Present and Future: Production of PET Radiopharmaceuticals, Regulatory Requirements & Clinical Use

American Association of Physicists in Medicine

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SCHOOL OF MEDICINE
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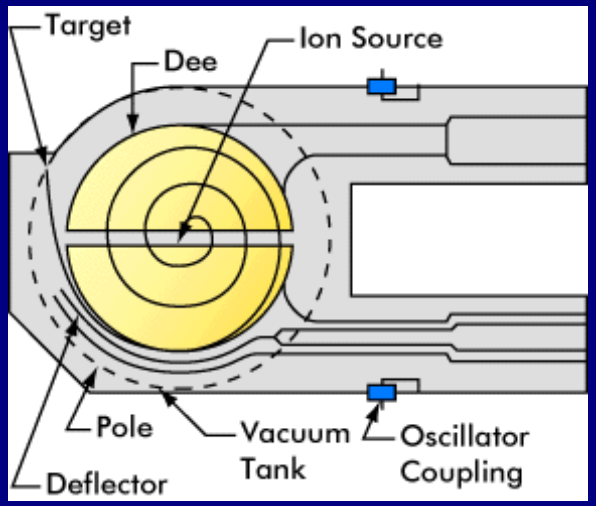
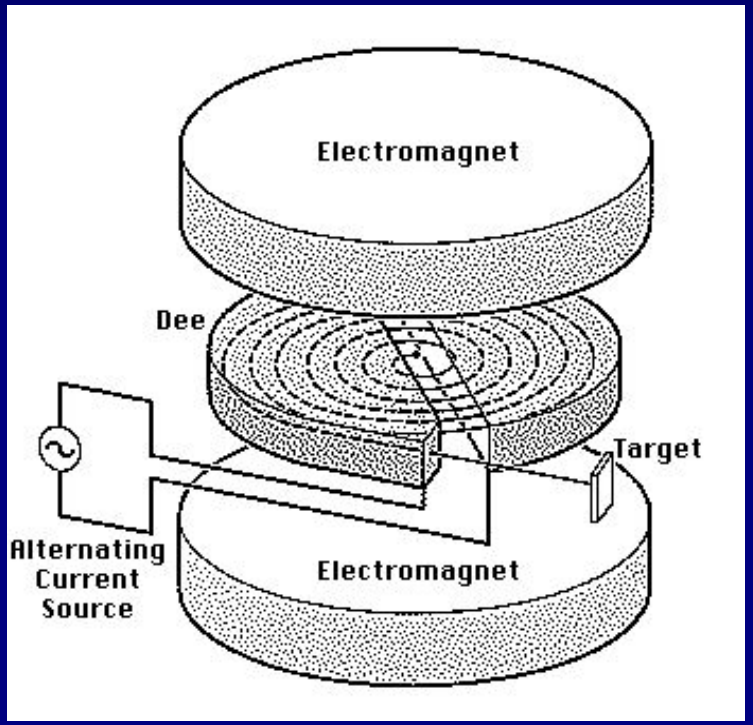
Overview

- Basics of cyclotron function
- Production of PET radiopharmaceuticals (RaPh)
- Historical overview of PET regulatory & FDA approval process
- Clinical PET drugs
- Investigational PET RaPh
- Future vision of PET drug commercialization

Cyclotron





Common PET Isotopes

$^{18}O(p,n)^{18}F$	$t_{½}$ = 109.7 min
$^{14}N(p,\alpha)^{11}C$	$t_{½}$ = 20.3 min
$^{16}O(p,\alpha)^{13}N$	$t_{½}$ = 9.97 min
$^{14}N(d,n)^{15}O$	$t_{½}$ = 2.0 min

Targets for Cyclotron Produced Nuclides

1. Gases:
   - $^{14}N(d,n)^{15}O$ ($H_2{}^{15}O$, $^{15}O_2$)
   - $^{15}N(p,n)^{15}O$
   - $^{14}N(p,\alpha)^{11}C$ (^{11}C-acetate, ^{11}C-choline)
   - $^{18}O(p,n)^{18}F_2$ (^{18}F-FDOPA)

2. Liquids:
   - $^{18}O(p,n)^{18}F$ (^{18}FDG, ^{18}F-FDOPA)
   - $^{16}O(p,\alpha)^{13}N$ (^{13}N-ammonia)

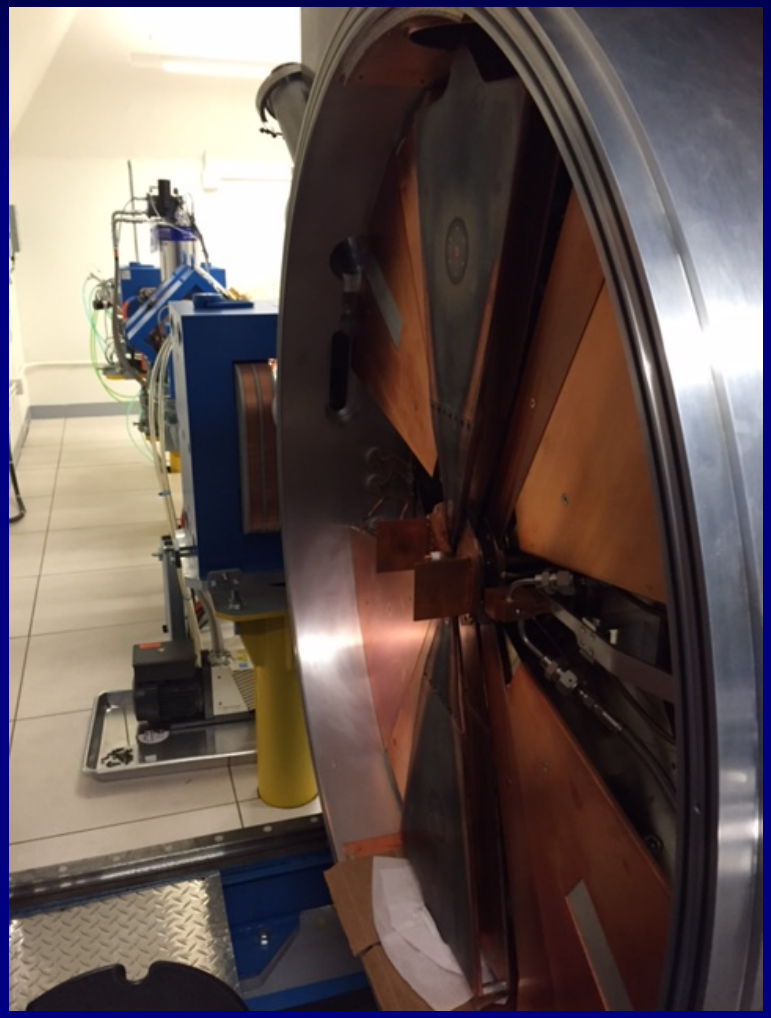
3. Metals:
   - $^{64}Ni(p,n)^{64}Cu$ (^{64}Cu-ATSM)

TR-19 Cyclotron: Isotope Production Capacity

TR19 can accelerate 200 µA protons from 14-19 MeV
or 50µA deuterons from 8- 9 MeV beam

Isotope (form)	Bombardment	Yield (Ci) Spec./Desired/Actual
C-11 CO_2	16 MeV 40µA proton 30 minutes	4.0/3.0/3.2
F-18 Fluoride	16 MeV 80 µA proton 120 minutes	10/8.0/10
N-13 NH_3	16 MeV 40 µA proton 120 minutes	1.0/0.5/
O-15 Oxygen	8MeV 40µA deuterons 4 minutes	-/0.6/
Solid Target	Varies	Depends on target thickness

TR-19 Cyclotron: Dees



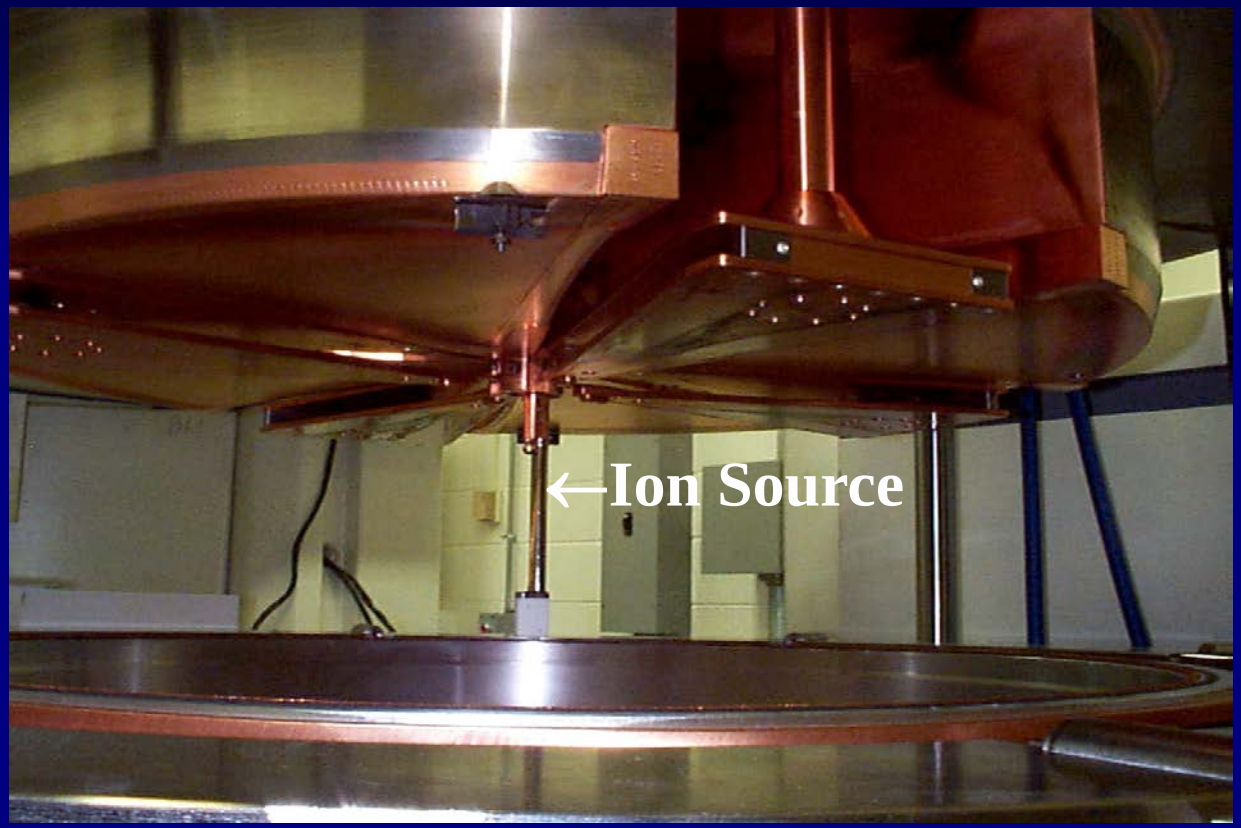
RDS Eclipse 11 MeV: 60µA proton dual beam

Isotope (form)	Bombardment	Yield (Ci) Desired/Actual
C-11 CO_2	11 MeV 60µA proton *60 minutes (dual)	3.0/3.6*
F-18 Fluoride	11 MeV 60 µA proton *120 minutes (dual)	6.0/7.5*
N-13 NH_3	11 MeV 60 µA proton 120 minutes	0.2/0.22
O-15 Oxygen	8MeV 60µA protons 8 minutes	2.0/2.0

