UT Southwestern
Medical Center
Radiology

New and Upcoming Radiopharmaceuticals

Marianna Dakanali, PhD
Assistant Professor of Radiology
Director of Cyclotron Regulatory Affairs

SWC – SNMMI Annual Meeting
March 25, 2023

PET Radiopharmaceuticals – An Emerging Field

FDA Approved PET Radiopharmaceuticals

^{18}F Sodium Fluoride **1972 (2011)**

^{82}Rb Rubidium Chloride (Cardiogen-82) **1989**

^{18}F Fludeoxyglucose (FDG) **1989**

^{13}N Ammonia **2000**

^{18}F Florbetapir (Amyvid) **2012**

^{11}C Choline **2012**

^{18}F Flutemetamol (Vizamyl) **2013**

^{18}F Florbetaben (Nuraceq) **2014**

18F Fluciclovine (Axumin) **2016**

^{68}Ga DOTATATE (Netspot) **2016**

^{68}Ga DOTATOC **2019**

^{18}F Fluorodopa (FDOPA) **2019**

^{18}F Flortaucipir (Tauvid) **2020**

^{18}F Fluoroestradiol (Cerianna) **2020**

^{64}Cu DOTATATE (DETECTNET) **2020**

^{68}Ga Gozetotide (PSMA-11) **2020**

^{18}F Piflufolastat (Pylarify) **2021**

^{68}Ga Gozetotide kit (Illuccix) **2021**

^{68}Ga Gozetotide kit (Locametz) **2022**

FDA Orange book: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm?resetfields=1

Prostate-Specific Membrane Antigen (PSMA) Targeting Agents

Prostate-Specific Membrane Antigen (PSMA)

- PSMA is a type II transmembrane glycoprotein that consists of 750 amino acids, with MW > 100 kD after glycosylation
- PSMA has a 3-part structure: internal portion (19 amino acids), transmembrane portion (24 amino acids) and external portion (707 amino acids)
- It is expressed in prostate glands, duodenum, kidney, salivary glands, neuroendocrine system, proximal renal tubules
- Elevated PSMA is associated with poor outcome such as local spread, relapses and metastasis

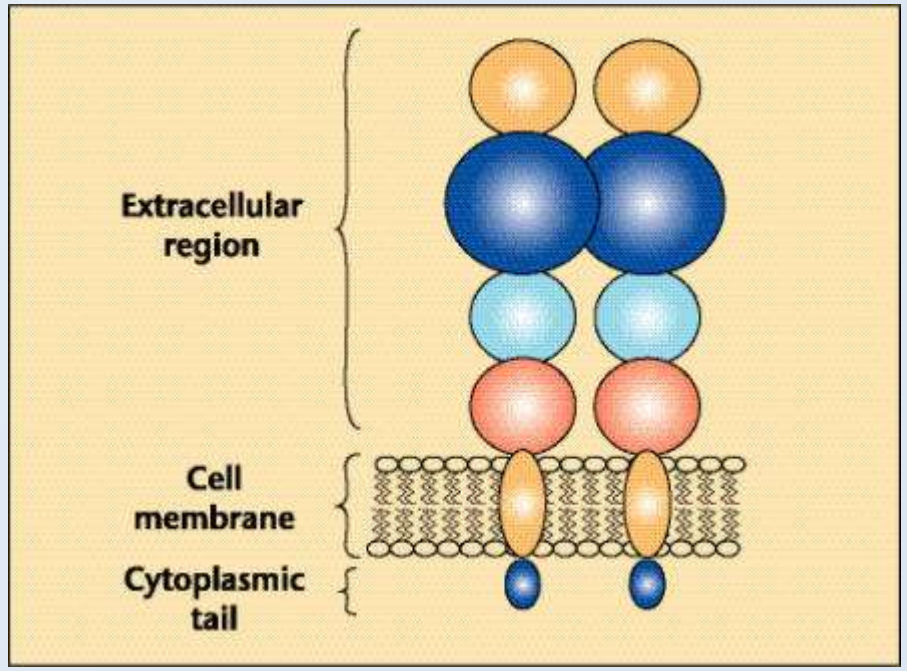


Image adapted from: Chang S. S., *Rev. Urol*. **2004**; *6(Suppl 10),* S13-S18

O'Keefe, D.S. et al. *J. Nucl. Med.* **2018**, *59*, 1007-1013
Debnath, S., Zhou, N. et al. *Int. J. Mol. Sci.* **2022**, *23*, 1158

PSMA as Target for Prostate Cancer Imaging and Therapy

- PSMA expression can be elevated 1000-fold higher than that in normal tissues
- PSMA expressed at nearly all stages of disease in a high proportion of prostate cancer tumors
- Increase PSMA expression is correlated with increased tumor grade, staging, aneuploidy and/or biochemical recurrence
- The transmembrane structure of PSMA enables internalization of bound agents
- PSMA belongs to the enzyme class of carboxypeptidases and the preferred substrate of PSMA is a peptide with a C-terminal glutamate

Two classes of compounds have been extensively evaluated for targeting PSMA:

- anti-PSMA antibodies or protein fragments
- small molecule inhibitors of the enzymatic activity of PSMA

Silver, D.A.; et al. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **1997**, *3*, 81
Bostwick, D.G.; et al. *Cancer* **1998**, *82*, 2256
Wright, G.L., Jr.; et al. *Urol. Oncol.* **1995**, *1*, 18
Rajasekaran, S.A.; et al. *Mol. Biol. Cell* **2003**, *14*, 4835

Monoclonal Antibodies (mAbs) vs Small Molecules (SMs) for Targeting PSMA

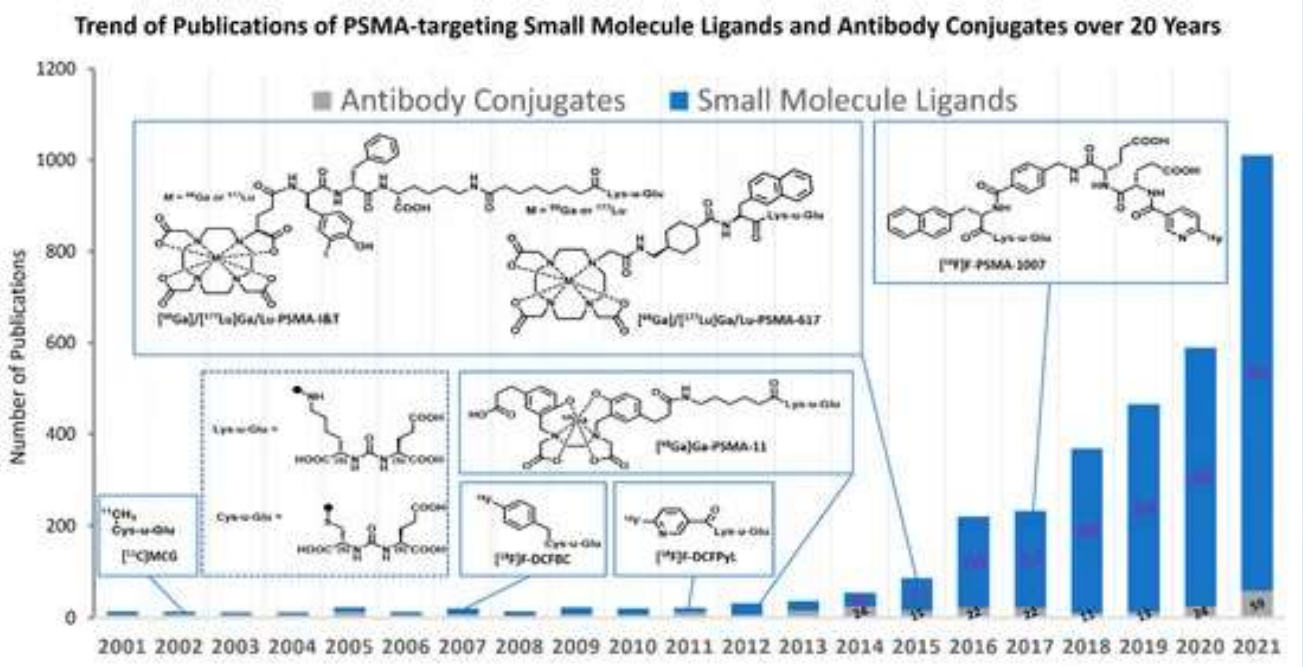


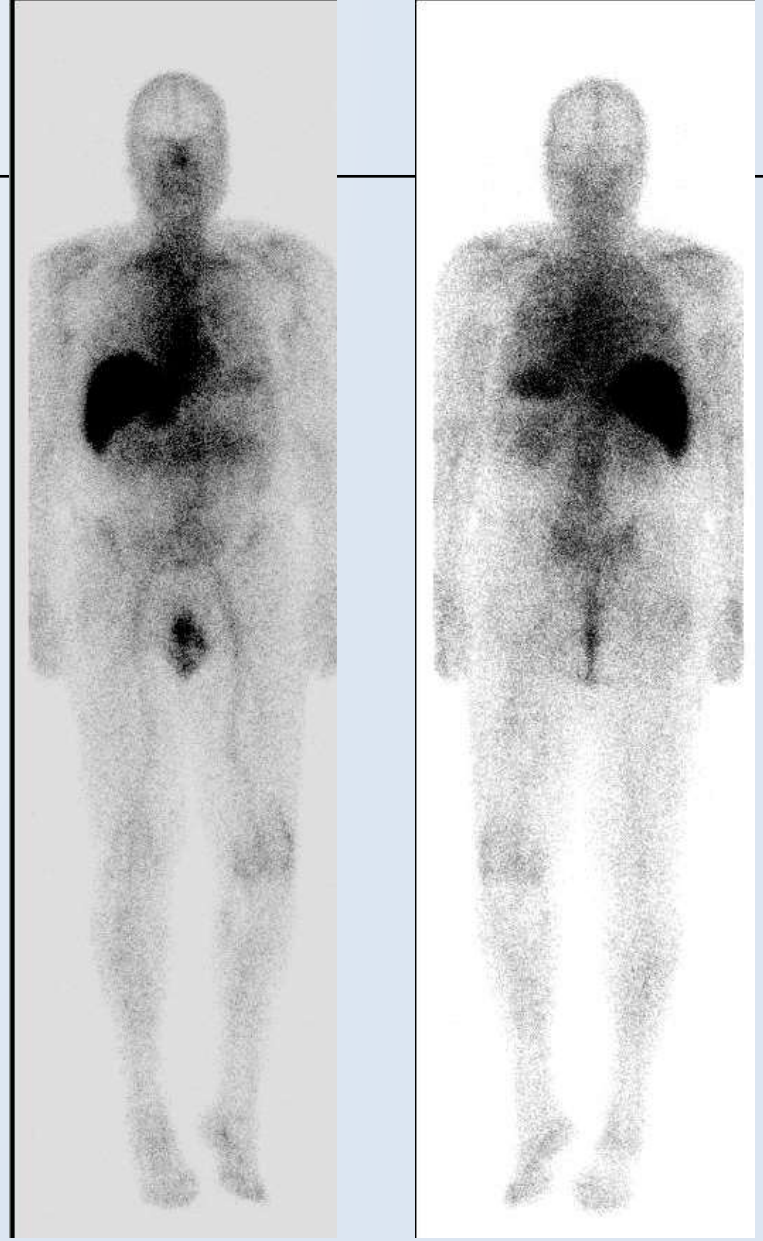
Image adapted from Debnath, S., Zhou, N. et. al. *Int. J. Mol. Sci.* **2022**, *23*, 1158

- mAbs show prolonged blood retention that results low tumor-to-background ratio
- SMs show rapid extravasation, quick diffusion in extravascular space and efficient blood clearance
- SMs inhibitors of PSMA have dominated the development of PSMA imaging and therapy agents
- Preferred substrates are peptides with a C-terminal glutamate based on the urea structure

Monoclonal Antibodies (mAbs) – ProstaScint

- ^{111}In-capromab pendetide (ProstaScint) was the first FDA approved radiopharmaceutical for prostate cancer imaging (approved 1999)
- mAb (7E11-C5) against the cytoplasmic domain of PSMA coupled with a chelator for ^{111}In labeling
- Low sensitivity and specificity

- The monoclonal antibody J591 is directed against an extracellular epitope of PSMA
- Currently in pilot studies for evaluation of its diagnostic (^{111}In, ^{99m}Tc, ^{64}Cu, ^{89}Zr) and therapeutic (^{177}Lu, ^{225}Ac) potential



Manyak, M.J.; et al. *Urology* **1999**, *54*, 1058
Evans, M.J.; et al. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 9578
Debnath, S., Zhou, N. et. al. *Int. J. Mol. Sci.* **2022**, *23*, 1158

