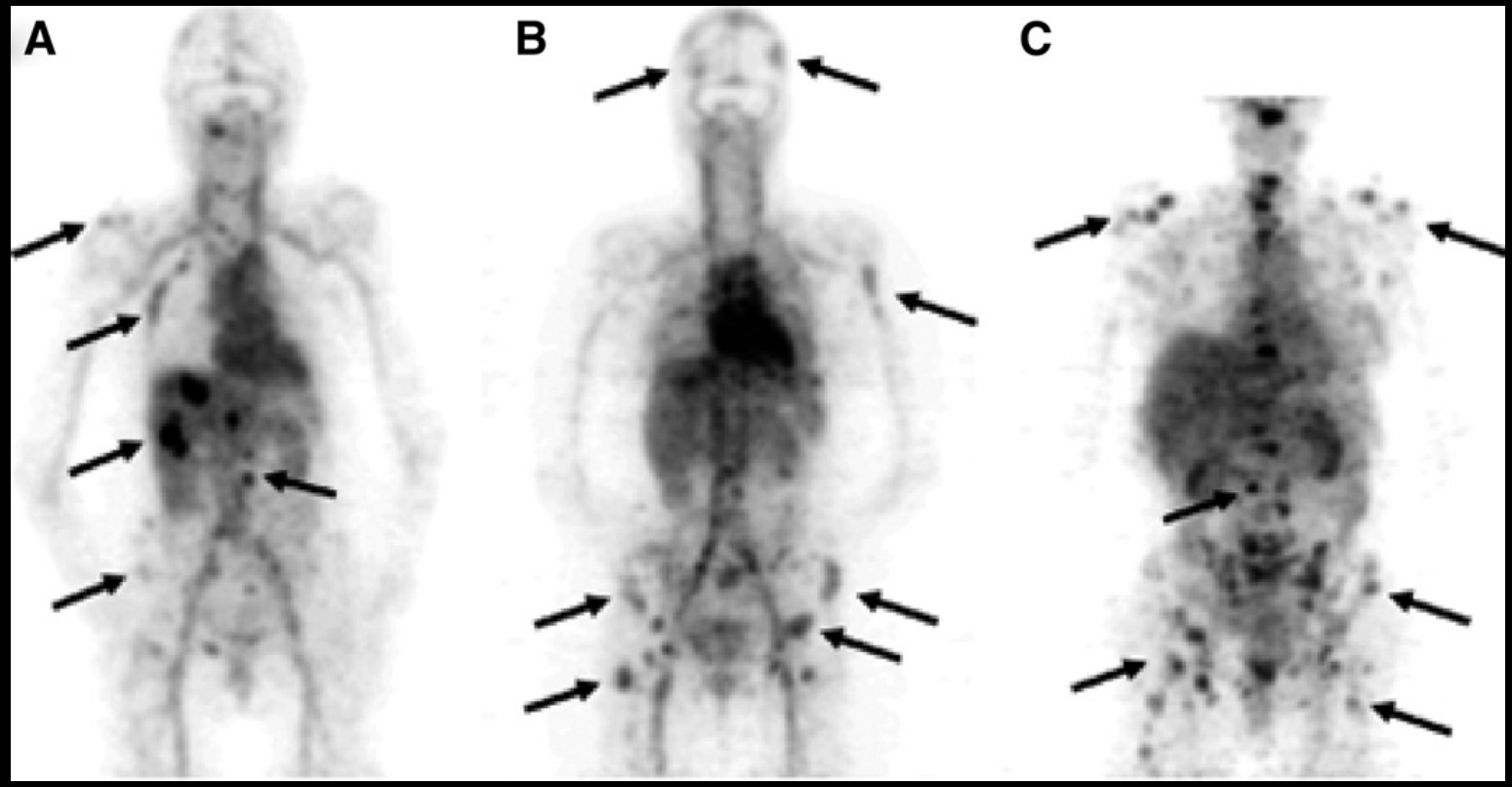
Which is more practical?

Radiolabeled Antibodies

- Very high affinity (nM) even after labeling
- >30 approved human monoclonal Abs
- But…
  - Slow clearance
  - Delayed Imaging