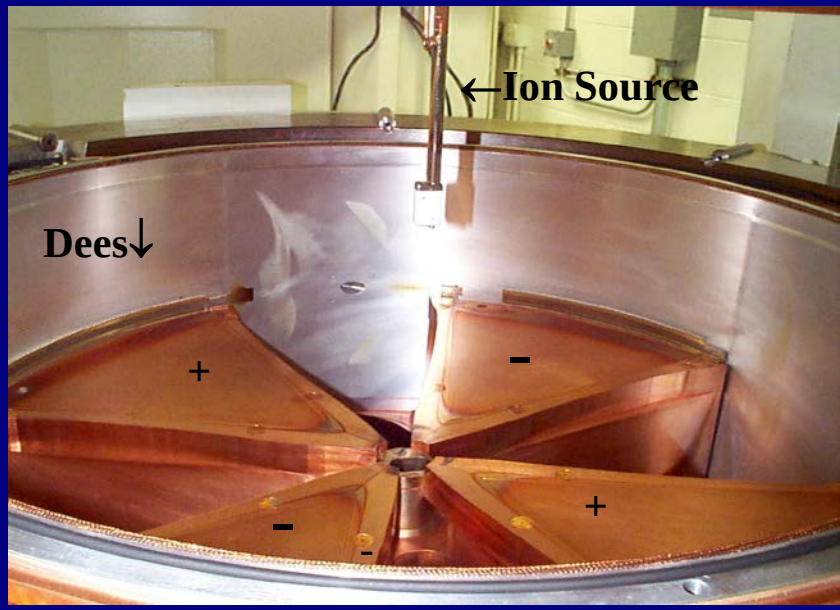
*** Dual Bombardment**

RDS Eclipse Shielding

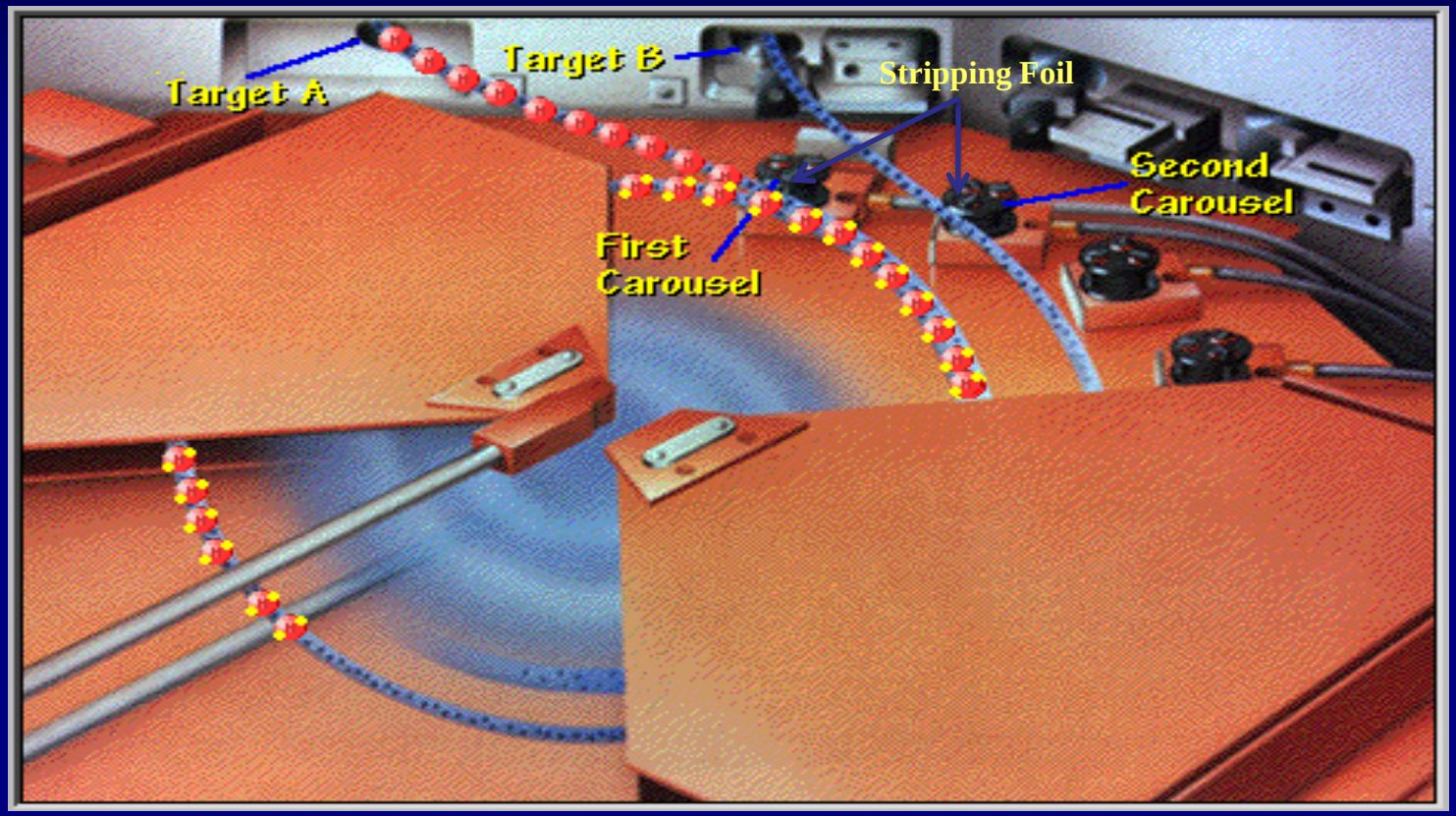
RDS Eclipse Ion Source



RDS Eclipse Dees

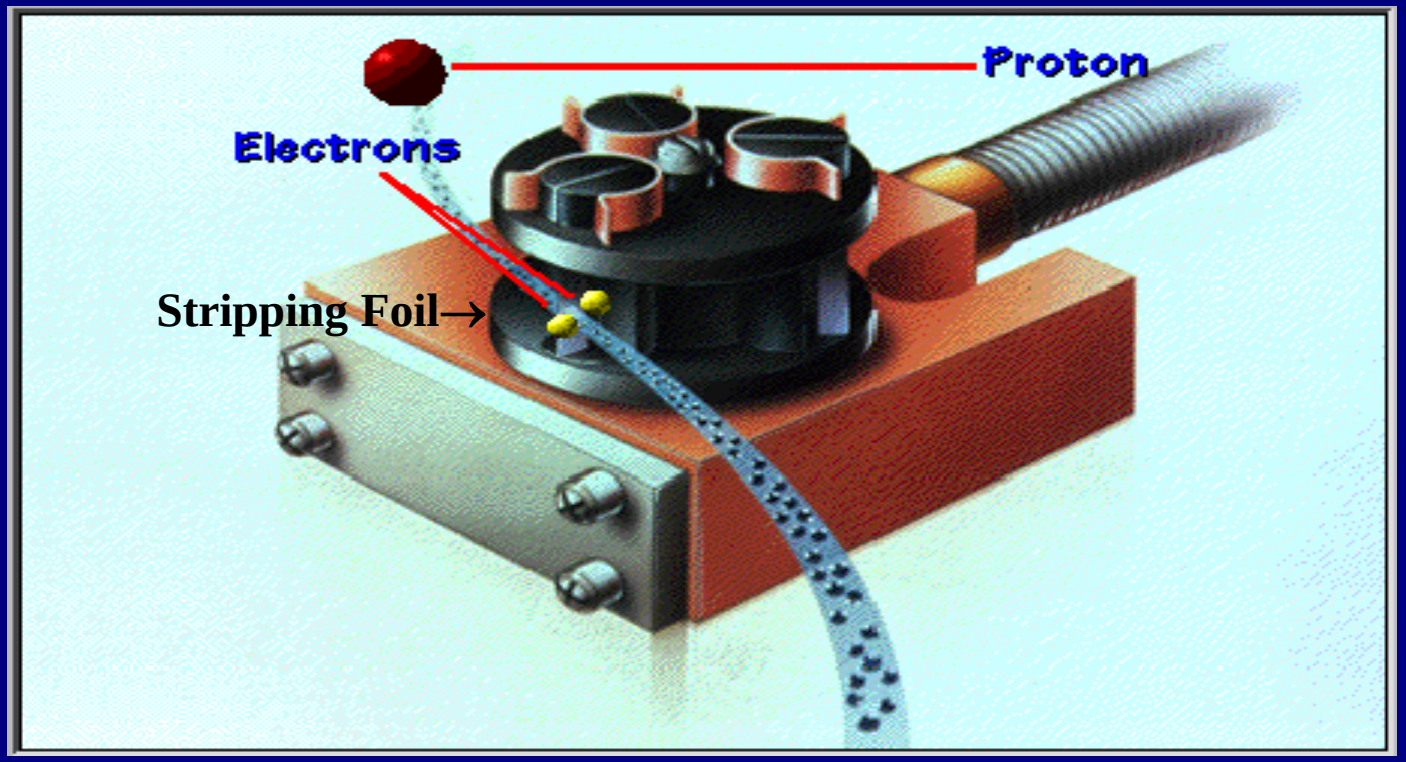


Two Target Irradiation Ports



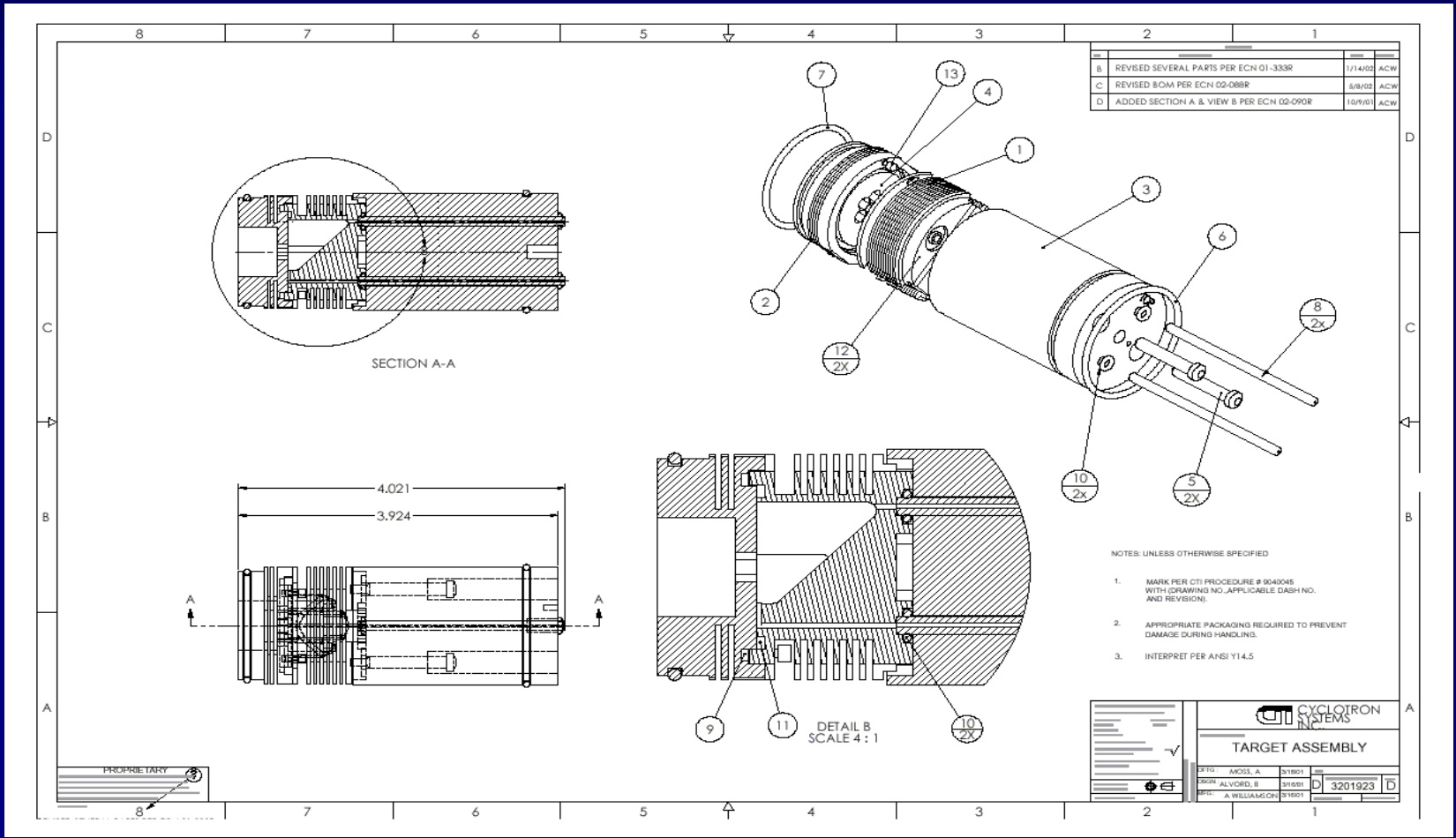
Negative Ion Machine

Stripping Foil

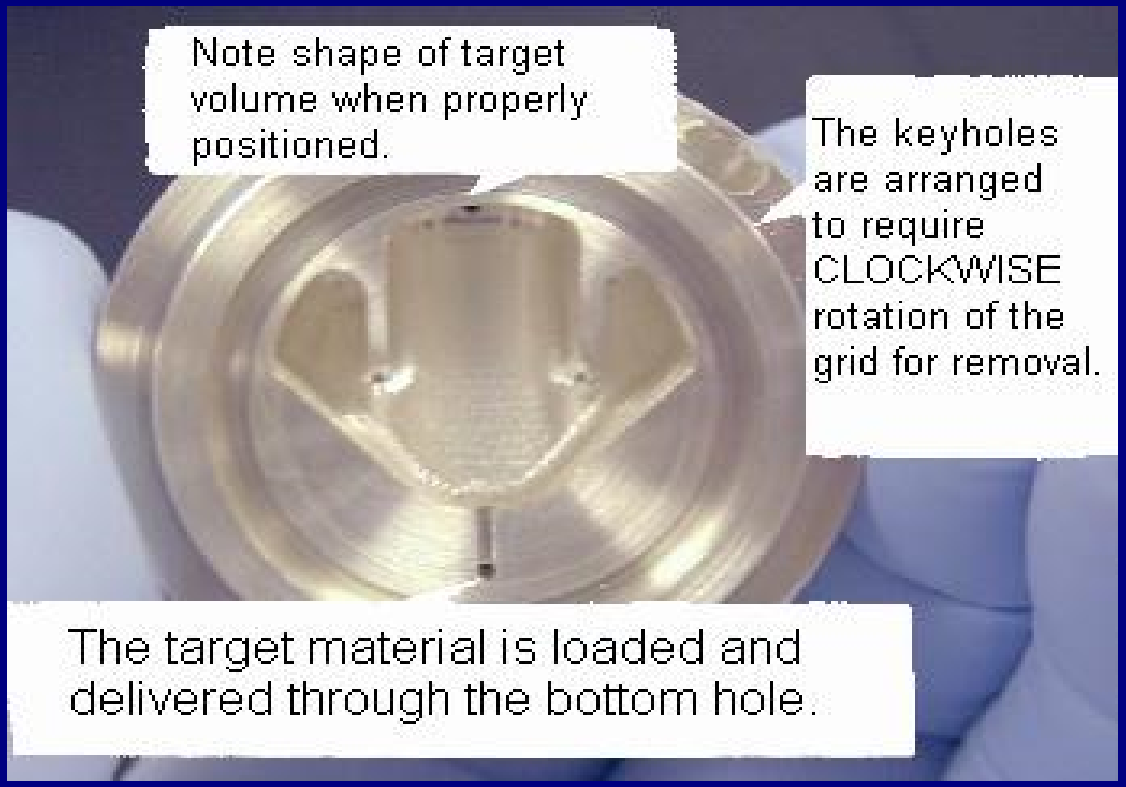


Carbon foil used to strip electrons from H^- ion

Eclipse High Pressure F-18 Target Assembly

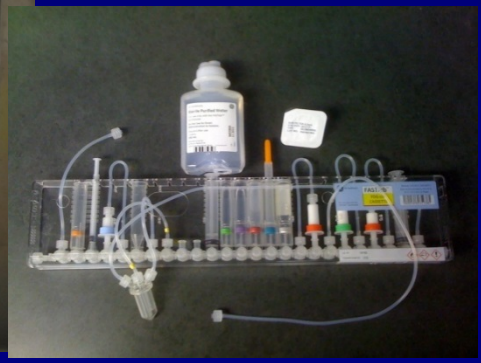


High Power Target Body



[^{18}F]FDG Synthesis Modules

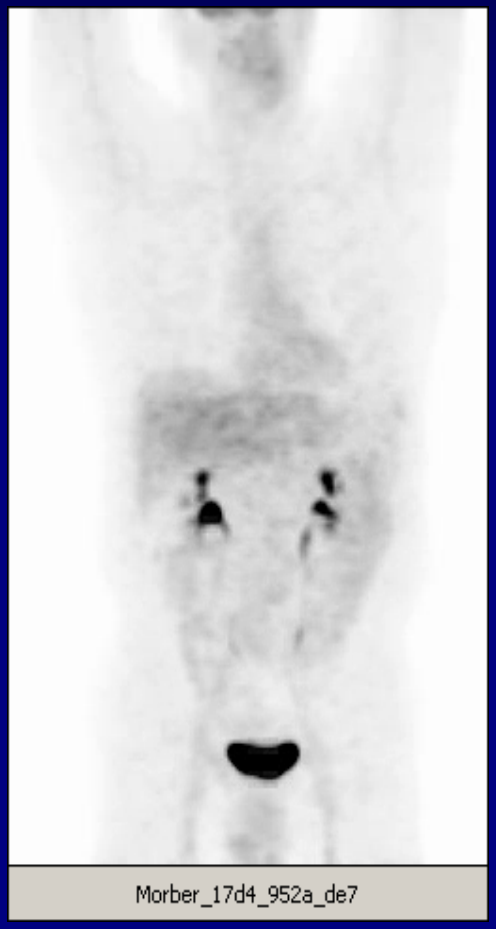
- GE FastLab (Citrate cassettes)
  Kryptofix® chemistry,
  Base hydrolysis



Citrate cassette

- GE FX_M
  Kryptofix® chemistry,
  Base hydrolysis

F-18 FDG Normal Whole Body Distribution



Prior to Injection:

Patient must be fasting 4-6 hours pi
Check serum glucose using Glucometer
Acceptable glucose < 150 mg/dL

- **Normal 80-120 mg/dL**
- **Steroids can raise glucose level**
- **Can go up to 200 mg/dL with MD approval**

Fludeoxyglucose F-18 Injection
Quality Control Pre-Release Testing

- Membrane Filter Integrity: Bubble point $\geq$ 50 psi
- Radionuclidic Identity : $T_{1/2}$ determination (105-115 min)
- 10 minute Dose Calibrator decay analysis
- pH = 4.5-7.5
- Radiochemical Purity : $\geq$ 90 % and Identity Analysis
  - ✓ TLC: Silica Gel; Solvent: Acetonitrile:Water (95:5)
- Residual Solvents: Gas Chromatography
  1. Acetonitrile: $\leq$ 0.04%./V* (0.41 mg/mL) (*FDG batch volume)
  2. Ethanol: $\leq$ 0.5%/V* (1-5 mg/mL)
- Chemical Purity: Kryptofix 222 Analysis: <50 ug/mL
- BET (Bacterial Endotoxin Test) $\leq$ 175units/V
- (V = maximum recommended total dose)

Post Release: Sterility Testing

US Food & Drug Administration Modernization Act (FDAMA) 1997

- 1997: US Food & Drug Modernization Act (FDAMA) required establishment of PET Radiopharmaceutical (RP) Good Manufacturing Practice (GMP) separate from traditional drugs (Part 211)
- FDAMA required a new approval path and separate Current Good Manufacturing Practices (CGMP) for PET from those cGMP for drugs
- Prior to adoption of final CGMP for PET rule, FDAMA required PET RP production to follow:

  USP General Chapter <823>, *Compounding of Radiopharmaceuticals for Positron Emission Tomography*

FDA Published Final Rule
21 CFR Part 212; Current Good Manufacturing (cGMP) for Positron Emission Tomography (PET) Drugs
December 10, 2009

- Regulation became effective June, 2012
- Regulation applies solely to PET drugs for routine clinical use