Image courtesy of Dana Mathews PhD, MD

Small Molecule Ligands for PSMA

- Small molecule inhibitors were developed against the enzymatic activity of PSMA for neurological disorders
- Phosphorus-based ligands bind to the binuclear zinc ions in the active PSMA domain
- Thiol-based ligands form disulfide bonds that show inadequate metabolic stability
- Urea-based ligands show high binding affinity and stability
- A linker between the PSMA binding motif and the chelator positions the chelating part outside the active site
- Negatively charged linkers reduce off-target retention
- Hydrophobic aromatic structures can reduce kidney uptake

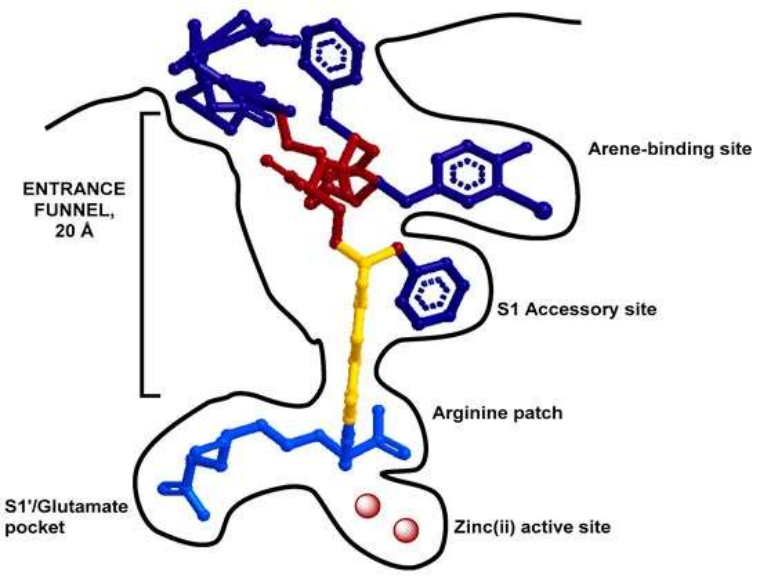
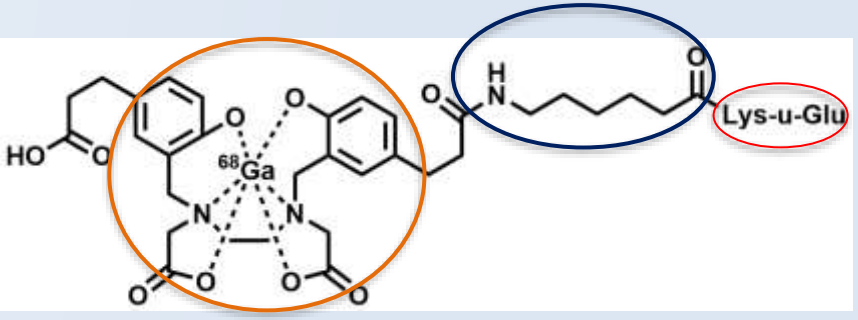


Image adapted from Debnath, S., Zhou, N. et al. *Int. J. Mol. Sci.* **2022**, *23*, 1158

^{68}Ga Gozetotide (PSMA-11)

- First-in-human ^{68}Ga PSMA-11 study was reported in 2012 by the German Cancer Research Institute and the University Hospital Heidelberg
- Structure consist of a) a Lys-u-Glu targeting moiety; b) an Ahx spacer; c) an HBED-CC chelator for ^{68}Ga labeling
- ^{68}Ga PSMA-11 shows high specific uptake to PSMA expressing tumors and relatively low liver uptake at 1 h p.i.
- UC Los Angeles and UC San Francisco jointly applied for FDA approval (NDA 212642 and NDA 212643)
- Clinical data from 2 phase III studies (PSMA-PreRP & PSMA-BCR)
- Approved (December 2020) for imaging of patients
  - with suspected metastasis who are candidates for initial definitive therapy
  - With suspected recurrence based on elevated PSA level

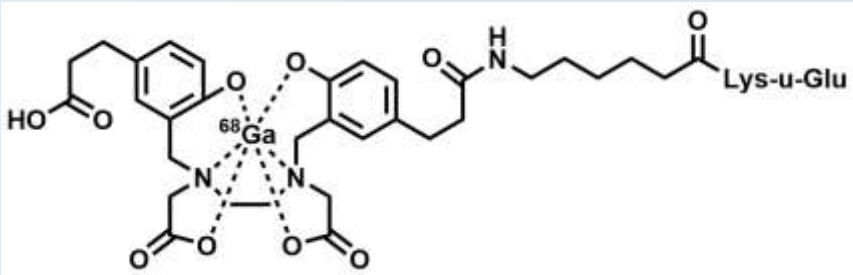


- Dose: 111 MBq to 259 MBq (3 – 7 mCi)
- Uptake time: 50 – 100 min

Eder, M. et al. *Bioconjugate Chem.* **2012**, *23* 688
Carlucci, G. et al. *J. Nuc. Med.* **2021**, *62*, 149

^{68}Ga Gozetotide (PSMA-11)

- Due to the short half-life approval/use of ^{68}Ga Gozetotide is site specific
- Clinical production requires submission and approval of an ANDA
- FDA allowed production under an expanded access (ea) IND



Need for commercially available ^{68}Ga Gozetotide

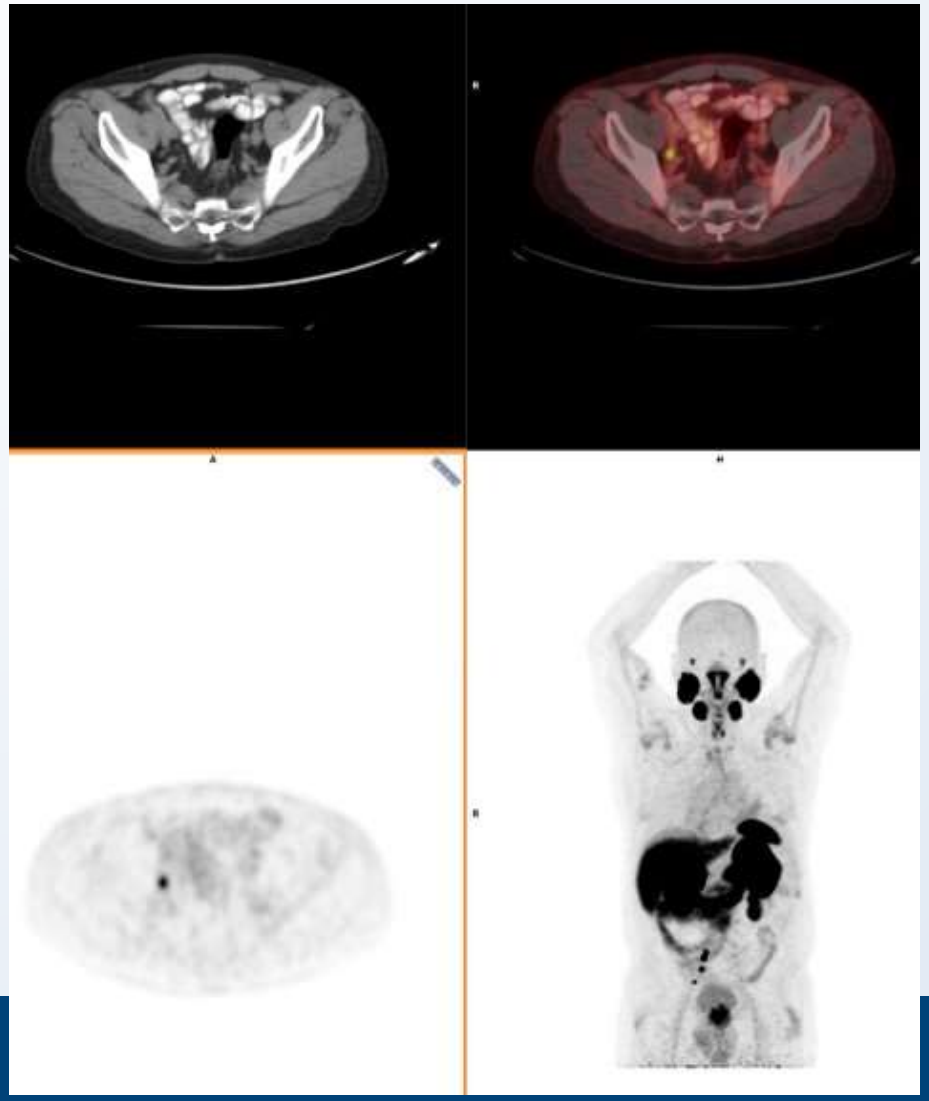
- Telix Pharmaceuticals Inc. obtained FDA approval for their kit Illuccix on December 17, 2021
  - Allows labeling with either generator or cyclotron produced Ga68
- AAA USA Inc (Novartis) obtained FDA approval for their kit Locametz on March 23, 2022
  - for selection of patients with metastatic prostate cancer, for whom lutetium Lu177 vipivotide tetraxetan PSMA-directed therapy is indicated

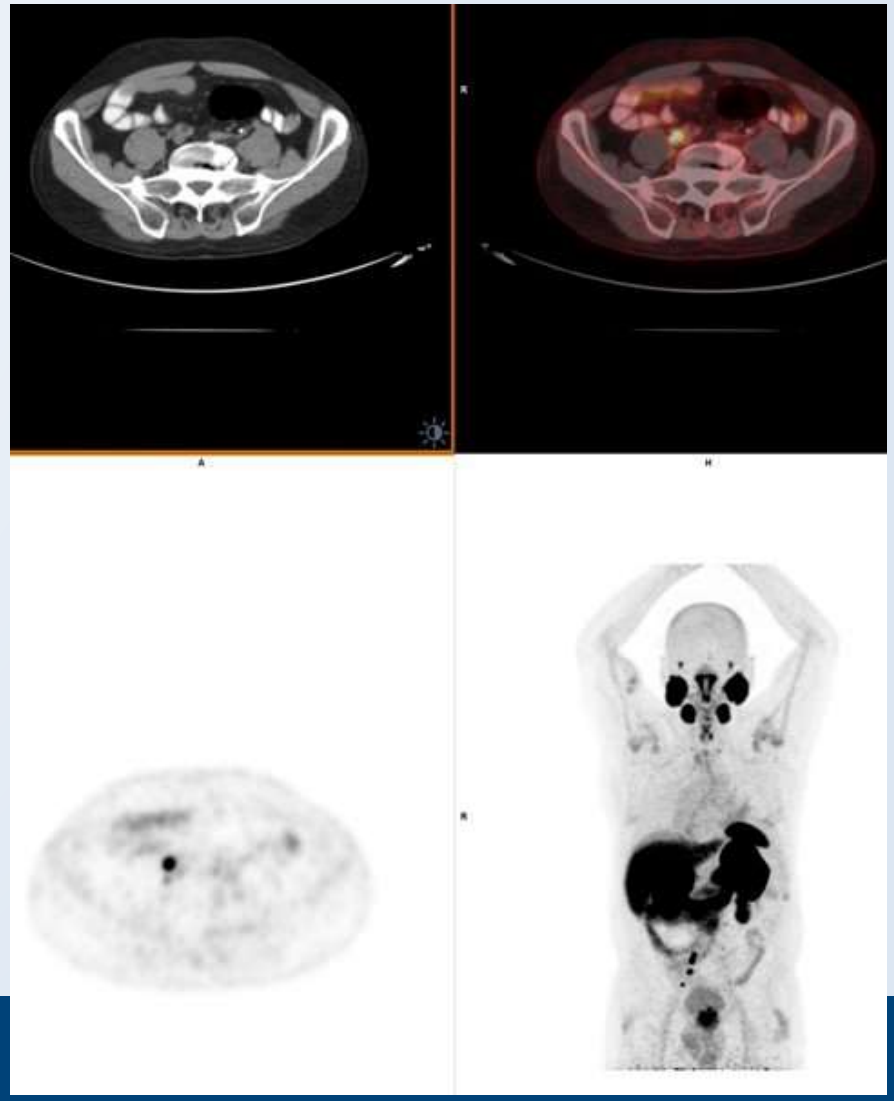
- eaIND approval at UTSW, March 2021
- 1st patient scanned, August 2021
- 550 scans completed until March 16, 2023
- Commercial sources also used since September 2022

ANDA: Abbreviated New Drug Application
IND: Investigational New Drug Application

^{68}Ga Gozetotide (PSMA-11)