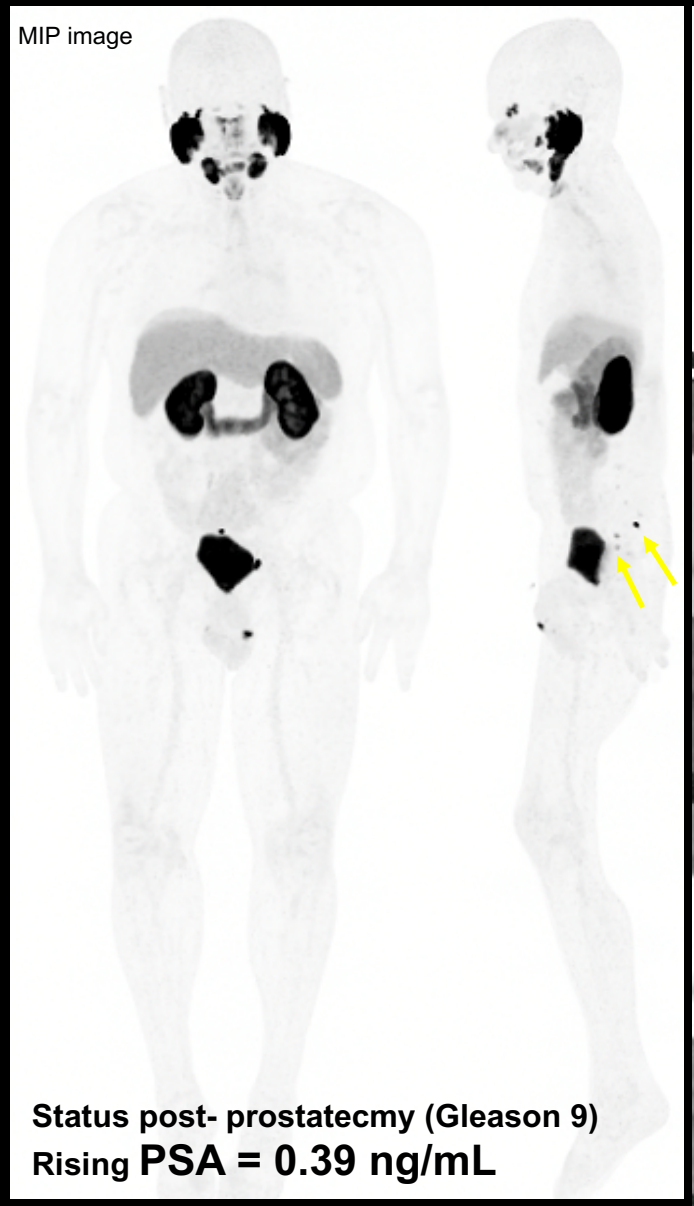


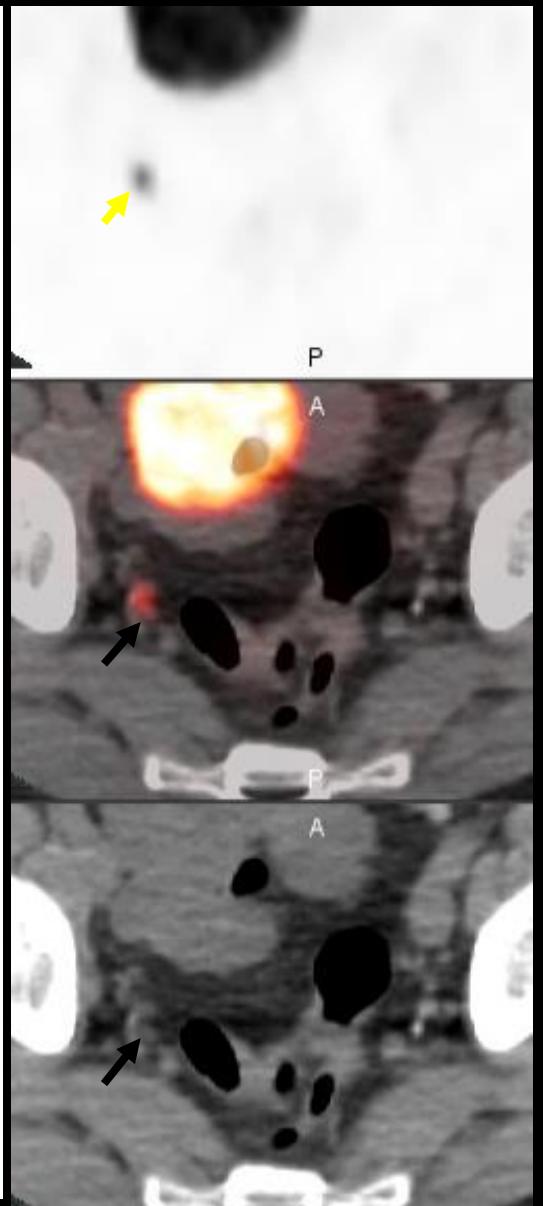
Zr-89 Trastuzumab



Dijkers EC., et al. Biodistribution of 89Zr-trastuzumab and PET imaging of
HER2-positive lesions in patients with metastatic breast cancer. Clin Pharmacol Ther 87:586-592, 2010.)

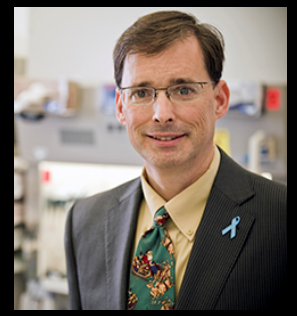
Detecting Nodal Metastases





- ✓ **^{18}F-DCFPyL PET imaging was able to detect positive findings at range of low PSA values (< 0.5 ng/mL)**

Ravi Madan



James Gulley

GUMB

Right internal iliac (3 mm) and presacral (5 mm) lymph nodes – SUVmax 12.2 and 45.3