- Submission of an New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) required for all FDA approved PET drugs

- F-18 FDG, F-18 Sodium Fluoride, N-13 Ammonia considered safe & effective for certain uses when produced under conditions specified in approved applications

21 CFR Part 212; Final Rule cGMP for PET Drugs

June 10, 2012

- The rule §212.5(b) also provides that **investigational and research** PET drugs, cGMP may be met by producing PET drugs
  - in accordance with Part 212, or
  - in accordance with USP General Chapter <823>

    "*Radiopharmaceuticals for Positron Emission Tomography – Compounding*,"
  - Includes:
    1. PET Drugs produced under Investigational New Drug (**IND**) and
    2. PET Drugs approved through a Radioactive Drug Research Committee (**RDRC**)
  - FDA has indicated that IND Phase 0-1-2 are research. Phase 3 usually indicates moving to commercialization & must follow Part 212.

Current Good Manufacturing Practice (cGMP)

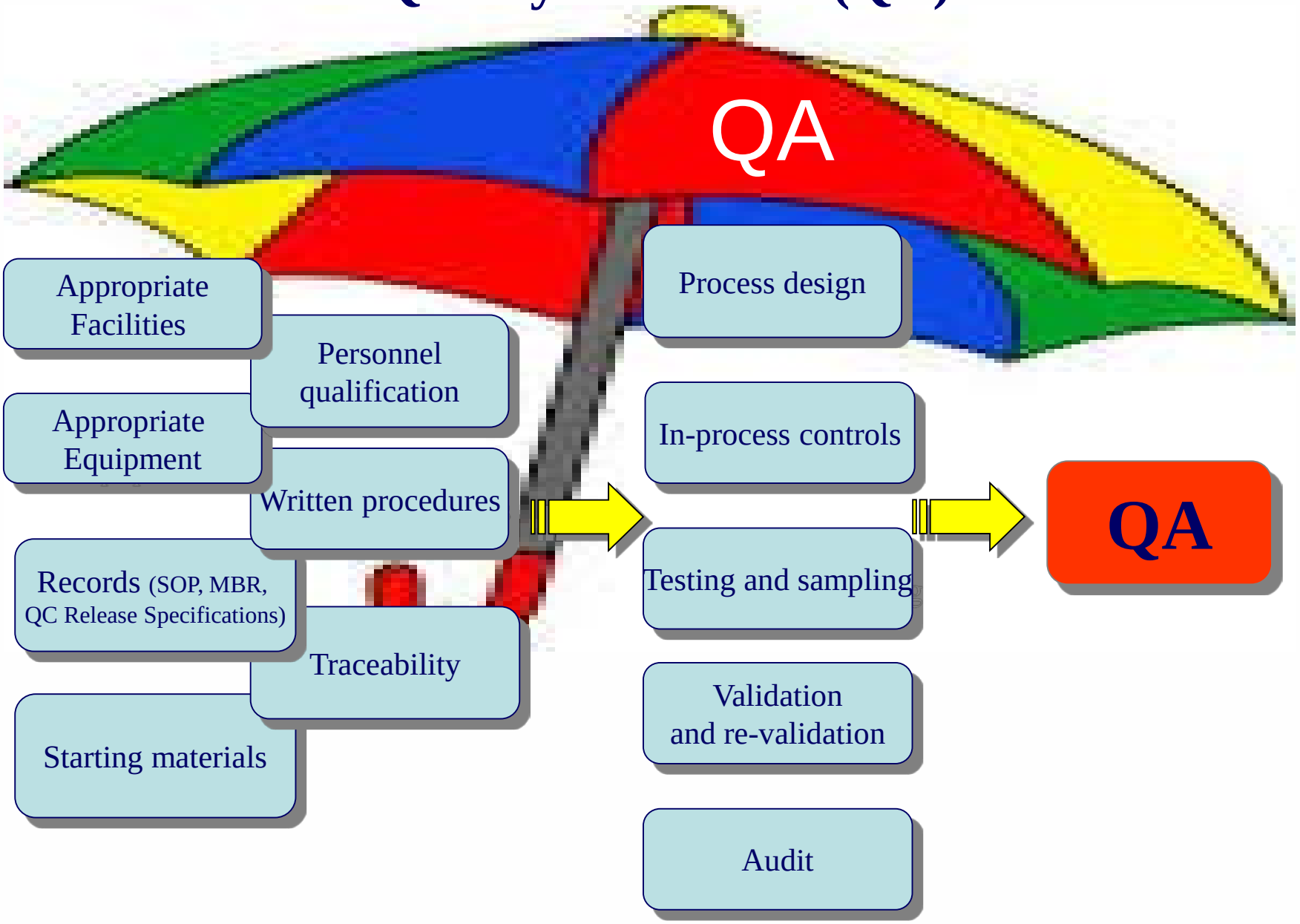
- What is Current Good Manufacturing Standards for PET Drugs (21 CFR **Part 212**)?
  - A rule (or regulation) that contains binding requirements that manufacturers must follow, and is enforceable in the courts.
  - CGMP is the **minimum standard** that each manufacturer must follow to produce the drug to help ensure a drug remains safe and effective over its labeled shelf-life.
    - ✓ Broad requirements-what you must do,
    - ✓ How to do, the details of compliance is detailed in manufacturer's SOPs

C = **current** practices employing up-to-date technology and the up to date version of the regulation

G = **good**: of a favorable character; adequate, satisfactory

MP = **manufacturing practices**: methods, facilities, and controls used in the preparation, processing, testing, packaging, or holding of a PET drug (Food Drug & Cosmetic Act)

Quality Assurance (QA)



Controlled PET Manufacturing Facility

Hotcell & ante-chamber

ISO Class 5
Laminar Air Flow Hood

Quality Control Area

ISO 7 Production Facility Hand Washing & Gowning

Handwashing

Gowning

Airlock

ISO Class 7 Facility

Biosafety Cabinets

ISO 5 Dispensing Hotcell

Pass through-
QC Laboratory
Shipping Area

Cardiac Perfusion Imaging

- N-13 Ammonia
- F-18 Flurpiridaz®

Nitrogen-13

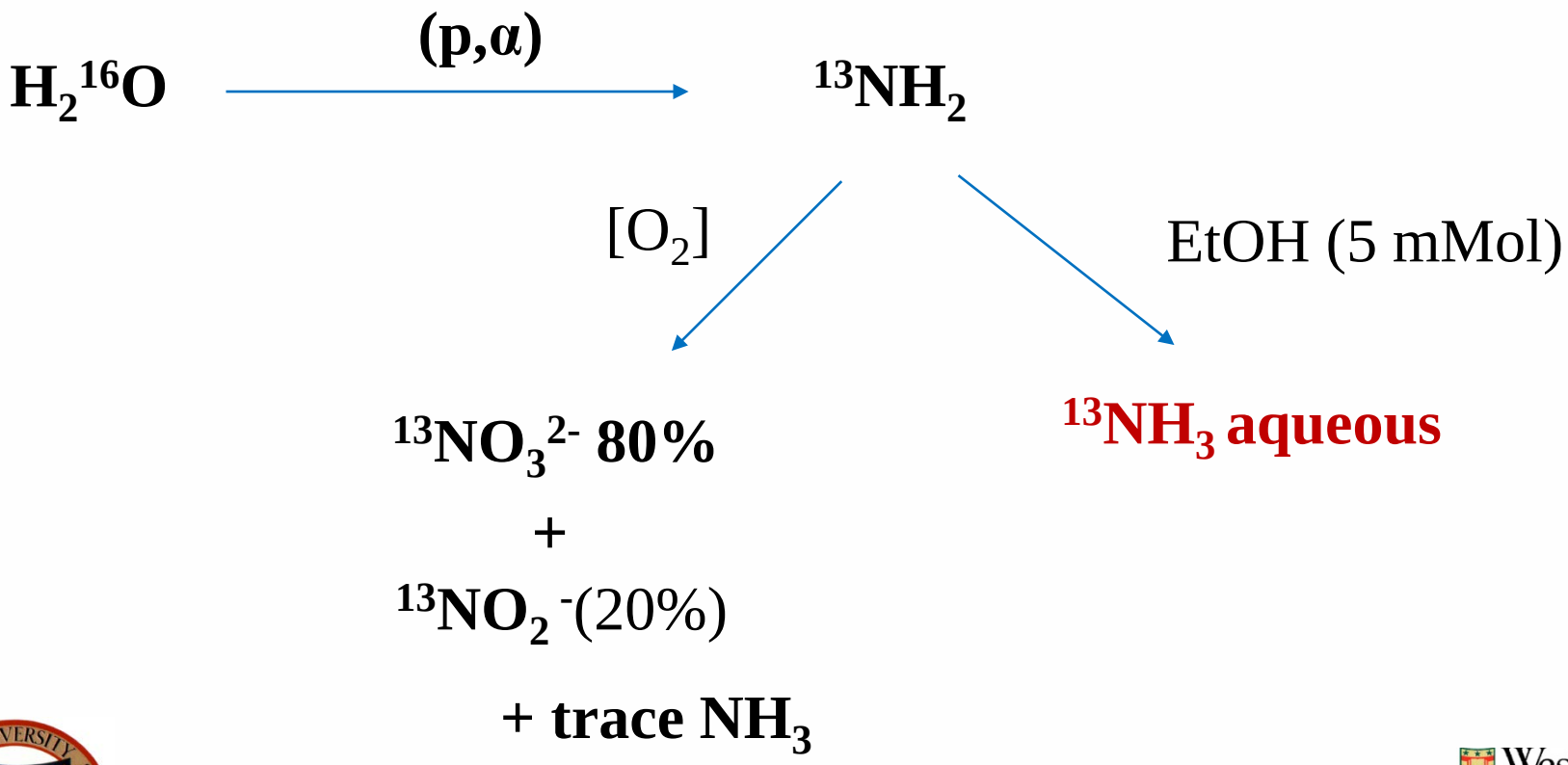
- **Half-Life** — **9.96 minutes**
- **Mode of Decay** — **β^+ (100%), $E_{\beta+\ max}$ 1.20 MeV**
- **Common Method of Production** — **$^{16}O(p,\alpha)^{13}N$**