Case 1: initial diagnosis, PSA > 20 – negative nodes on CT

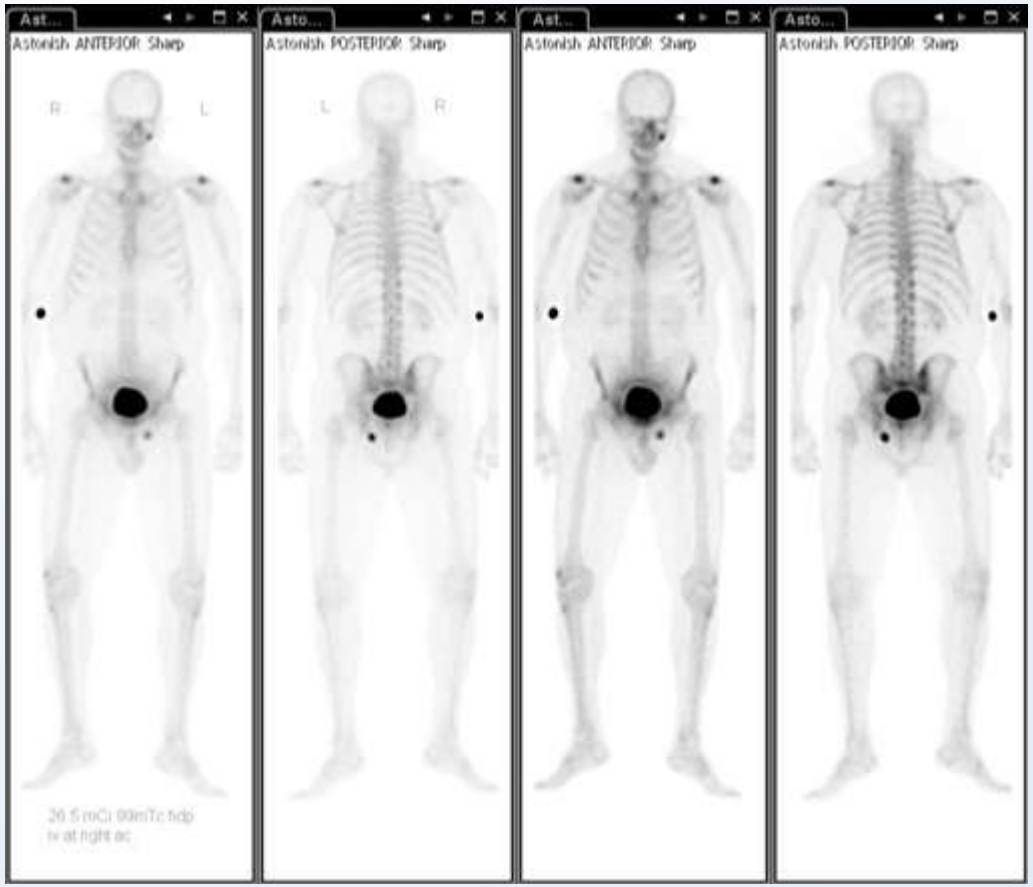


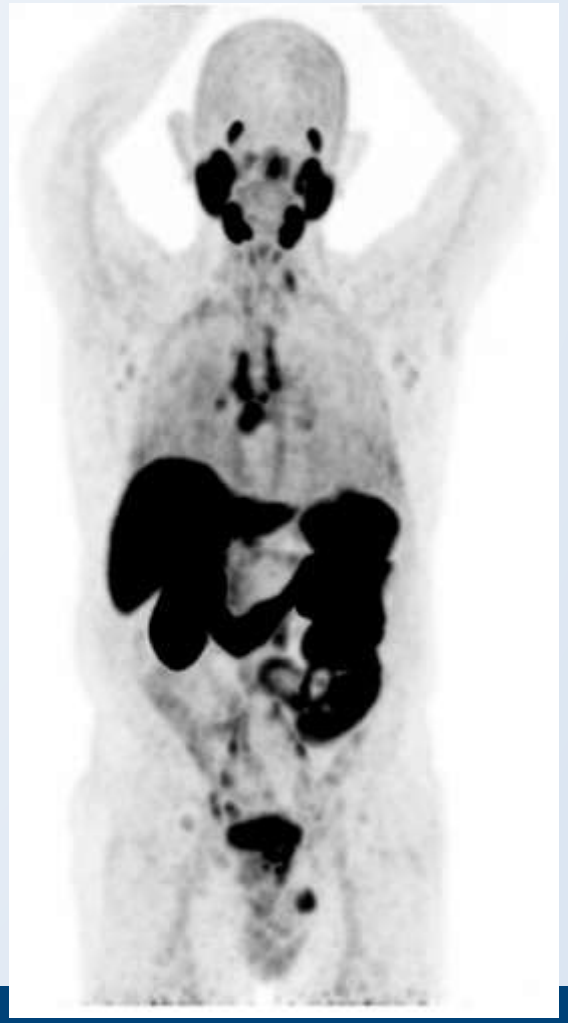


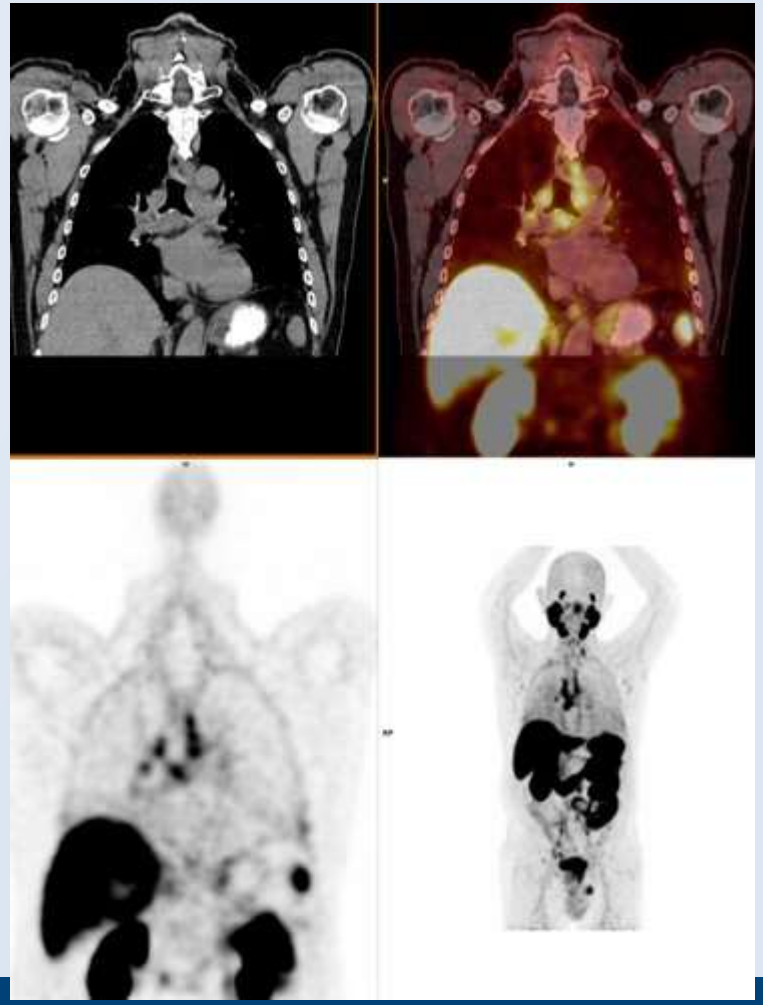
Images courtesy of Orhan K. Öz MD, PhD

^{68}Ga Gozetotide (PSMA-11)

Case 2: initial diagnosis, PSA 5.78, prior CT C/A/P called negative, bone scan showed 1 – 2 lesions

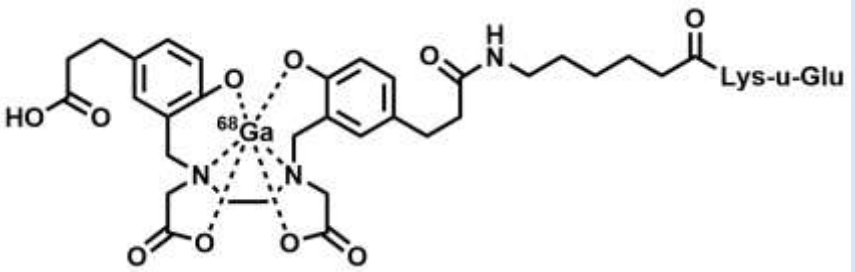






Images courtesy of Orhan K. Öz MD, PhD

^{68}Ga Gozetotide (PSMA-11)



- Due to the short half-life approval/use of ^{68}Ga Gozetotide is site specific
- Clinical productio
- FDA allowed pro

Need for commercia

- Telix Pharmaceu
  on December 17
  - Allows labeling
- AAA USA Inc (Novartis) obtained FDA approval for their kit Locametz on Mar
  - for selection of lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated

UTSW, March 2021

August 2021

ed until March 16, 2023

s also used since ??

FDA approves Pluvicto for metastatic castration-resistant prostate cancer

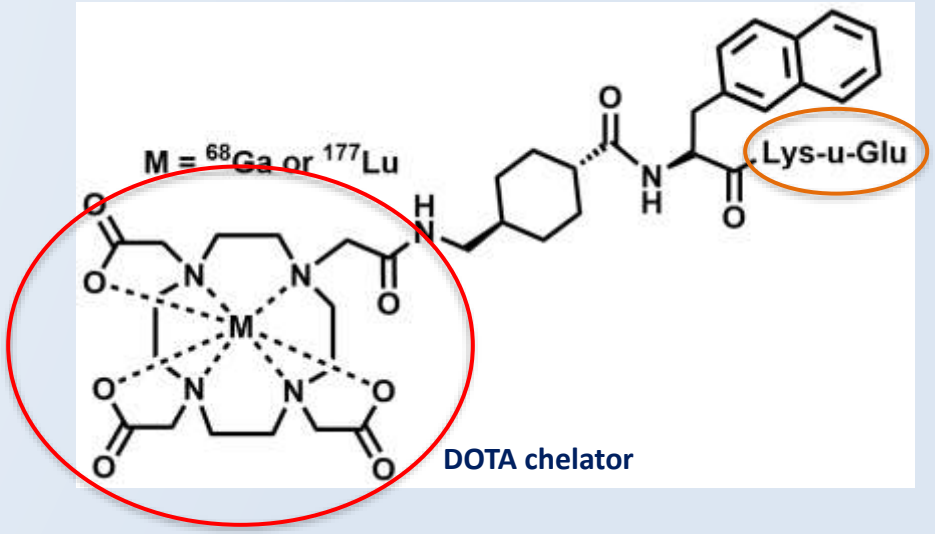
Share | Tweet | Linkedin | Email | Print

On March 23, 2022, the Food and Drug Administration approved Pluvicto (lutetium Lu 177 vipivotide tetraxetan, Advanced Accelerator Applications USA, Inc., a Novartis

Patients with previously treated mCRPC should be selected for treatment with Pluvicto using Locametz or another approved PSMA-11 imaging agent based on PSMA expression in tumors. PSMA-positive mCRPC was defined as having at least one tumor lesion with

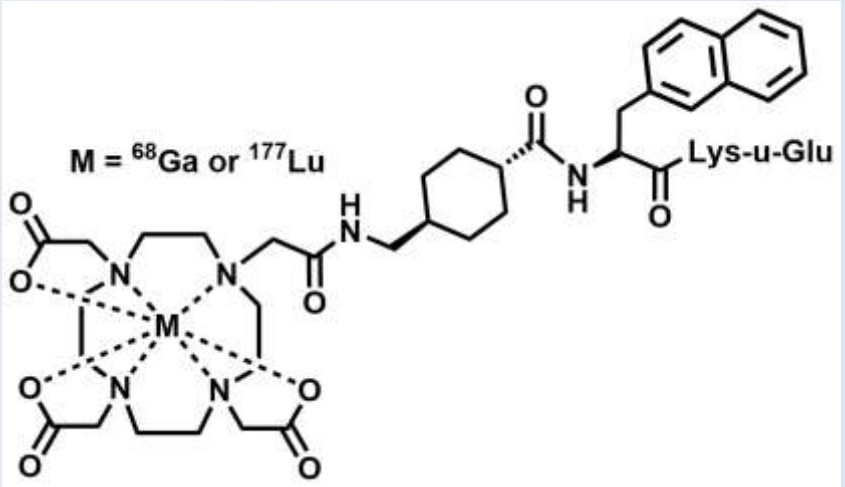
^{68}Ga/^{177}Lu PSMA-617

- HBED-CC does not form stale complexes with therapeutic radionuclides
- PSMA-617 consists of:
  - a DOTA chelator
  - a naphthalynic spacer
  - the Lys-u-Glu PSMA targeting structure
- ^{177}Lu PSMA-617 when compared to ^{68}Ga PSMA-11 showed:
  - better binding affinity
  - more internalization
  - higher tumor-to-background contrast
  - faster kidney clearance
- Data from multiple clinical trials showed increased survival
- Vision trial showed:
  - prolonged progression free survival (8.7 vs 3.4 months)
  - increased overall survival (15.3 vs 11.3 months)