Cardiac PET Perfusion Tracers for Clinical Use

N-13 Ammonia

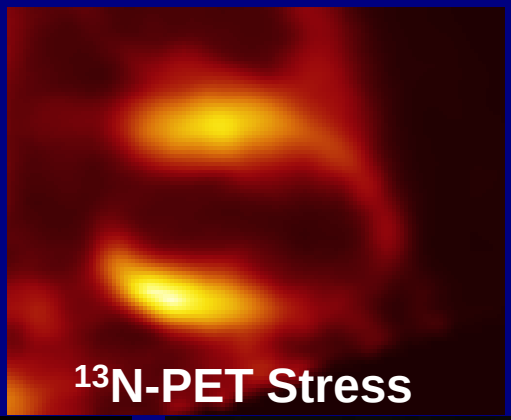
- FDA approved PET drug
- cyclotron-produced - half-life is 9.9 min
- complex uptake mechanisms: diffusion of uncharged lipophilic ammonia; fixed as ^{13}N-glutamine by enzymatic conversion of glutamic acid
- renal excretion

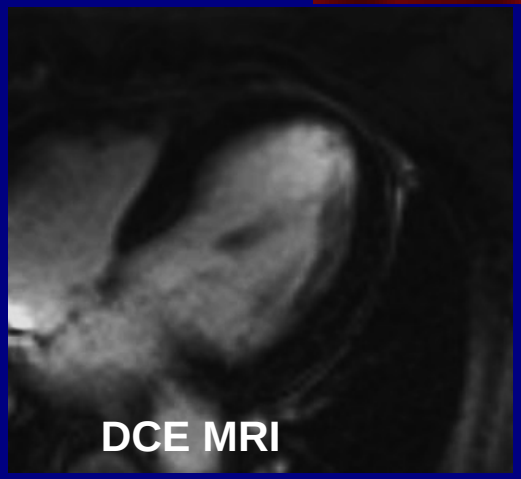
N-13 Ammonia Produced “In Target” Chemistry

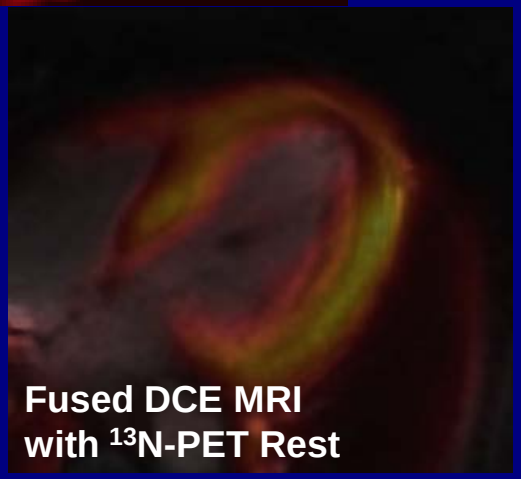


N-13 Ammonia: PET/MR

- 72 y/o woman with hx CAD and left arm pain and had Tc-99m SPECT positive for Myocardial Infarction
- Pharmacologic Stress PET MPI and LGE MRI shows ischemia but **NO infarction** *(Simultaneous injection of 10 mCi ^{13}N-ammonia and 0.075 mmol/Kg gadobenate dimeglumine, IV with simultaneous PET-MR acquisition.)*

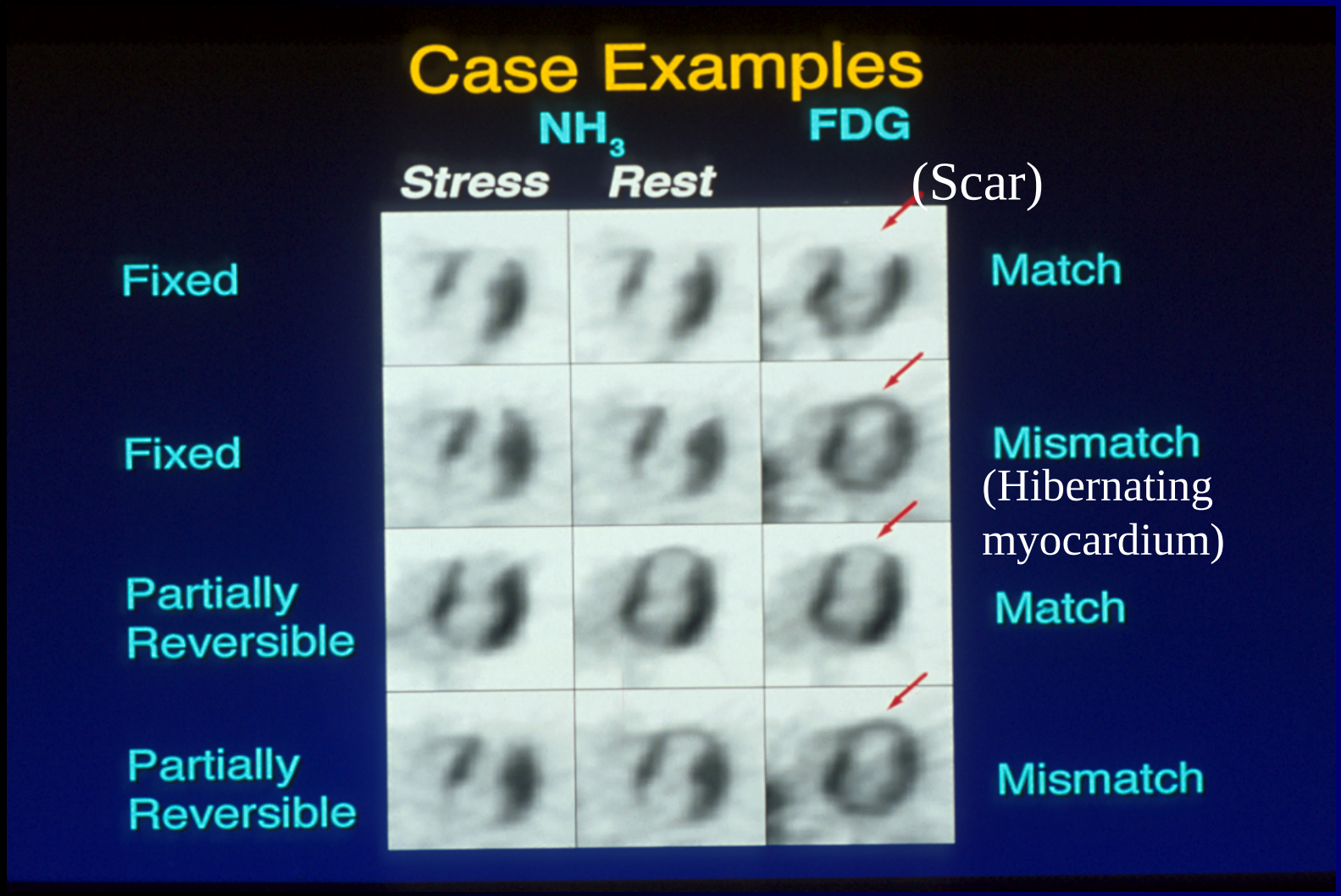






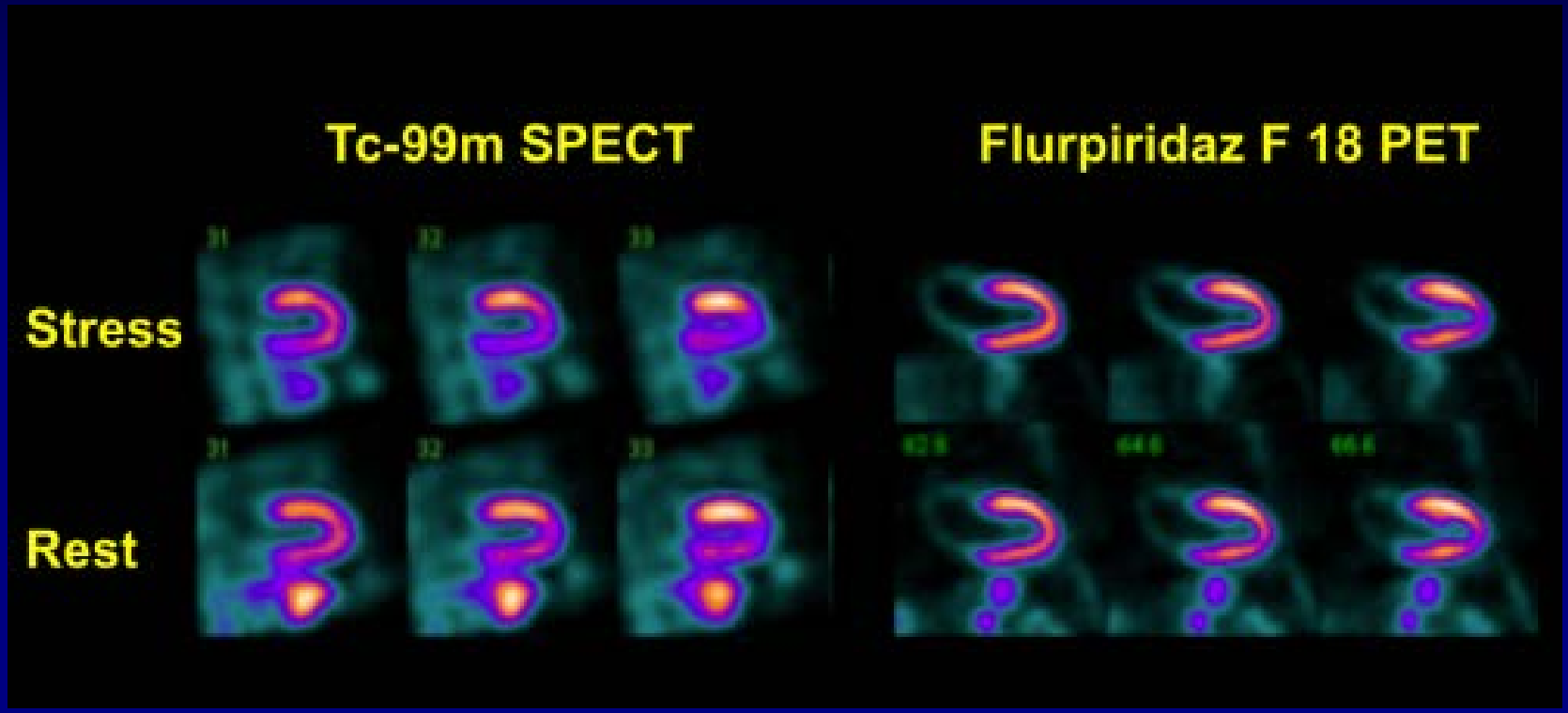
Lau J, et al. J Nuc Cardiol, 2013

Perfusion Image: $^{13}NH_3$
Metabolism: ^{18}FDG



Investigational Perfusion Agent

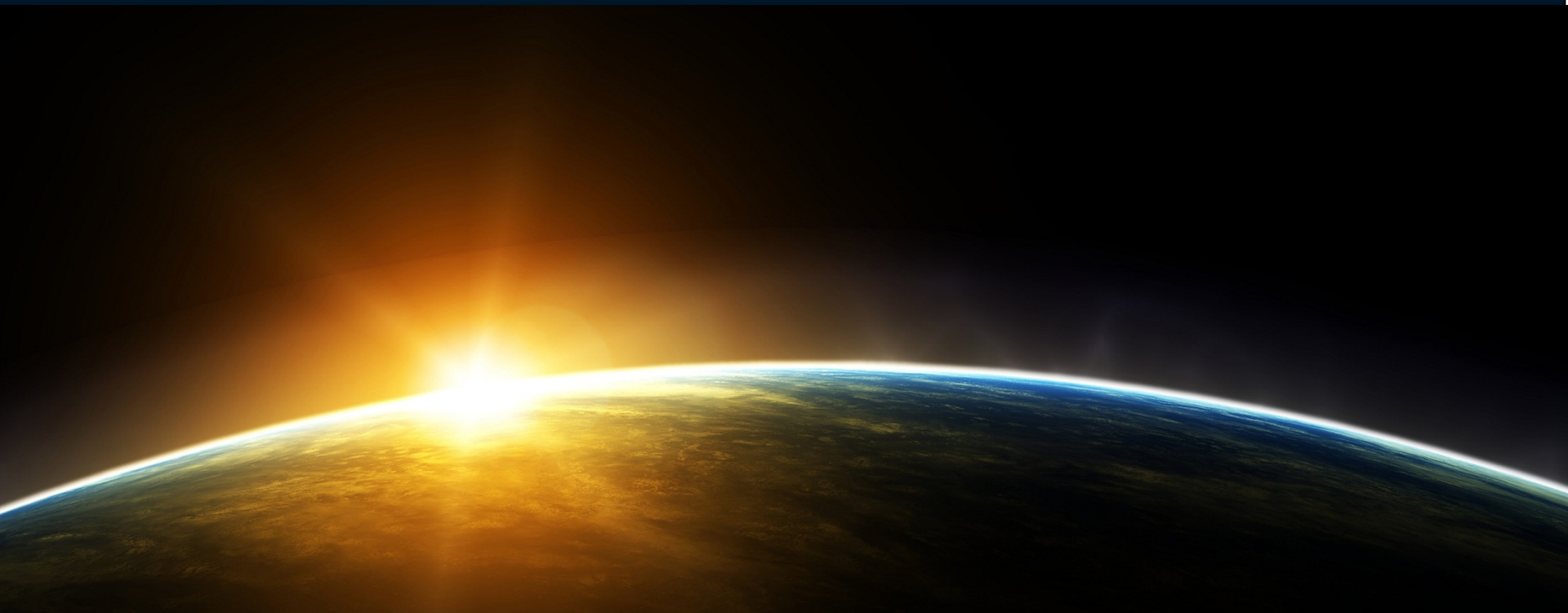
F-18 Flurpiridaz PET vs Tc-99m SPECT MPI



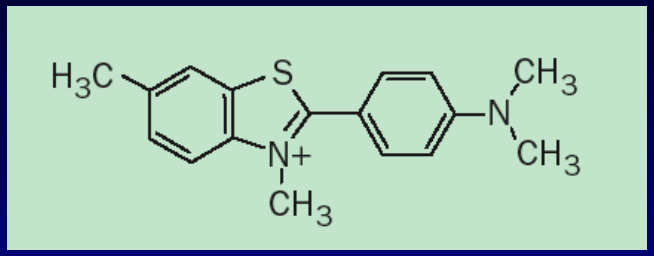
- Developed by Lantheus
- June 2013: Initiated Phase 3 clinical trials to assess diagnostic efficacy compared to SPECT MPI in detection of CAD

Neuroimaging Alzheimer's

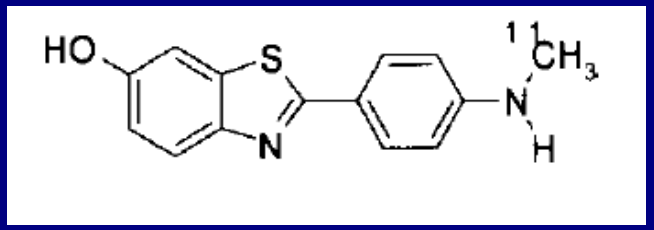
- C-11 PIB
- Amyvid®
- Vizamyl®



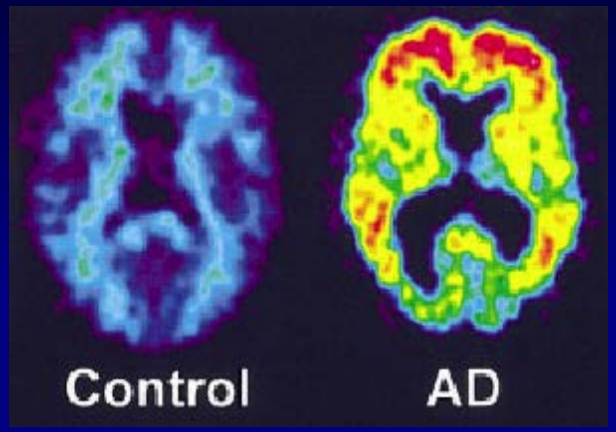
[C-11]PiB Amyloid PET- Klunk and Mathis - 2004



Thioflavin T



[^{11}C]PiB



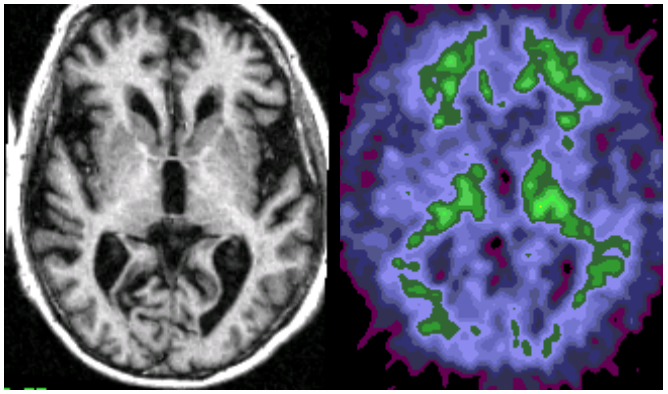
- Derivative of thioflavin T (amyloid binding dye)
- Crosses BBB; high affinity for human amyloid
- ^{18}F-labeled tracers for amyloid developed because of more convenient 110 min $T_{1/2}$, capability for centralized commercial distribution

Brain Structure

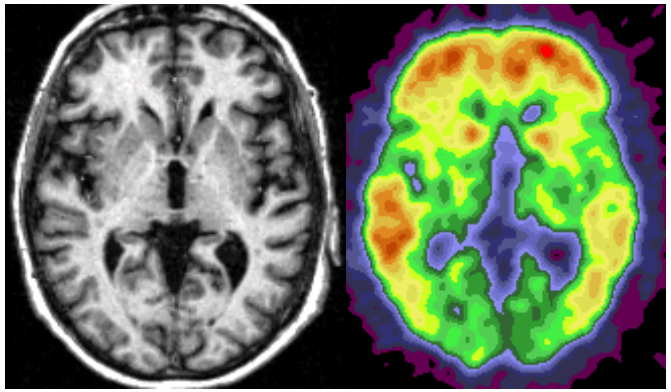
Brain Chemistry

MRI

C-11 PIB PET

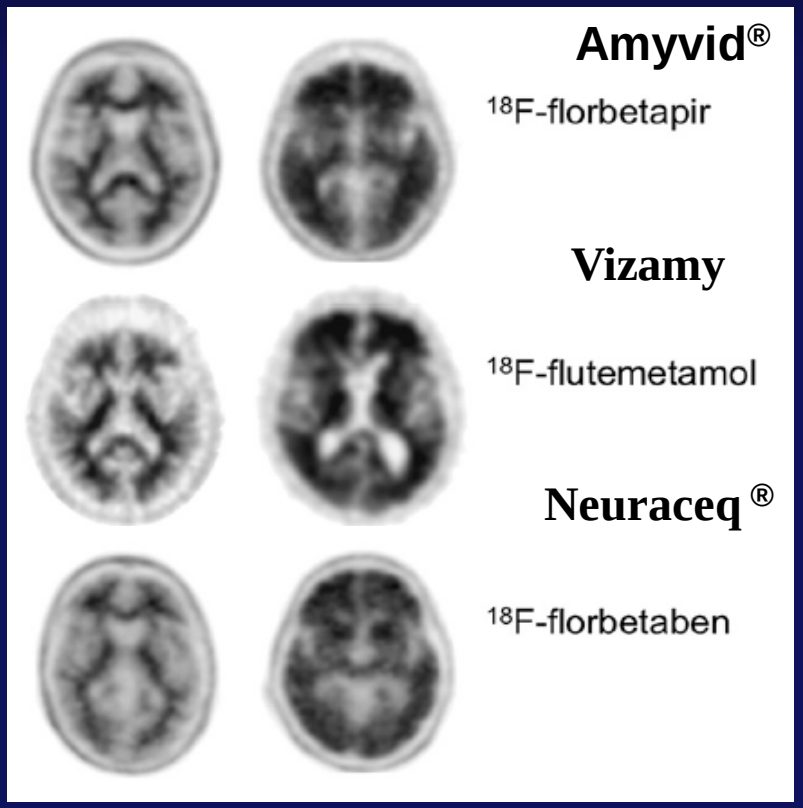


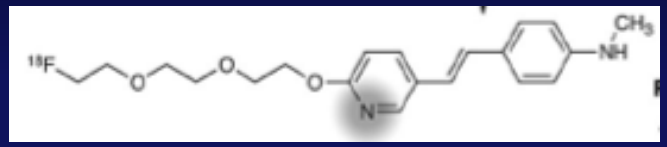
Normal



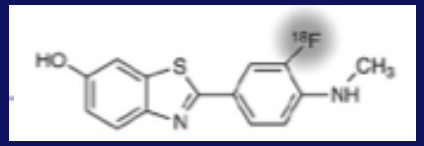
Alzheimer’s Disease

FDA-Approved ^{18}F Amyloid Radiotracers

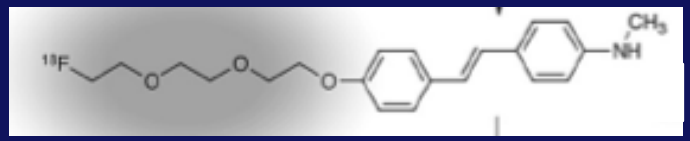




2012



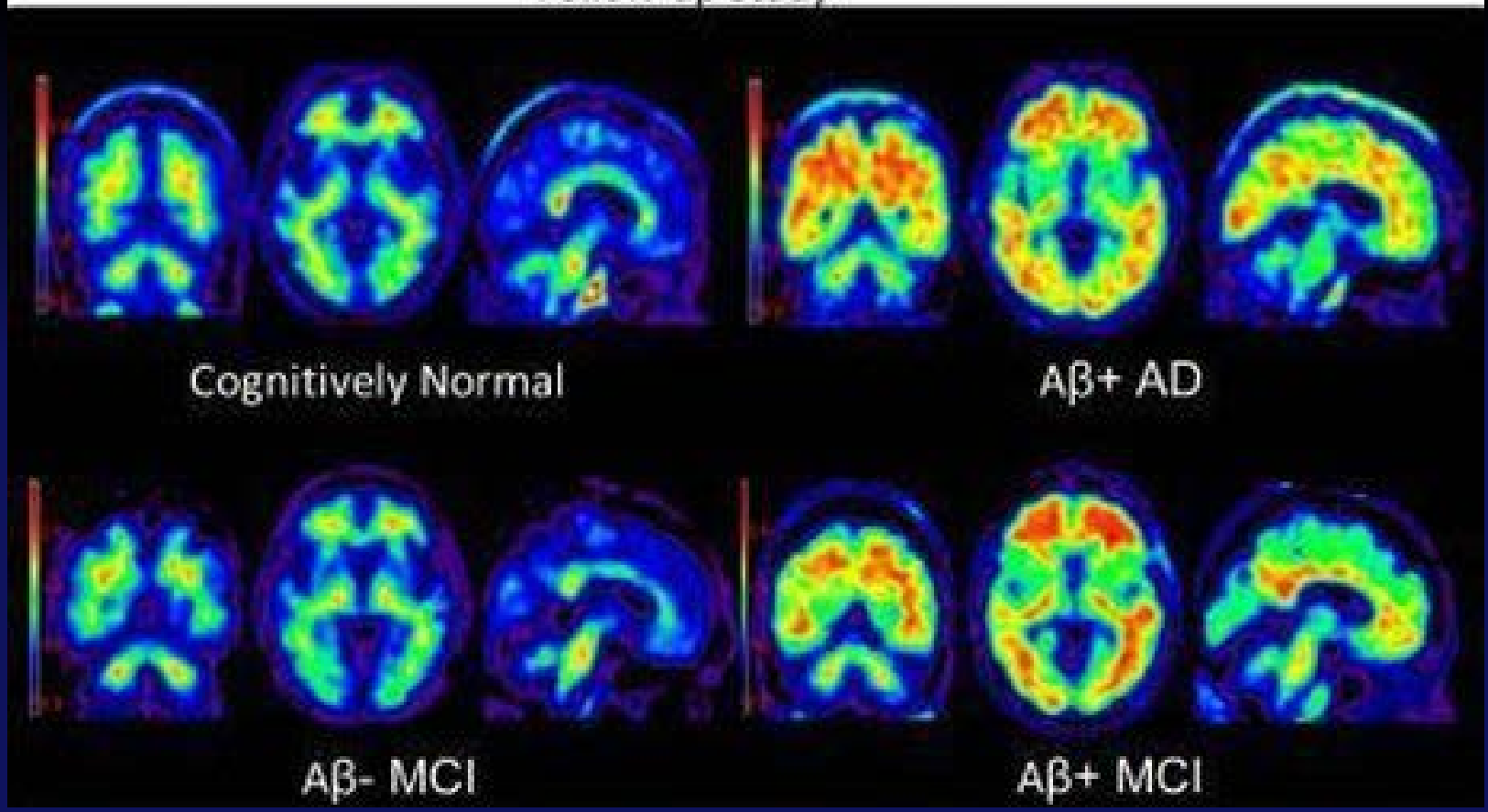
2013



2014

Rowe and Villemagne 2011

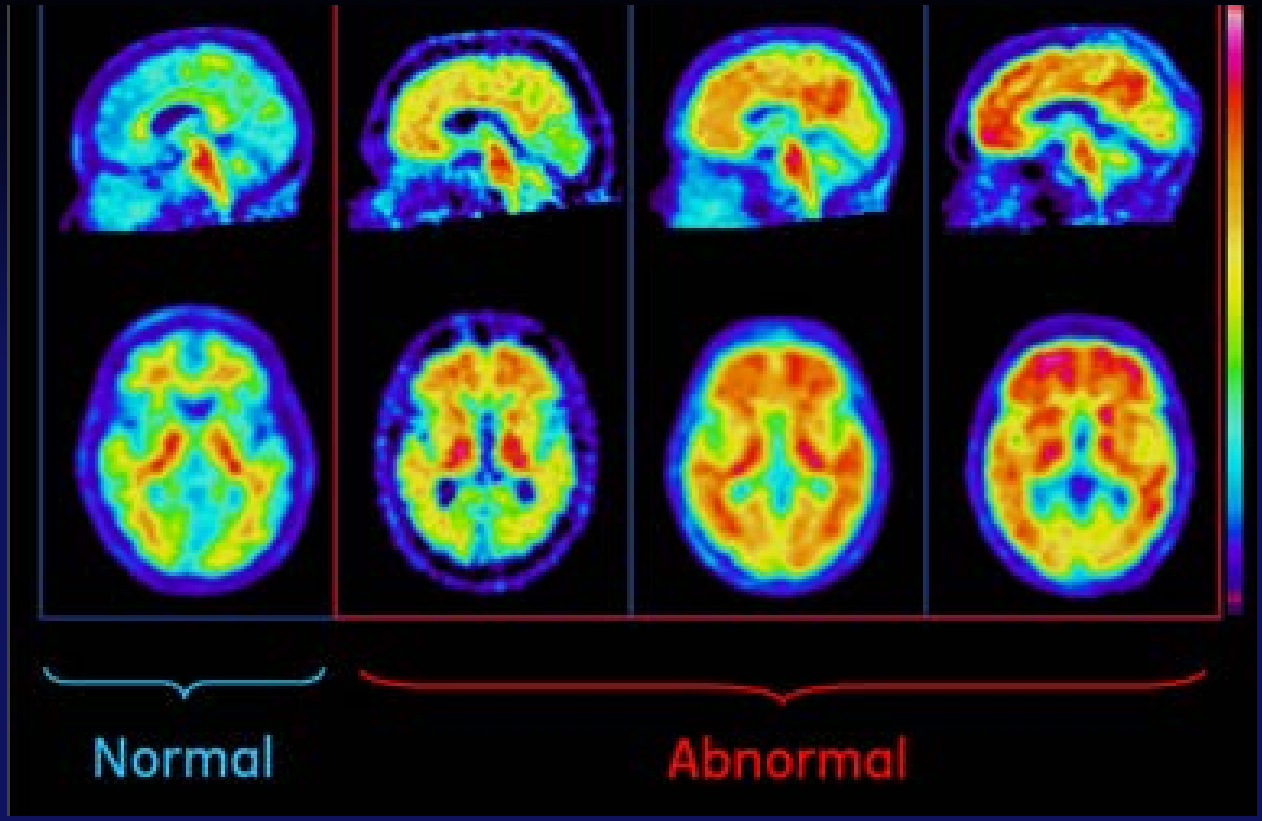
Amyvid® Study



Clockwise from top left:

1. Cognitively normal subject
2. Amyloid-positive subject with Alzheimer's disease
3. Patient with mild cognitive impairment who progressed to dementia during a study

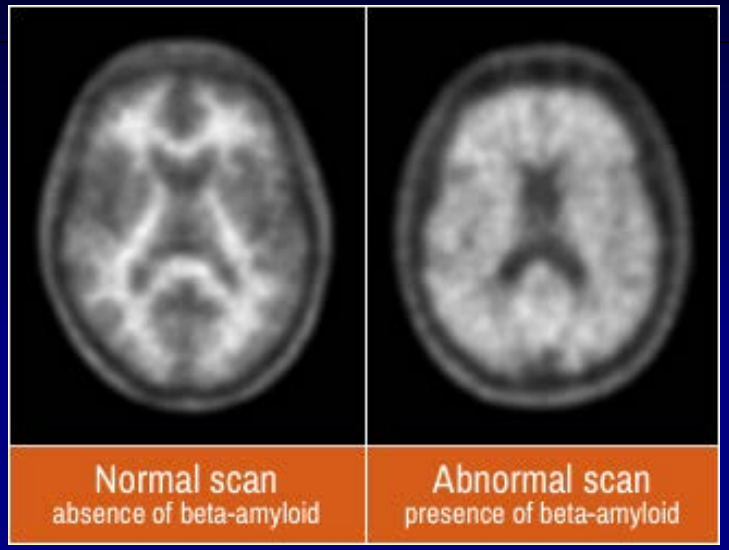
F-18 Flutemetamol (Vizamyl®)



- FDA approved 10-25-13
- Developed by GE Healthcare
- Approved to estimate the beta amyloid neuritic plaque density, using color images, in adults being evaluated for AD and other causes of cognitive decline
- Commercially available in 2014

http://finance.yahoo.com/news/ge-healthcare-announces-fda-approval-174500811.html

Florbetaben (Neuraceq ®)



- Approved by FDA in 2014
- Piramal® Imaging
- Indication: Imaging of beta-amyloid neuritic plaques in the brain

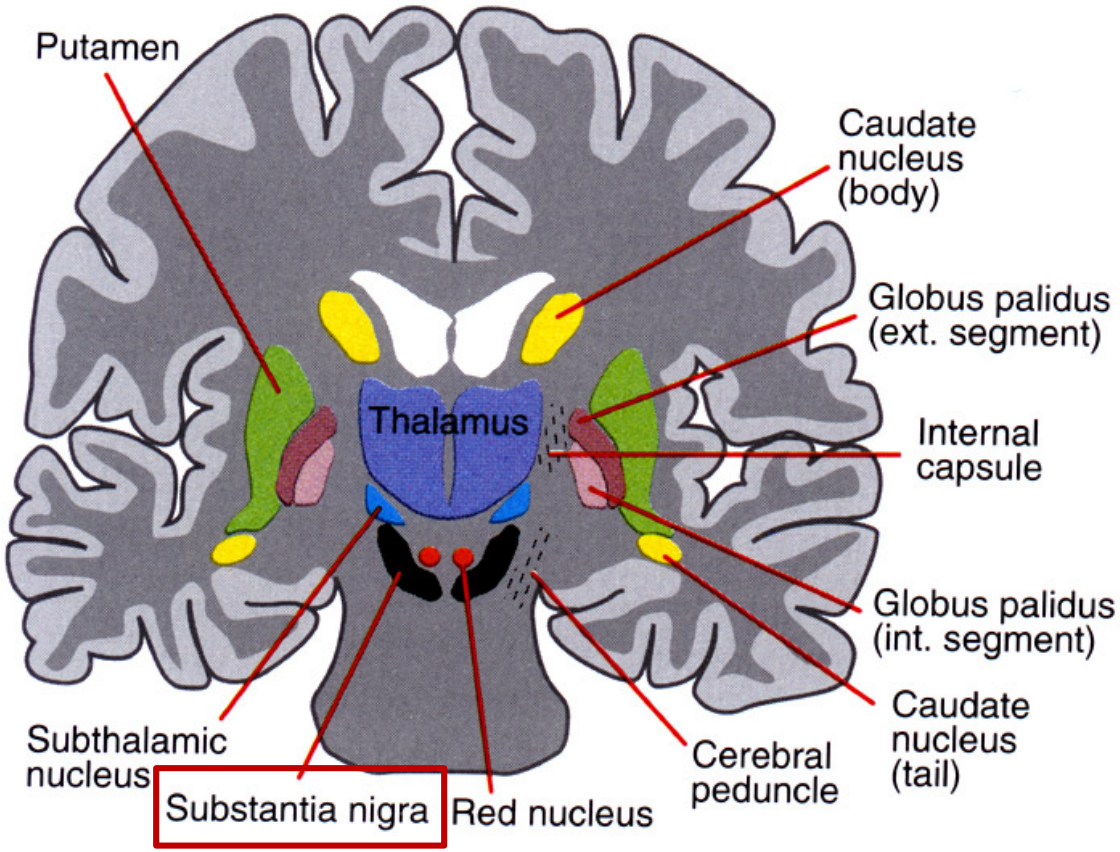
Neuroimaging Parkinson’s

- F-18 FDOPA (FDOPA)

Parkinson's Disease (PD)

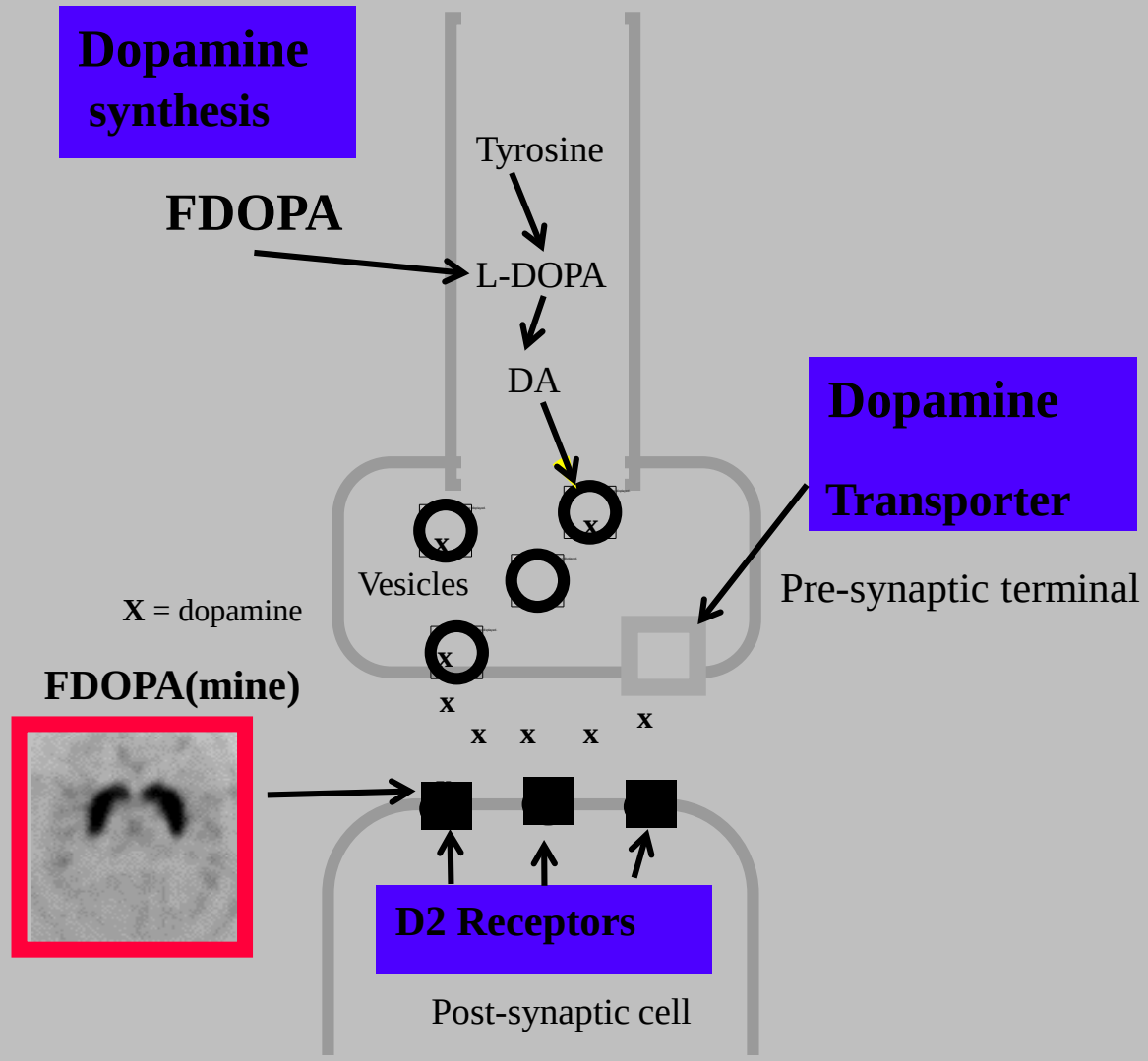
- Progressive degenerative disease
- Loss of nigrostriatal dopaminergic system underlies major motor manifestations of PD
- Symptoms emerge when depletion exceeds 80-90%
- Image dopaminergic terminals:
  - FDOPA

Parkinson's Disease (PD):

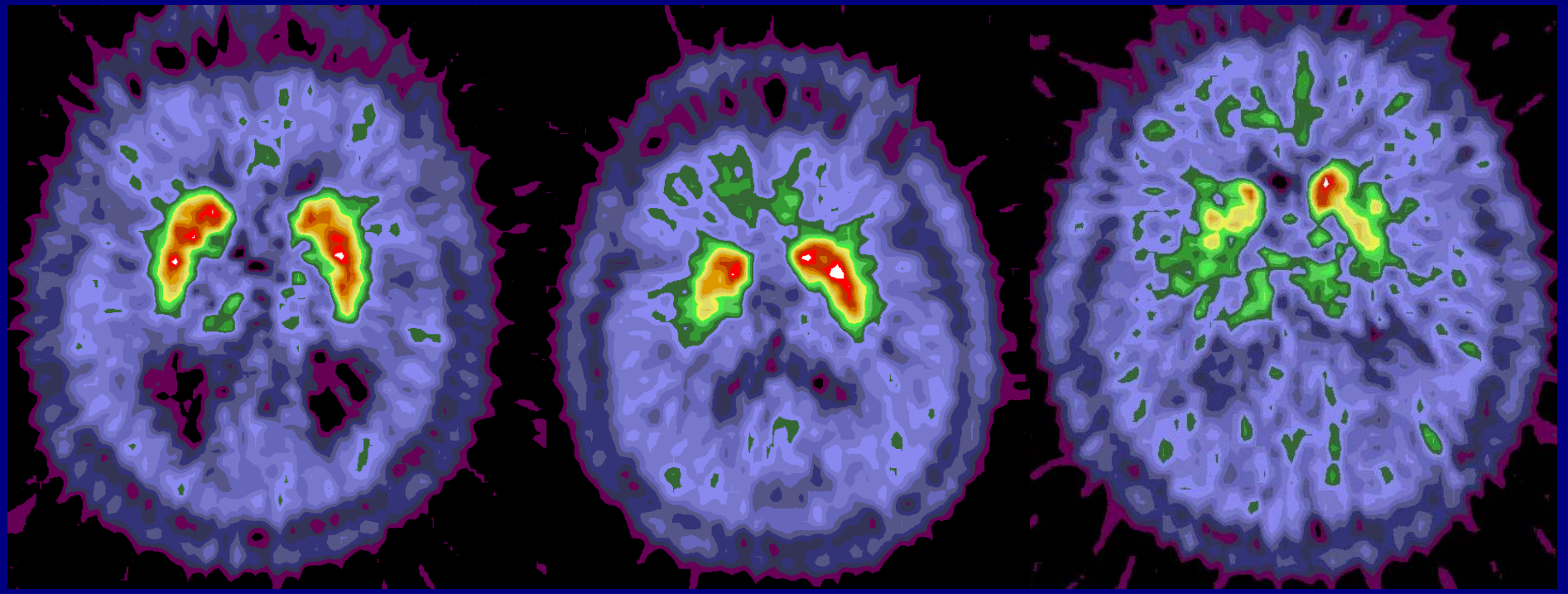


- Decrease in dopaminergic neurons located in the basal ganglia, specifically in the substantia nigra (area which controls movement)
- FDOPA selectively localizes in dopaminergic neurons
- As PD progresses FDOPA accumulation decreases, which correlates with severity of PD