^{177}Lu PSMA-617

- AAA USA Inc (Novartis) obtained FDA approval for Pluvicto (lutetium Lu 177 vipivotide tetraxetan) injection on March 23, 2022
- Pluvicto is indicated for treatment of patients with PSMA positive mCRPC who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy
- Dosage: 7.4 GBq (200 mCi) every 6 weeks for up to 6 doses

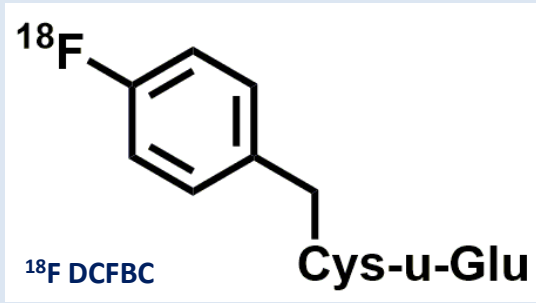


Lutetium Lu 177 Vipivotide Tetraxetan (Pluvicto) Injection
Status: Currently in Shortage
»**Date first posted:** 03/07/2023
»**Therapeutic Categories:** Oncology

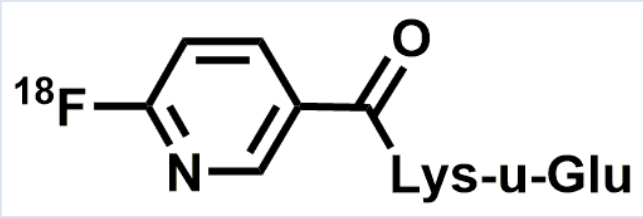
Presentation	Availability and Estimated Shortage Duration	Related Information	Shortage Reason (per FDASIA)
PLUVICTO® (lutetium Lu 177 vipivotide tetraxetan) injection, for intravenous use 27 mCi/mL; Colorless Type I glass 30 mL single-dose vial containing 7.4 GBq (200 mCi) ± 10% of lutetium Lu 177 vipivotide tetraxetan (NDC 69488-010-61)	Availability: Limited; Estimated Duration of Supply Shortage: Approximately four months	There are challenges in meeting demand and no therapeutic equivalents are available. For more information, please see the attached: Novartis Update for Patients on Supply of PLUVICTO and FAQs	Other

^{18}F Labeled PSMA-Targeting Agents – ^{18}F DCFPyl (^{18}F Piflufolastat)

- The Pomper group in 2002 reported a urea based ^{11}C tracer with cysteine and glutamine residues with desired imaging profile
- In 2008 the 1st generation ^{18}F DCFBC tracer was developed
- In 2011 the 2nd generation ^{18}F DCFPyL was developed
- ^{18}F DCFPyL showed improved tumor uptake, reduced kidney uptake, faster clearance from non-target tumors
- ^{18}F Piflufolastat (Pylarify) was FDA approved on May 26, 2021
- The CONDOR trial:
  - correctly localized disease in 85% of men with biochemically recurrent prostate cancer
  - Of those 73% underwent a change in management



^{18}F DCFBC



^{18}F DCFPyL

Pomper, M.G. et al. *Mol. Imaging* **2002**, *1*, 15353500200202109
Mease, R.C.; et al. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2008**, *14*, 3036
Chen, Y.; et al. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2011**, *17*, 7645
Morris, M. J.; *Clin. Cancer Res.* **2021**, *27*, 3674

^{18}F DCFPyl vs ^{68}Ga PSMA-11

- Similar biodistribution
- In a study, when compared to PSMA-11 in patients with BCR, it showed higher sensitivity for low PSA values (0.5 – 3.5 μg/L)
- Insufficient evidence to favor one PSMA tracer over the other

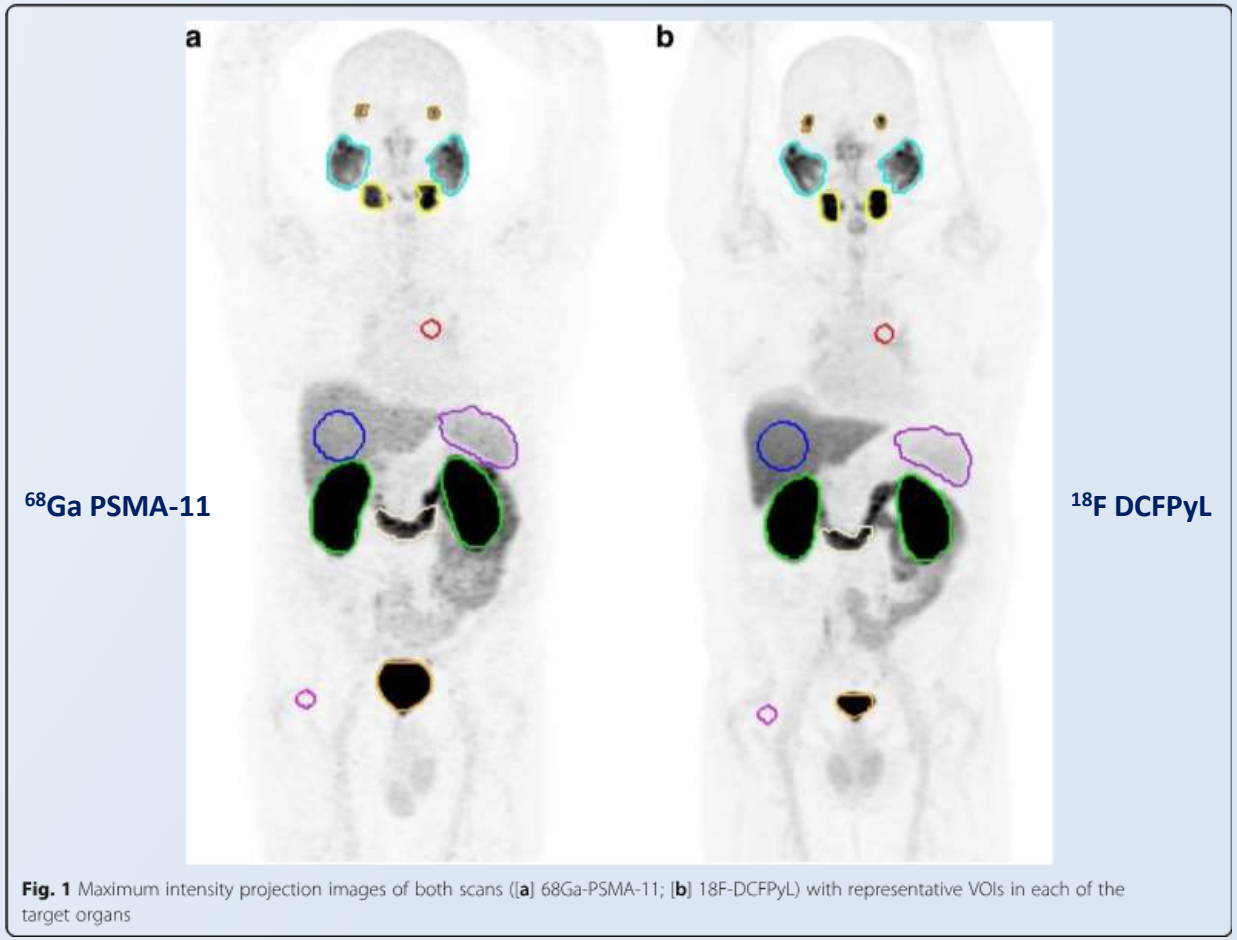
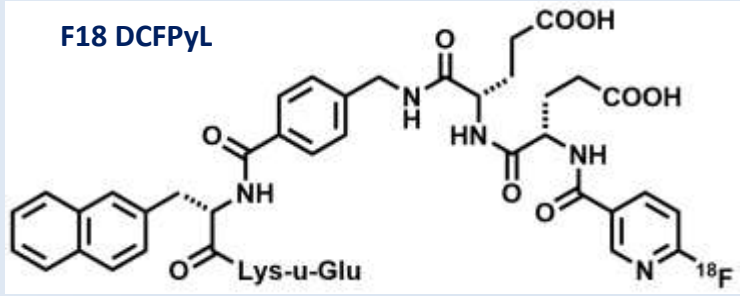


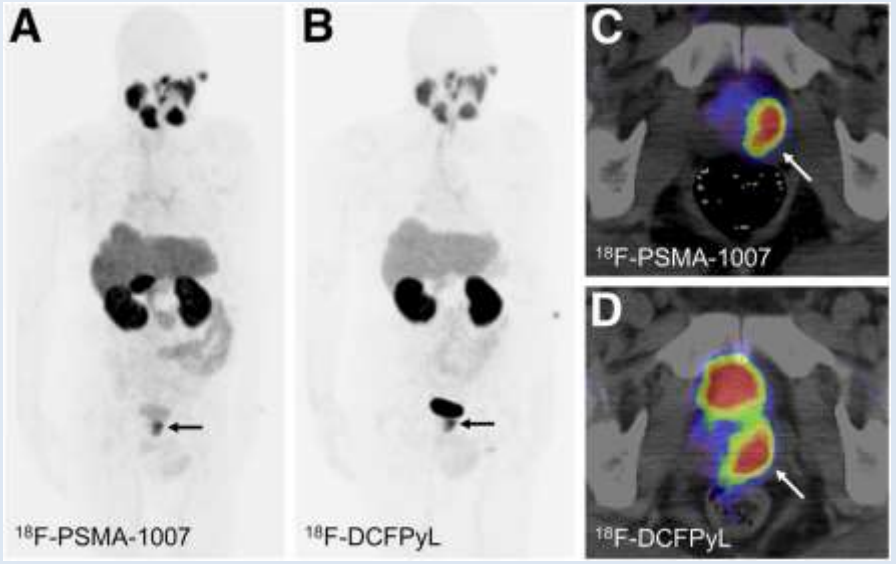
Fig. 1 Maximum intensity projection images of both scans ([**a**] 68Ga-PSMA-11; [**b**] 18F-DCFPyL) with representative VOIs in each of the target organs

Dietlein, F. et al. *J. Nuc. Med.* **2017**, *58*, 947
Ferreira, G.; et al. *Cancer Imaging* **2019**, *19*, 23
Alberts, I. L.; et al. *Eur. J. Nucl. Med. Mol. Imaging* **2021**, *48*, 2978

^{18}F PSMA-1007

- ^{18}F PSMA-1007 includes a modified spacer from PSMA-617 that leads to increased hydrophilicity
- Showed high tumor cell internalization in vitro and high tumor uptake in vivo
- Showed comparable detection sensitivity and specificity to ^{18}F DCFPyl
- Decreased signal from the ureters and bladder within the imaging time interval
- Improved identification of local recurrence or pelvic lymph node metastasis
- Higher liver uptake
- Currently in phase III clinical trials