Targets for dopaminergic ligands—FDOPA



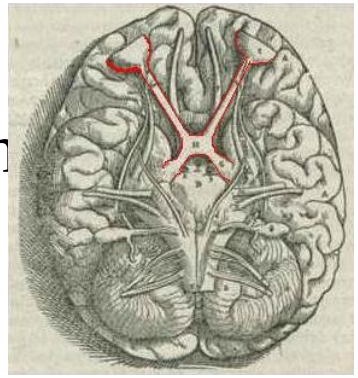
FDOPA in PD

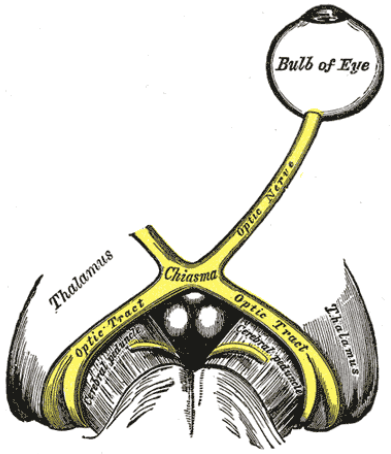


Normal Mild Moderate

Use of FDOPA In Glioma Imaging

- Glioma: Most common form of primary brain tumor
- Diagnosis: MRI, CT and PET
- FDOPA PET: useful in detection and recurren glioma
- Optic gliomas:
  - Rare, occur in children usually before age 20
  - Can affect one or both optic nerves or the optic chiasm where the optic nerves cross



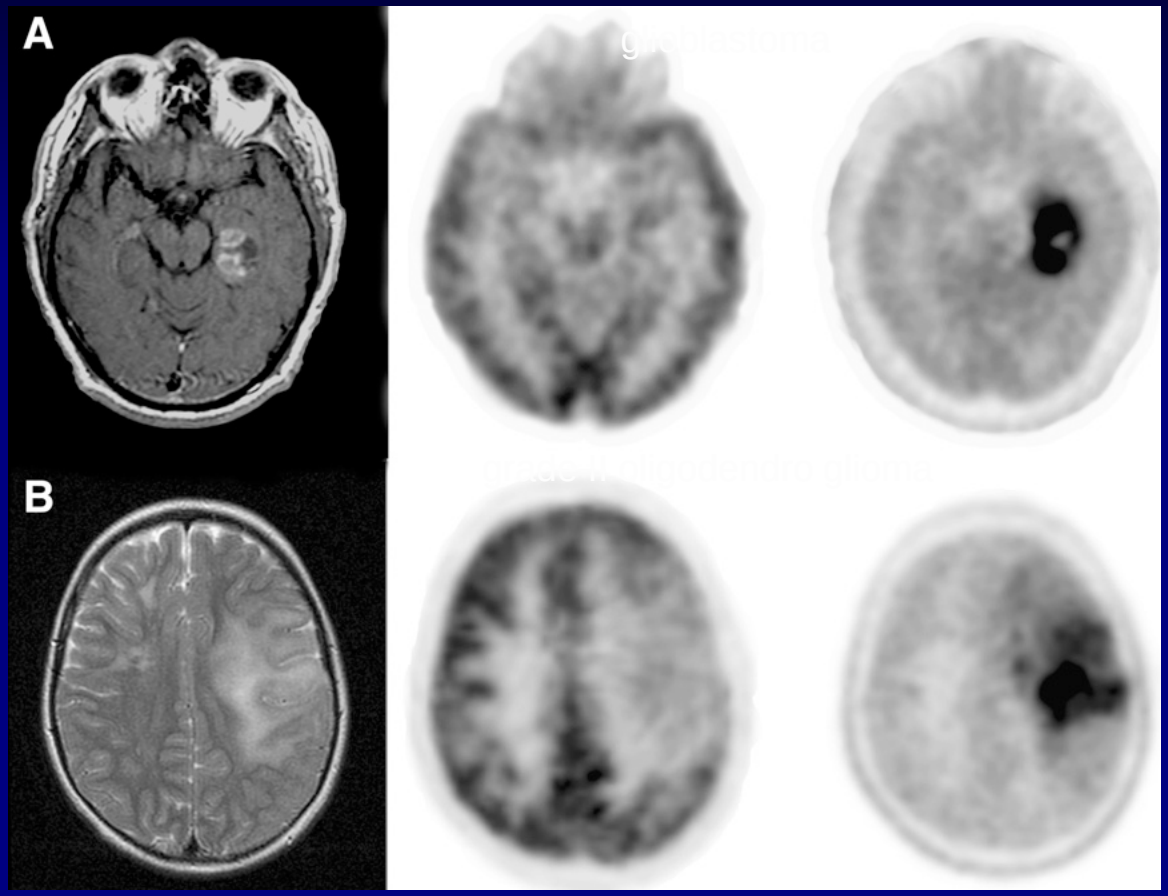


FDOPA in Glioma

- The L-type amino acid transporter 1 (LAT1) is responsible for membrane transport of large neutral amino acids in normal cells.
- This study assessed the relationship between LAT1 expression and F-18 FDOPA uptake in human astrocytomas.
- LAT1 mRNA and protein expression varies in GBM, and the extent of ^{3}H-L-DOPA uptake was positively correlated with endogenous LAT1 expression.

Youland RS et al. J Neuroonc 2013 Jan;111(1)

FDOPA is more sensitive than FDG for the detection of gliomas



MR

[^{18}F]FDG

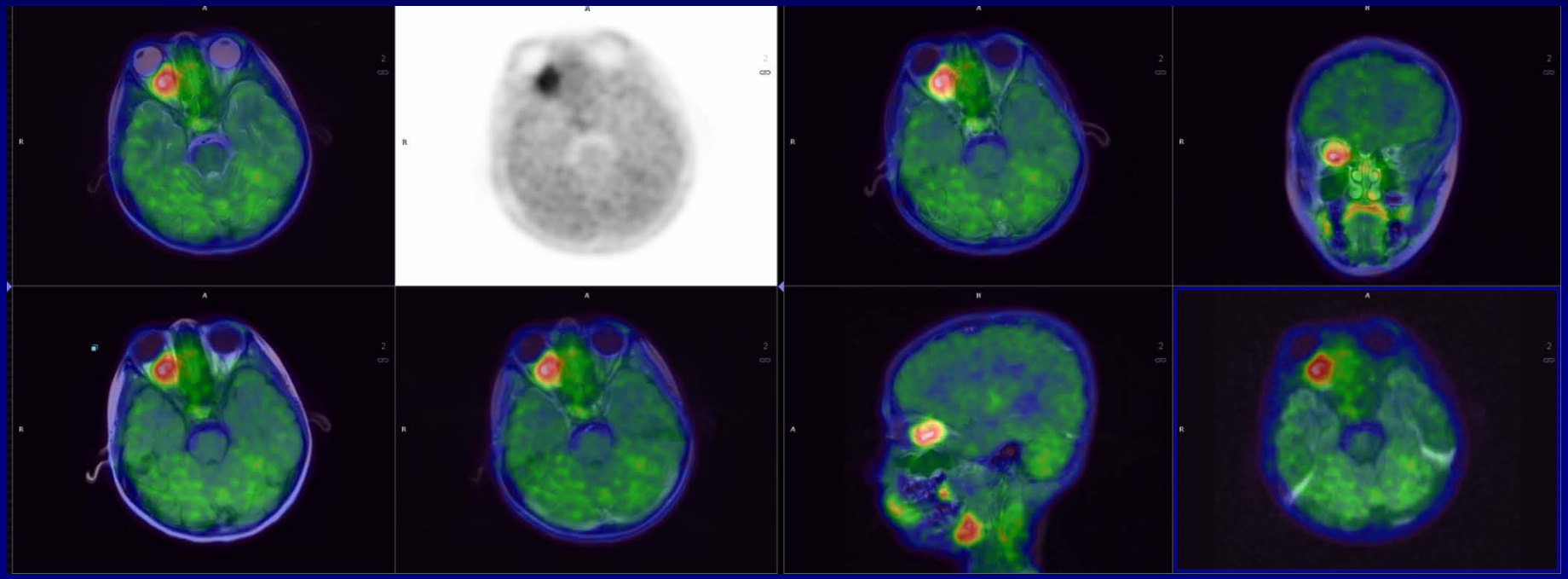
Sensitivity = 61%
(78% for high grade)

[^{18}F]FDOPA

Sensitivity = 96%

Chen, W., 2007. Clinical applications of PET in brain tumors, J Nucl Med. 48: 1468.

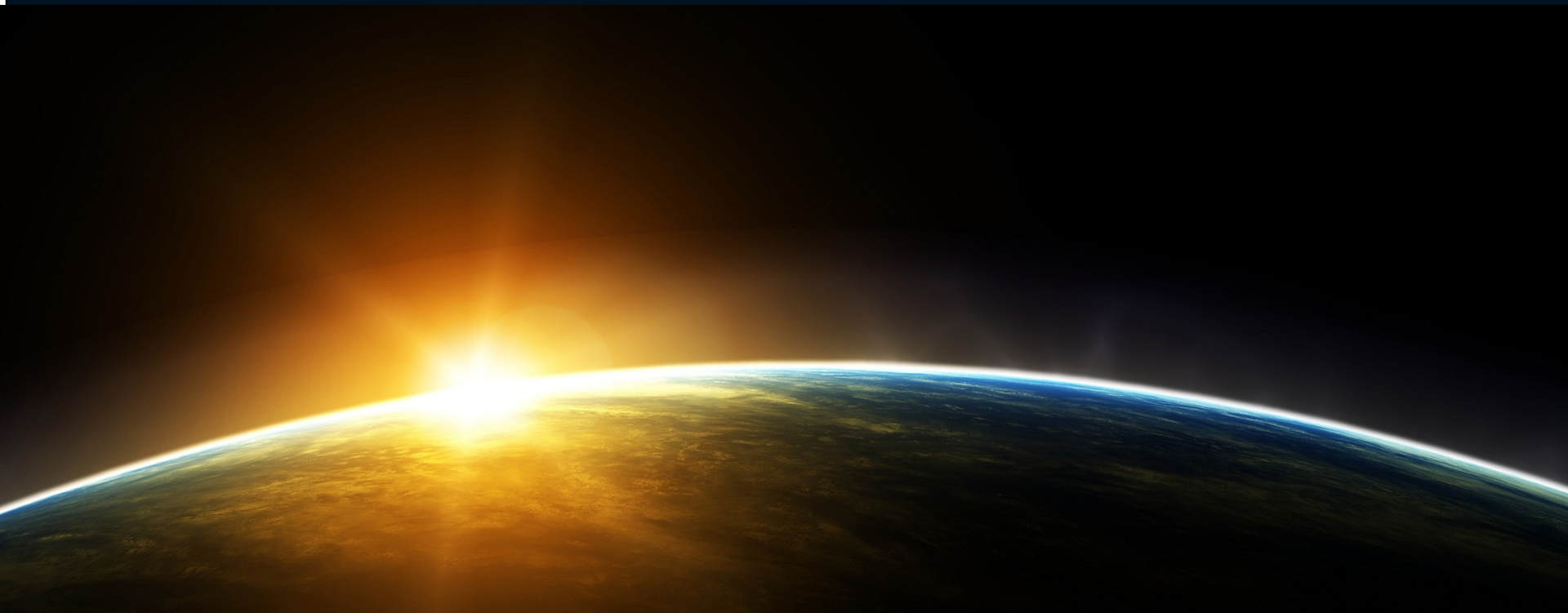
FDOPA-PET/MR in a Pediatric Patient with Optic Pathway Gliomas