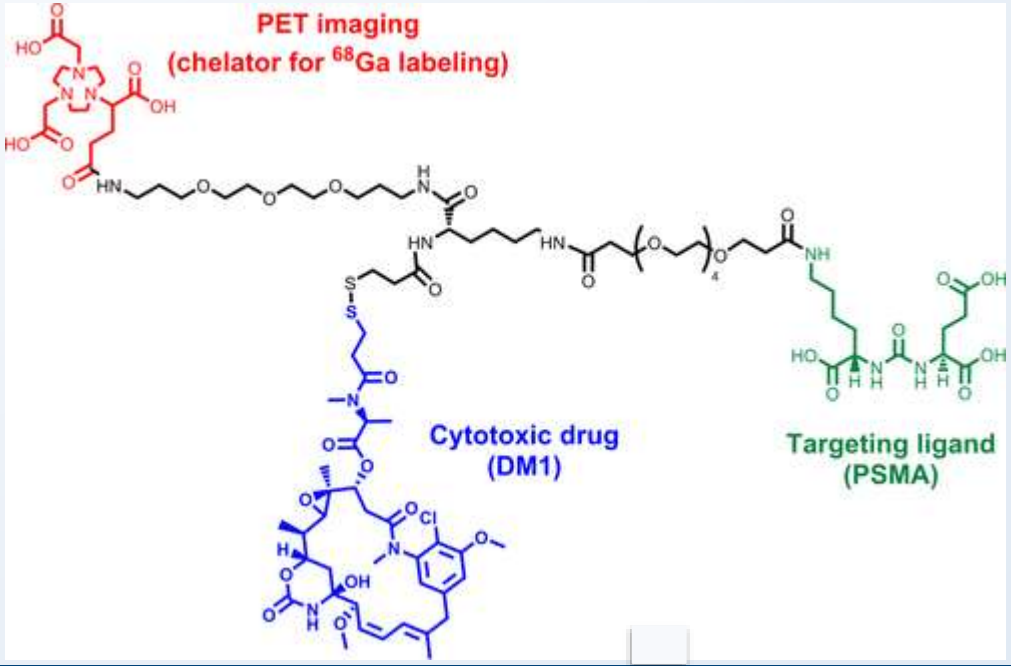


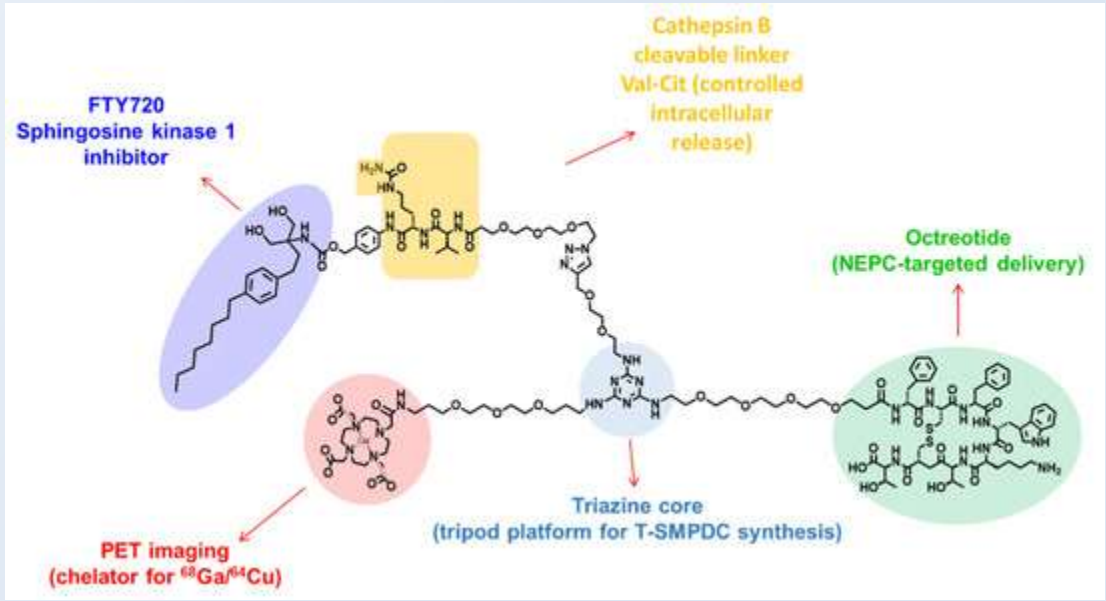
Giesel, F. L.; et al. *J. Nuc. Med.* **2018**, *59*, 1076
Wang, Y.; et al. *Nature Review* **2022**, *19*, 475

Image adapted from Giesel, F. L.; et al. *J. Nuc. Med.* **2018**, *59*, 1076

Future Perspectives

- Identical pair of agents for diagnosis and therapy
- Modifications on the linker without compromising the PSMA specific binding affinity
  - Minimize side effects
  - Enhance tumor uptake
- Development of concurrent theranostic strategy



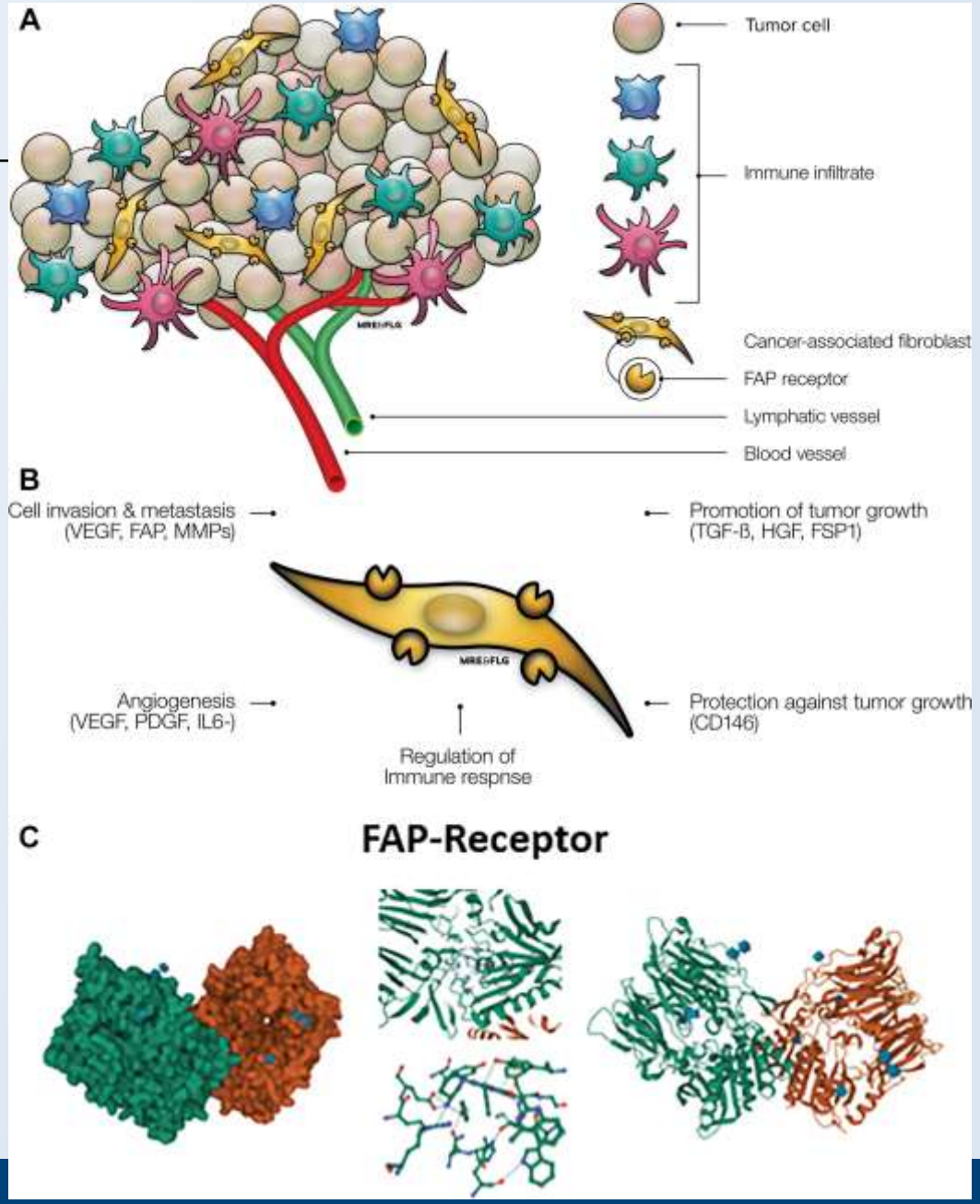


Kumar, A.; et al. *Bioconjug. Chem.* **2016**, *27*, 1681
Gonzalez, P.; et al. *Pharmaceutics* **2023**, *15*, 481

Fibroblast Activation Protein Inhibitor (FAPI) Use in Imaging

Activated Fibroblasts in Tumor Microenvironment

- Tumor microenvironment has gained considerable attention for the development of new diagnostic and therapeutic strategies
- Tumor stroma develops around malignant cells (1 – 2 mm) and plays an important role in the development of tumors
- Cancer associated fibroblasts constitute the main component of the tumor stroma
- Activated via stimuli such as hypoxia and oxidative stress to release growth factors
- Transformed to cells expressing surface markers
- Fibroblast Activation Protein (FAP) most specifically upregulated surface protein



Mori, Y.; et al. *Radiology.* **2023**, *306*, e220749
Loktev. A; et al. *J. Nuc. Med.* **2018**, *59*, 1423
Fitzgerald, A. A.; et al. *Cancer Metastasis Rev.* **2020**, *39*, 783

Image adapted from Mori, Y.; et al. Radiology. 2023, 306, e220749

Fibroblast Activation Protein

- Fibroblast Activation Protein (FAP) is a transmembrane type II glycoprotein belonging to the dipeptidyl peptidase 4 (DPP4) family
- FAP expression is associated with poor prognosis
- FAP consists of 760 amino acids, with a large extracellular domain (734 amino acids)
- Catalytic domain located extracellularly
- FAP is expressed in more than 90% of human epithelial cancers
- It is absent from normal tissues
- These properties suggest:
  - Low background activity with high image contrast
  - Low frequency of side effects
  - Application in many different tumor types

Airo Farulla, L. S.; et al. *Clin. Transl. Imaging* **2023**, *11*, 95
Zi, F.; et al. *Mol. Med. Rep.* **2015**, *11*, 3203
Lindner, T.; et al. *J. Nuc. Med.* **2018**, *59*, 1415

Fibroblast Activation Protein Inhibitors (FAPI)

- Several quinoline based FAP inhibitors have been reported to the literature
- First ^{68}Ga labeled inhibitors were synthesized by Lindner et al. with specific binding to FAP
- ^{68}Ga FAPI-02 and -04 showed comparable dosimetry to ^{18}F FDG and ^{68}Ga DOTATATE
- 1st generation FAPIs showed short tumor retention
- ^{68}Ga FAPI-46 displays longer tumor retention
- FAPI tracers reach quickly a stable physiological distribution
- Demonstrate only minimal changes between 10 min and 3 h p.i.

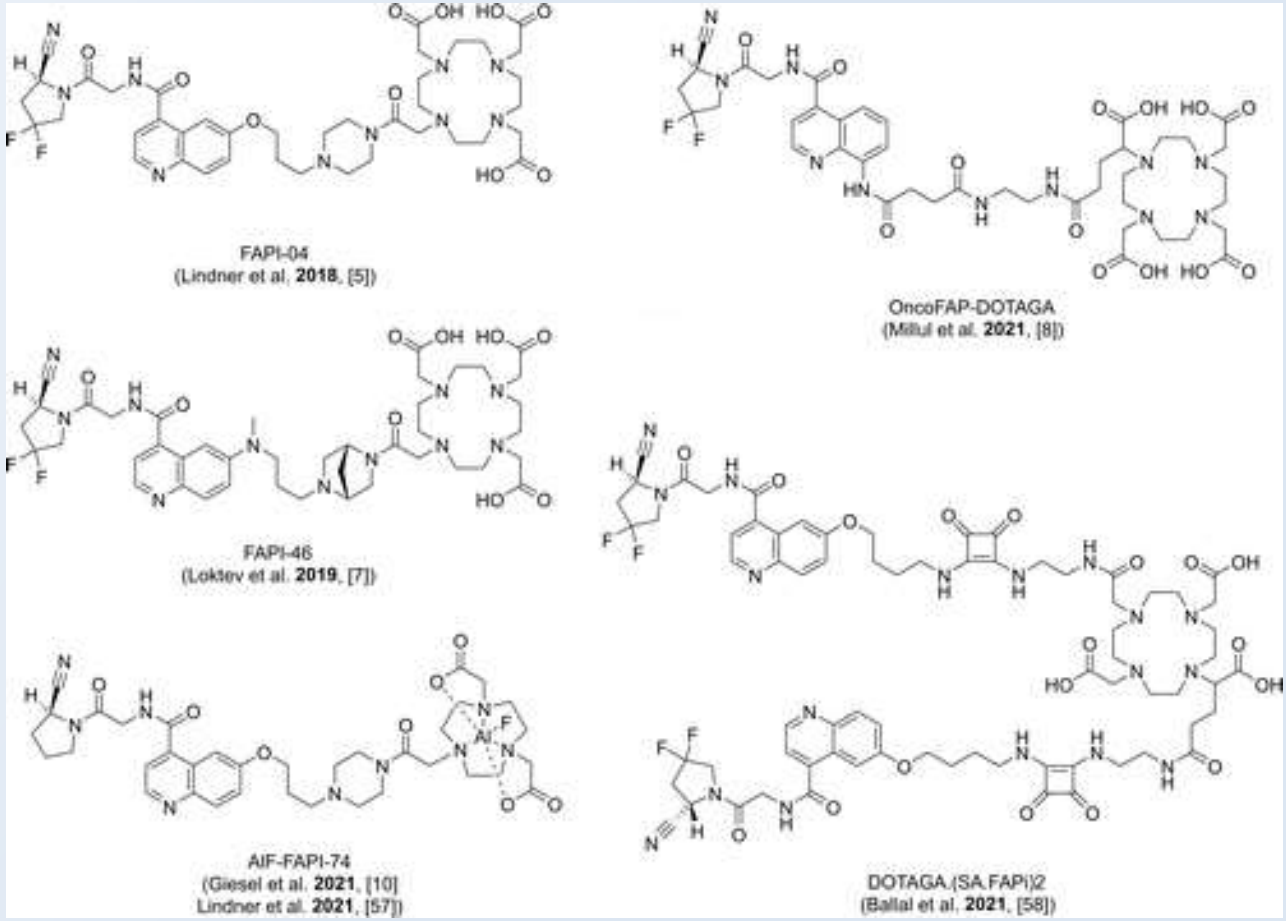
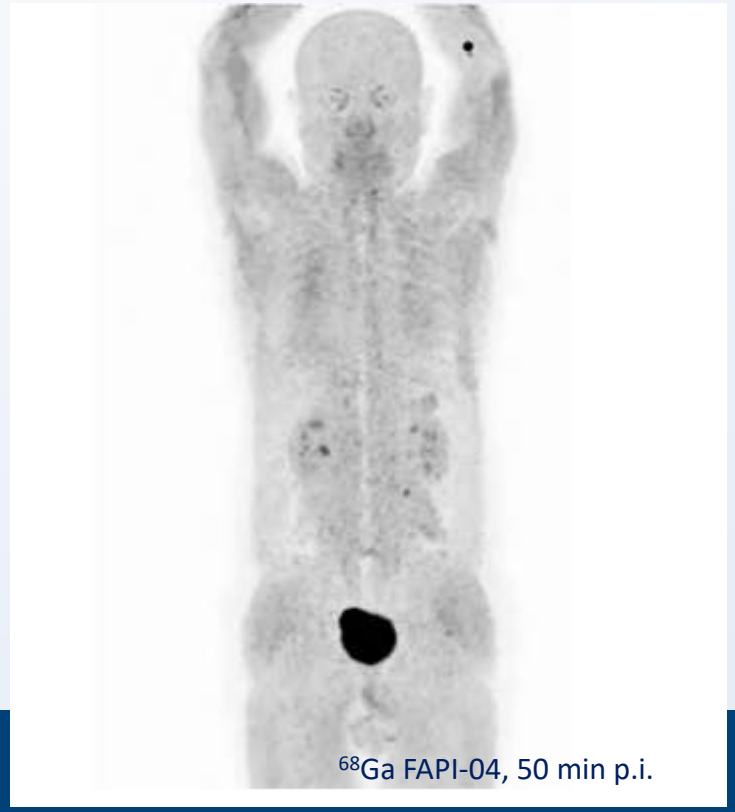


Image adapted from Mori, Y.; et al. Radiology. 2023, 306, e220749

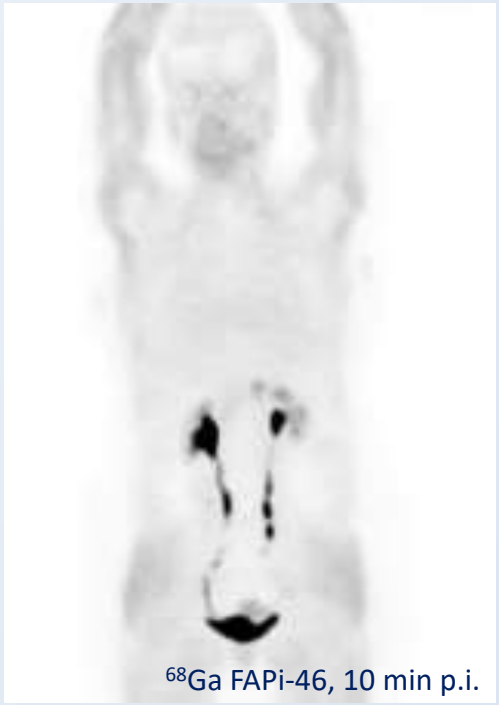
Mori, Y.; et al. *Radiology.* **2023**, *306*, e220749
Lindner, T.; et al. *J. Nuc. Med.* **2018**, *59*, 1415
Loktev, A.; et al. *J. Nuc. Med.* **2019**, *60*, 1421

FAPI Normal Biodistribution

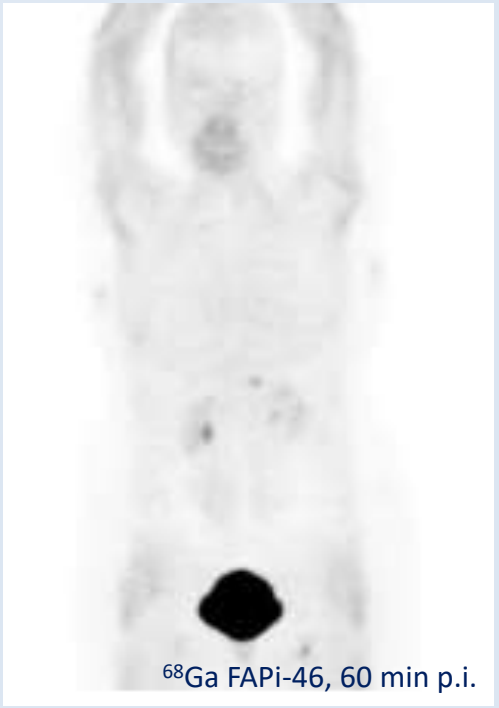
- ^{68}Ga labeled FAPIs show intense radioactivity in the urinary tract
- Moderate uptake observed in the submandibular gland, thyroid and pancreas
- Minimal uptake in brain, liver, lung, muscle etc.
- Nonspecific uptake at sites of wound healing



^{68}Ga FAPI-04, 50 min p.i.



^{68}Ga FAPi-46, 10 min p.i.



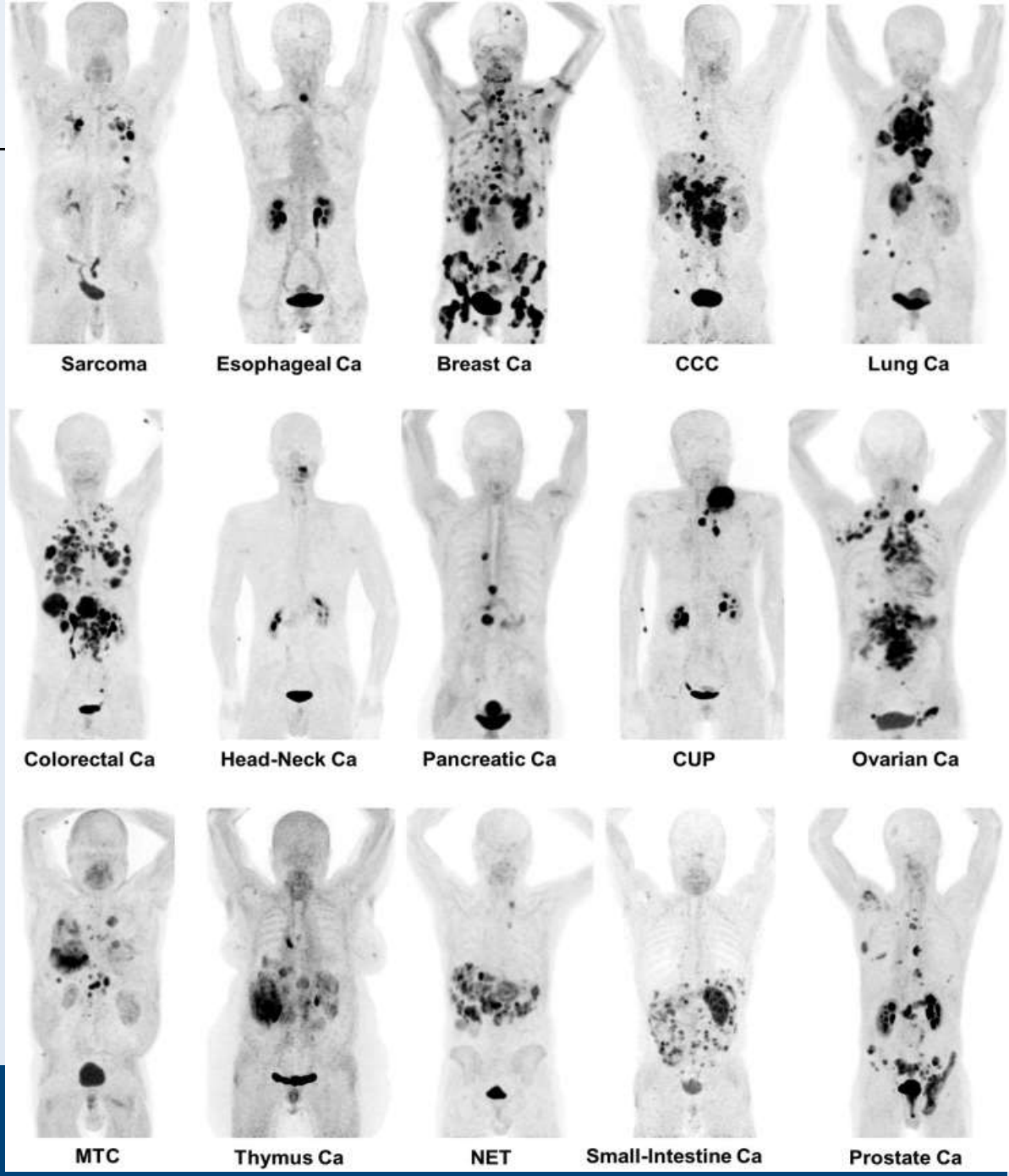
^{68}Ga FAPi-46, 60 min p.i.

Images adapted from Airo Farulla, L. S.; et al. *Clin. Transl. Imaging* **2023**, *11*, 95

FAPI Use in Oncology

- ^{68}Ga labeled FAPIs have been used for imaging of a variety of cancers and have been compared with other imaging radiotracers or modalities
- Potential theranostic applications using ^{90}Y, ^{177}Lu, ^{225}Ac

^{68}Ga FAPI-4, 60 min p.i.

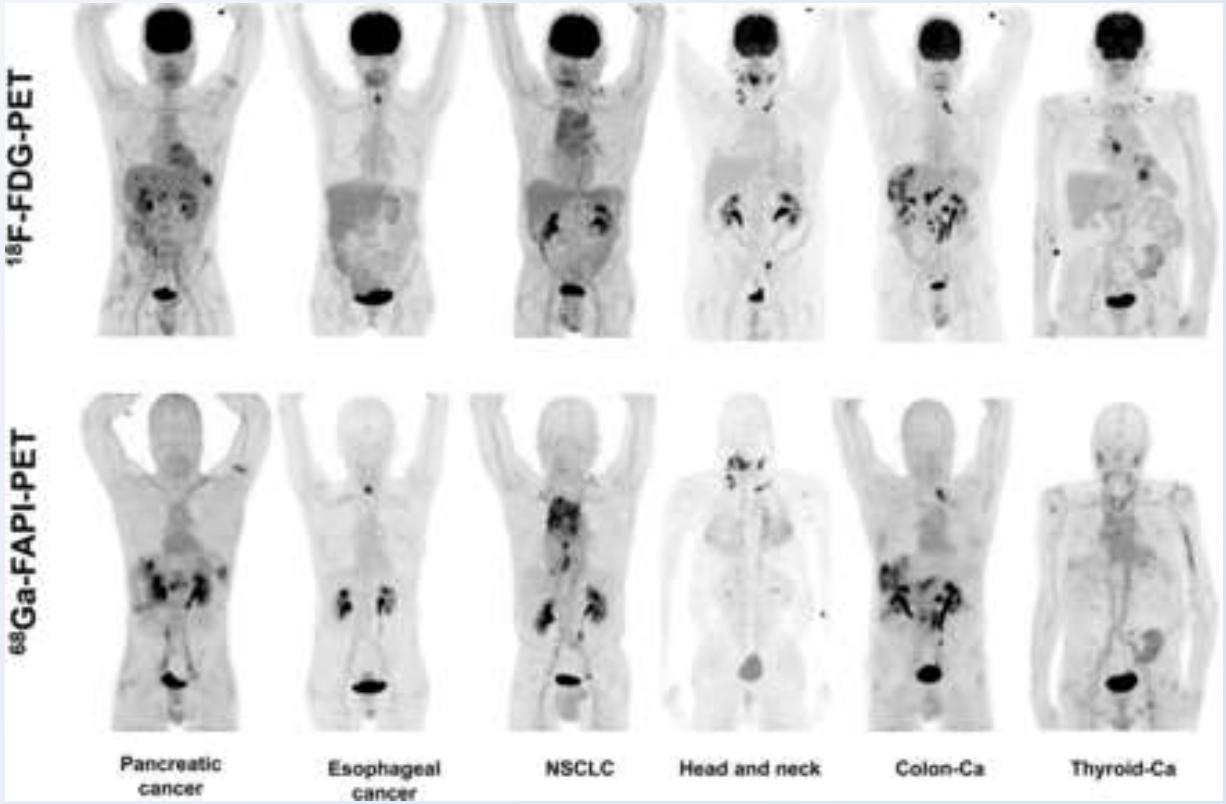


Kratochwil, C.; et al. *J. Nuc. Med.* **2019**, *60*, 801
Abdou Sidrak, M. M.; et al. *Int. J. Mol. Sci.* **2023**, *24*, 3863

Image adapted from Kratochwil, C.; et al. *J. Nuc. Med.* **2019**, *60*, 801

FAPI Use in Oncology

- FAPI performs better than FDG: esophageal, breast, lung cancer, cholangiocellular carcinoma, sarcoma
- FDG performs better than FAPI: thyroid cancer, lymphoma, multiple myeloma
- No differences in performance: prostate, head and neck cancer



^{68}Ga FAPi-2, 60 min p.i.

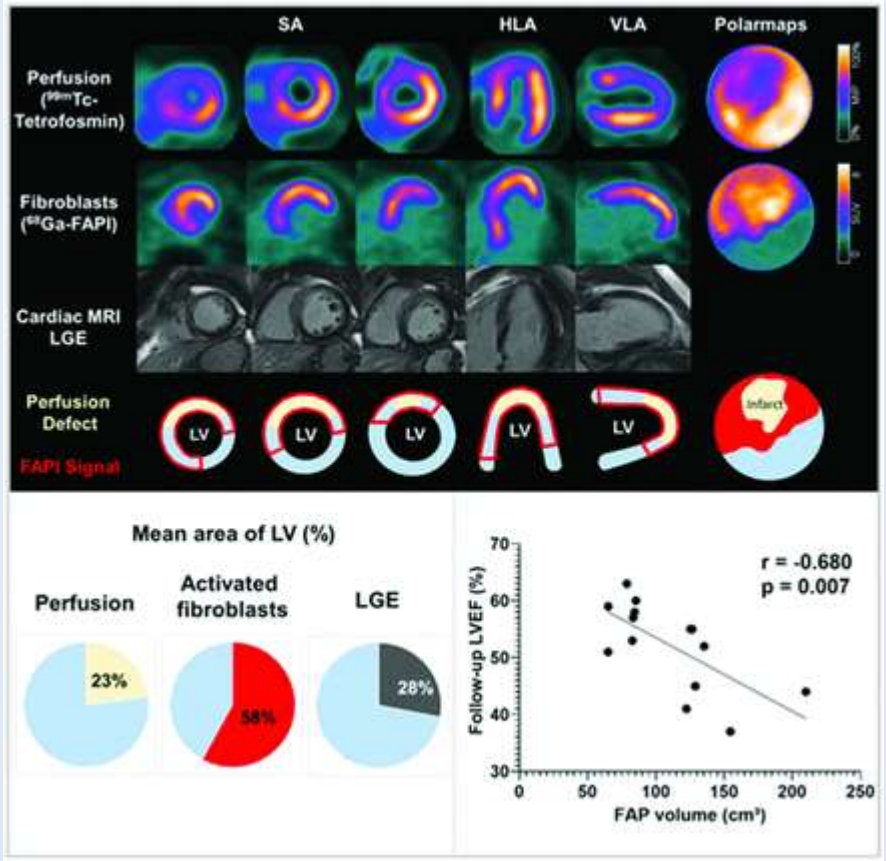
Giesel, F. L.; et al. *J. Nuc. Med.* **2019**, *60*, 386

Image adapted from Giesel, F. L.; et al. *J. Nuc. Med.* **2019**, *60*, 386

FAPI Use in non-Oncologic Applications

- Activated fibroblasts found in scar formation, chronic inflammatory processes, fibrosis and benign tumors
- Preliminary studies show potential use of FAPI for imaging liver, kidney and lung fibrosis
- FAPI was evaluated early in patients with acute myocardial infarction and showed a significantly elevated signal in the territory of the culprit infarct vessel compared to SPECT and Cardiac MRI
- Study suggests a relationship between the extent of fibroblast activation and more severe adverse ventricular remodeling

^{68}Ga FAPi-46, 60 min p.i.



SNMMI 2022 Image of the year

Diekmann, J.; et al. *J. Nuc. Med.* **2022**, *63*, 1415

Radionuclide Tracers for Myocardial Perfusion Imaging

Myocardial Perfusion Imaging (MPI)

- Noninvasive tool for the diagnosis and risk stratification of Coronary Artery Disease (CAD)
- Both SPECT and PET routinely used for evaluation of MPI
- Diagnostic and prognostic value of MPI significantly improved due to:
  - Technical improvements of SPECT cameras
  - Availability of PET radiotracers
- SPECT represents the most common practice
  - Lower cost
  - Availability of SPECT cameras
- PET imaging considered the gold standard
  - Higher spatial resolution
  - Ability to obtain attenuation correction

Mannarino, T.; et al. *Cardiol. Clin*. **2023**, 10.1016/j.ccl.2023.01.003

Tracers for Myocardial Perfusion Imaging (MPI)

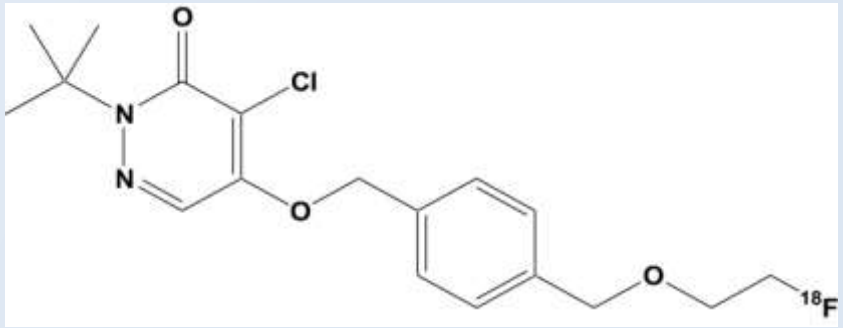
- Exercise or pharmacologic stress is a power tool for imaging of myocardial ischemia and infarction
- Tracers should have the ability to be taken up by the tissue and irreversibly retained
- Ideal tracer:
  - High first-pass extraction fraction
  - Linear correlation to coronary blood flow
  - Adequate myocardial retention
  - Isotope with favorable dosimetry, half-life and energy

Tracer	Modality	Half-Life	First-Pass Myocardial Extraction
^{15}O Water	PET	2 min	100%
^{13}N Ammonia	PET	10 min	80%
^{82}Rb	PET	72 sec	70%
^{18}F Flurpiridaz	PET	2 h	94%
^{99m}Tc Sestamibi	SPECT	6 h	68%
^{99m}Tc Tetrofosmin	SPECT	6 h	54%

Mannarino, T.; et al. *Cardiol. Clin*. **2023**, 10.1016/j.ccl.2023.01.003

^{18}F Flurpiridaz

- Currently in Phase III clinical trials
- Binds to mitochondrial complex 1
- Has higher extraction rate than other available PET and SPECT tracers
- Could be used for patients that require exercise stress test
- ^{18}F half-life can lead to commercial distribution
- Phase I trial showed that flurpiridaz is safe with acceptable dosimetry
- Phase II trial revealed improved coronary artery disease diagnostic performance, image quality and confidence of interpretation when compared to SPECT



Mannarino, T.; et al. *Cardiol. Clin.* **2023**, 10.1016/j.ccl.2023.01.003
Maddahi, J.; et al.; *J. Am. Col. Card.* **2020**, *76*, 391

^{18}F Flurpiridaz Phase III Trial

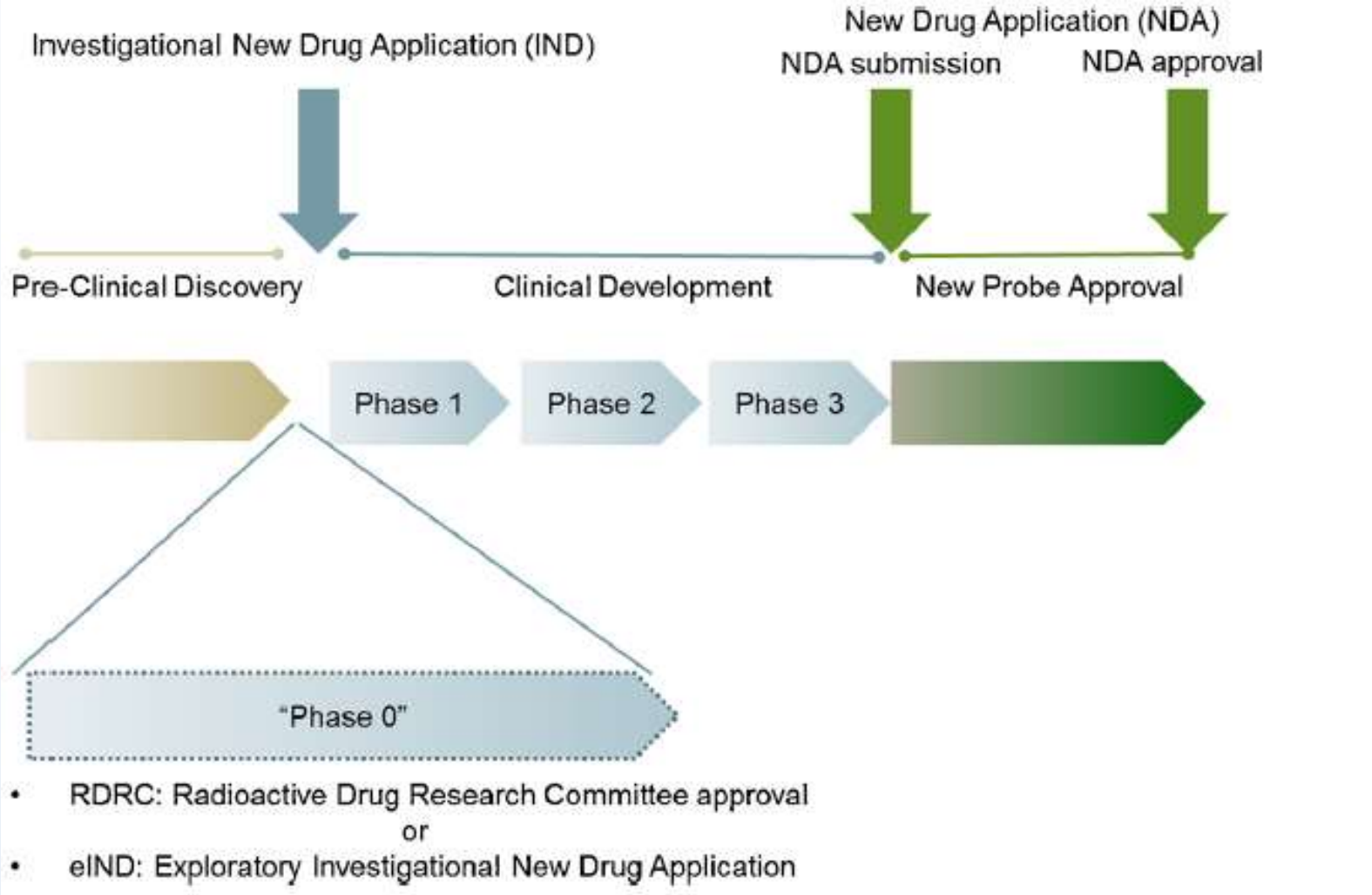
To evaluate the diagnostic performance of flurpiridaz versus SPECT for the detection and evaluation of coronary artery disease (CAD) (≥50% stenosis by quantitative invasive coronary angiography)

- Flurpiridaz showed improved sensitivity in detecting coronary CAD compared to SPECT (71.9% vs 53.7%, $p < 0.001$)
- Specificity did not meet the noninferiority criterion (76.2% vs 86.6%)
- Inter- and intrareader agreements were high
- Flurpiridaz showed higher sensitivity in identifying multivessel disease (41% vs 27.5%, $p < 0.001$)
- Image quality for PET was significantly higher than for SPECT for both rest and stress images (89.1% vs 73.9%, $p < 0.01$ and 97.6% vs 86.9%, $p < 0.01$)
- Diagnostic certainty was higher
- Radiation exposure was less for PET compared to SPECT
- 7.4% of adverse events were evaluated as possibly related to flurpiridaz, none serious
- 0.5% of adverse events were related to flurpiridaz (dysgeusia and injection site pain)

Mannarino, T.; et al. *Cardiol. Clin.* **2023**, 10.1016/j.ccl.2023.01.003
Maddahi, J.; et al.; *J. Am. Coll. Cardiol.* **2020**, *76*, 391

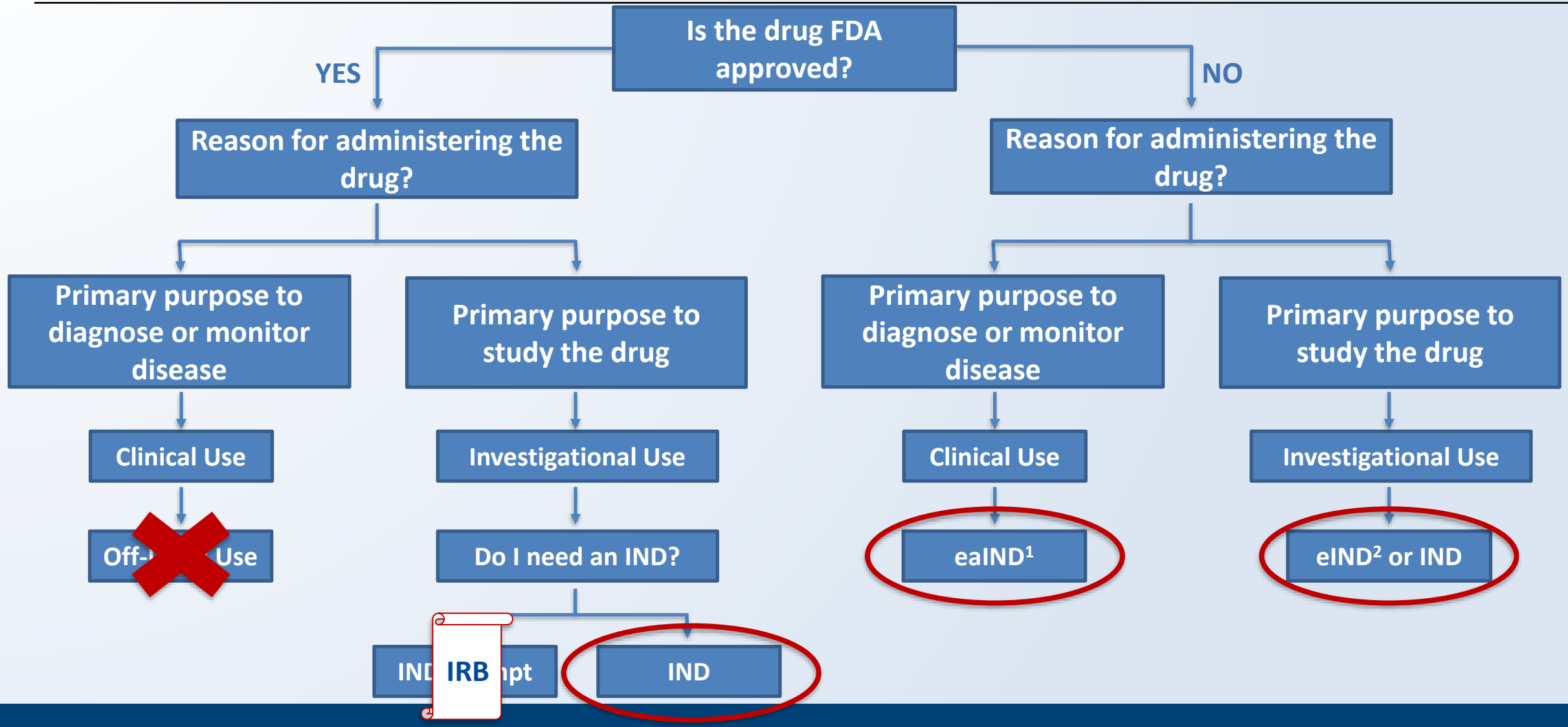
Radiopharmaceuticals Lifecycle

Premarketing Pharmaceuticals Lifecycle



Mosessian, S. et al. *Molecular Imaging & Biology* **2014** *16*, 441

Do I need an IND?



[1] ea = expanded access
[2] e = exploratory

Clinical Investigations Exempt from IND Requirements

The sponsor is responsible to determine whether the study is exempt

- Certain Research Involving Marketed Drug Products
- Bioavailability or Bioequivalence Studies in Humans

➢ **Certain Research Involving Marketed Drug Products**

Depends on intent of investigation and degree of risk. Exempt if **ALL** apply:

✓ Drug lawfully marketed in the US

✓ Not intended to support new indication or changing the label of the drug

✓ Not intended for a significant change in the advertising of the drug

✓ Does not involve a route of administration, dose, patient population or other factor that increases the risk

✓ Is in compliance with the IRB review and informed consent

✓ Not intended to promote or commercialize the product

Information Needed in INDs

- Preclinical data – Animal pharmacology, toxicology and dosimetry studies
- Drug manufacturing information – Site specific
- Clinical Protocol
- Investigator information – Site specific

Pre-IND Consultation Program

CDER's Pre-IND Consultation Program enables early communication between sponsors and the FDA's review divisions to provide guidance on the data necessary for a successful IND submission

- Data needed to support the rationale for testing a drug in humans;
- Design of nonclinical pharmacology, toxicology, and drug activity studies
- Initial drug development plans, and regulatory requirements for demonstrating safety and efficacy

https://www.fda.gov/drugs/investigational-new-drug-ind-application/pre-ind-consultation-program

IND Content

Required Forms:

- Form 1571: contact information and specified commitments
- Form 1572: Investigator, institution, IRB etc. information
- Form 3674: Certification of Compliance

At a minimum an IND should contain:

- Table of contents
- Introductory Statement
- General Investigation Plan
- Investigator's Brochure

Note: An Investigator's Brochure is not required for sponsor-investigators

- Clinical Protocol
- Chemistry, Manufacturing and Controls
- Pharmacology and Toxicology
- Summary of Previous Human Experience
- Other Relevant Information (Radiation Absorbed Dose)

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-applications-clinical-investigations-regulatory-and-administrative-components

Exploratory and Traditional IND

- An eIND applies to early Phase 1 (Phase 0) studies to access feasibility for further development.
  - Involves very limited human exposure to the drug (dosing < 7 days)
  - Studies have no therapeutic or diagnostic intent (microdose studies)

- Examples of exploratory IND studies:
  - Determine if mechanism of action defined by animal studies is also observed in humans
  - Pharmacokinetics or biodistribution of the investigational drug
  - Select most promising product for further development

- A traditional IND applies to Phases 1 – 3 studies to evaluate safety and/or effectiveness of a non-approved drug in humans for a potential diagnostic or therapeutic indication

- Microdose is defined as less than 1/100th of the dose of a substance calculated to yield a pharmacologic effect (based on animal data) of the test substance with a maximum dose of less than or equal to 100 micrograms (µg). The maximum dose for protein products is less than or equal to 30 nanomoles (nmol).

- Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies (January 2006)
- Guidance: Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs (December 2012)
- Draft Guidance for Industry: Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators (May 2015)

Microdose Radiopharmaceutical Diagnostic Drugs

Unique nature of PET drugs:

Radioactive, single dose, microdose

- Facilitate the timely conduct of clinical trials
- Reduce use of animals
- Reduce use of drug development resources

Table 1: Recommendations for Nonclinical Studies for Microdose (≤ 100 µg) Radiopharmaceutical Diagnostic Drugs

Study Type	Phase	Comments
Pharmacology	Before phase 1	These studies can include in vivo and in vitro pharmacologic characterizations (e.g., receptor/target/off-target profiling, imaging/radiation dosimetry studies). These studies should provide evidence that radiolabeling of an unlabeled moiety does not significantly alter pharmacologic characterizations. The studies should be of sufficient sensitivity to rule out pharmacologic effects at the anticipated clinical dose.
Extended single-dose toxicity in one species (usually a rodent)	Before phase 1	FDA accepts the use of extended single-dose toxicity studies in animals to support single-dose clinical trials in humans. When a toxicity study is recommended, a sponsor can use a single mammalian species (both sexes). The route of exposure in animals should be the intended clinical route.* To establish safety margins, the sponsor should use a formulation that is as similar as possible to the formulation intended for use in clinical trials for marketing approval.**

Table 1, continued

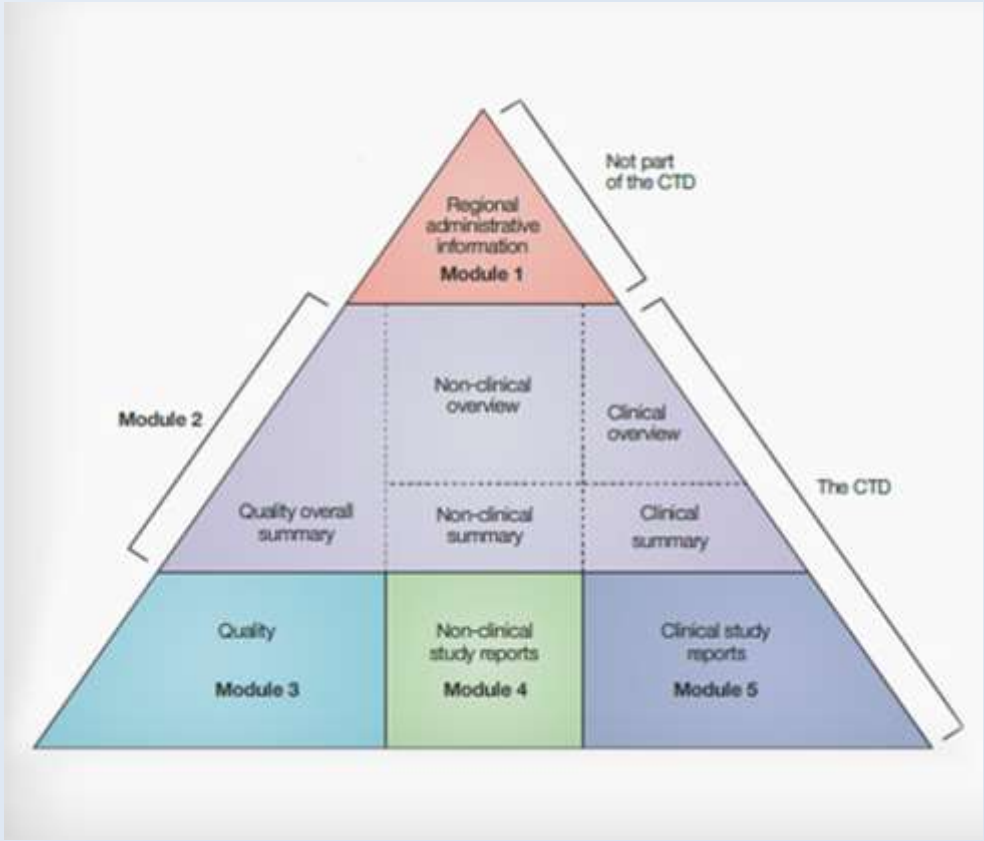
Study Type	Phase	Comments
Genotoxicity	Not needed	The exploratory IND guidance states, "Because microdose studies involve only single exposures to microgram quantities of test materials and because such exposures are comparable to routine environmental exposures, routine genetic toxicology testing is not needed." This applies to any phase of clinical development when considering that the mass dose remains the same through marketing approval. Genotoxicity risk could be, by default, incorporated in labeling language regarding radiation exposure risk.
Safety pharmacology	Not needed	Safety pharmacology studies are not recommended because of the low subpharmacologic dose.
Repeat dose toxicity	Not needed	
Pharmacokinetic	Before phase 3	Information on pharmacokinetics (e.g., absorption, distribution, metabolism, excretion) in test species and in vitro biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects to the investigational drug.
Developmental and reproductive toxicity	Waiver obtained as per § 312.10	With a waiver, these studies are not necessary because of the inherent radiation risk to the fetus from the radiopharmaceutical drug, which would be reflected in labeling.
Special toxicity	As per ICH M3(R2)	FDA does not recommend investigating IV local tolerance of a drug substance for microdose studies. The use of novel vehicles or excipients should be governed by applicable ICH and FDA guidances for industry.

- Guidance for Industry: Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (August 2018)

New Drug Applications (NDA)

- NDA is the approval pathway for new drugs that are to be marketed and sold in the US (21 CFR part 314)
- Required for a New Molecular Entity or an Indication not FDA approved
- Requires submission of: preclinical studies, clinical studies, manufacturing processes, quality control
- Application must be submitted in CTD format:

The International Conference of Harmonisation (ICH) developed the CTD structure in order to create a standardized way to organize information within a submission



Abbreviated New Drug Applications (ANDA)

- ANDA is the approval pathway for generic drugs that are to be marketed and sold in the US (21 CFR part 314)
- DOES NOT require data from: animal studies and clinical studies
- DOES Require:
  - To be comparable to a Reference Listed Drug (RLD) in: characteristics, dosage, formulation, intended use, quality, administration, strength
- A Reference Listed Drug is a drug product approved in a New Drug Application under Section 505(c) of the FD&C Act based on full reports of investigations of safety and effectiveness

FDA Review and Approval

- The review team has 6 to 10 months to make a decision on whether to approve the drug. The process includes the following:
  - each member of the review team conducts a full review of his or her section of the application there is also a supervisory review
  - FDA inspectors travel to clinical study sites to conduct a **routine inspection**. The Agency looks for evidence of fabrication, manipulation, or withholding of data
  - The project manager assembles all individual reviews and other documents, such as the inspection report, into an "action package." This document becomes the record for FDA review. The review team issues a recommendation, and a senior FDA official makes a decision

- Based on a recent report, CDER's average time for approval in 2022 was 17.7 months

- On average it takes 10 years and millions of dollars to get a new drug approved by FDA

Thank you