15-20 min after FDOPA injection

Prostate Cancer Imaging

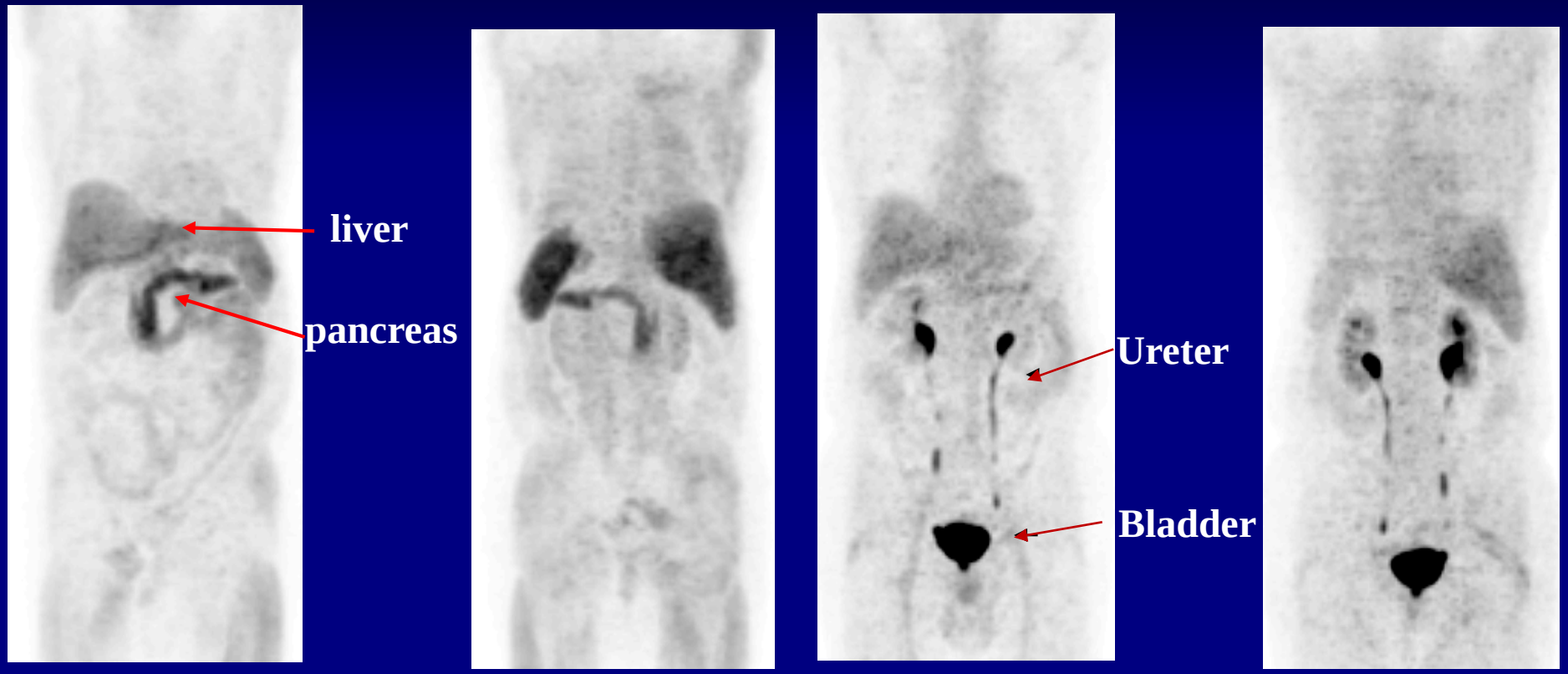
- C-11 Acetate
- C-11 Choline



Normal Biodistribution

C-11 Acetate

F-18 FDG



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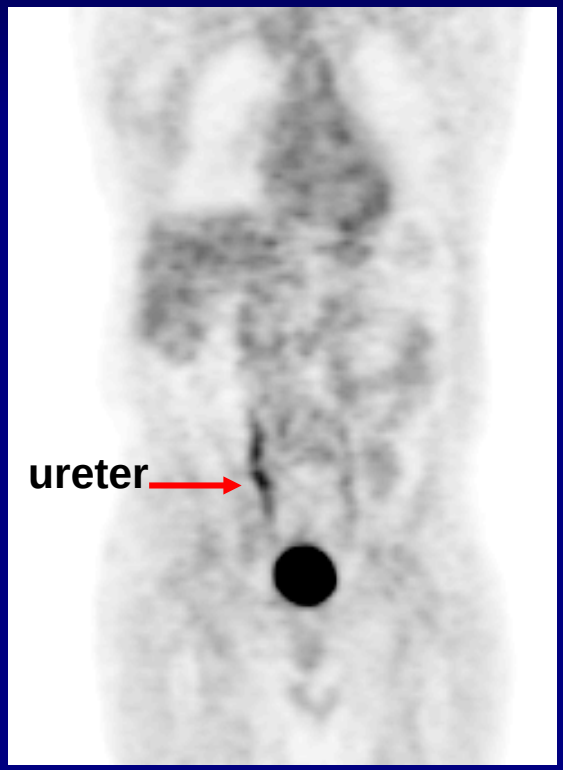
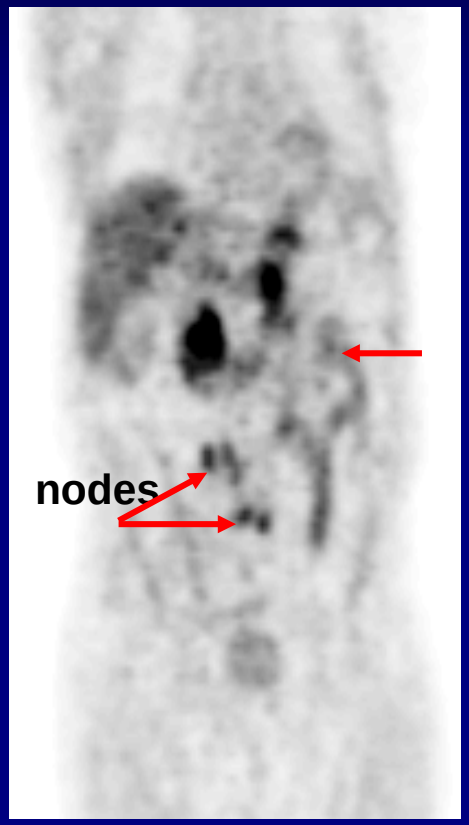
No renal excretion of C-11 Acetate

C-11 Acetate
Prostate Cancer: Recurrence



FDG



AC-PET

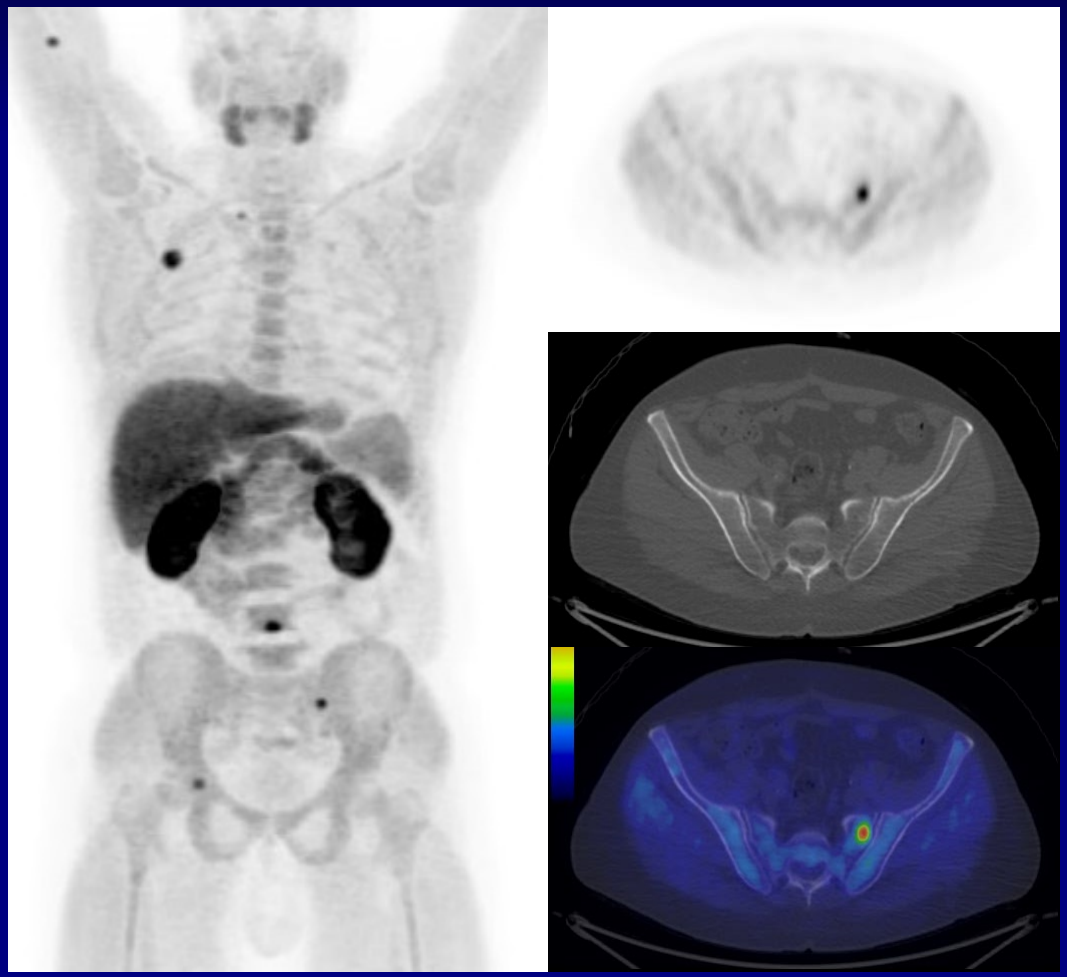
- 77 y/o man with prior prostatectomy
- Gleason score 8
- T2N0M0
- PSA 10.5 ng/mL

C-11 Choline PET/CT in Biochemical Recurrence of Prostate Cancer

- FDA approved NDA for Mayo Clinic Rochester production: September 12, 2012
- C-11 choline transport and metabolism is increased in prostate cancer -- marker of cell membrane synthesis
- Clinical volume ~150 patients/month in April 2014
- Local CMS provider approved reimbursement beginning: October 1, 2013

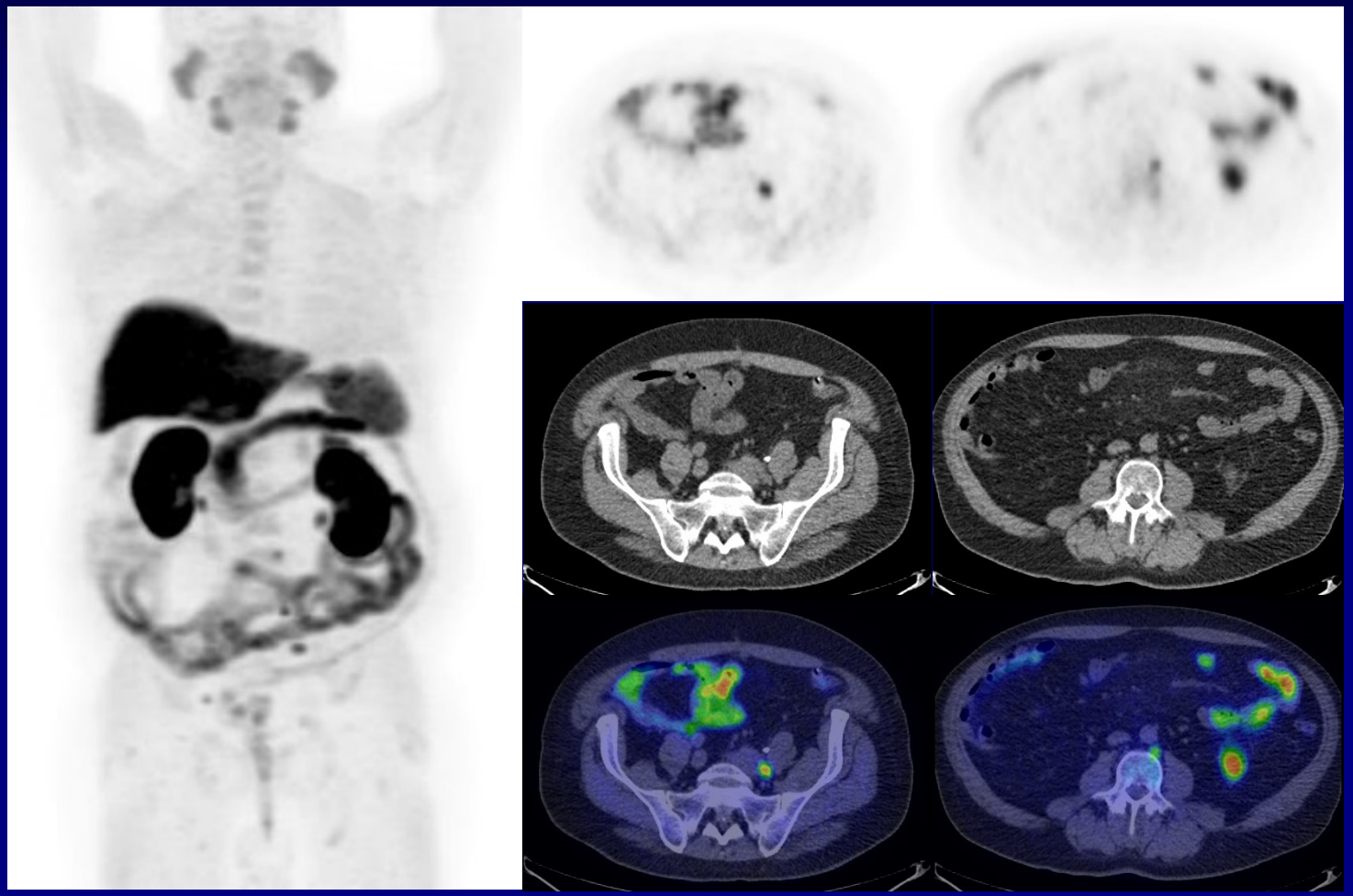
Slide courtesy of Pat Peller, M.D., Mayo Clinic

C-11 Choline PET/CT in Prostate Cancer



Slide courtesy of Pat Peller, M.D., Mayo Clinic

C-11 Choline PET/CT in Prostate Cancer

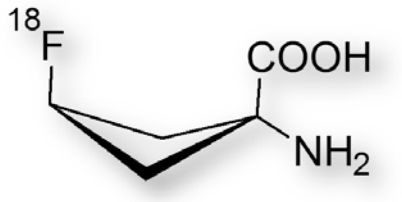


Slide courtesy of Pat Peller, M.D., Mayo Clinic

F-18 Fluciclovine (FACBC)
anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid

Active Uptake by Prostate Cancer Cells

- Artificial amino acid analog labelled with F-18
- Preclinical studies show preferential uptake into cells and tissues with enhanced amino acid transport.
- Prostate cancer, like other tumors, has increased needs for amino acids inducing overexpression of amino acid transporters[1]
- *In vitro* studies demonstrate:[2-4]
  - Prostate cancer cells take up higher levels of F18 F-18 Fluciclovine
  - Fluciclovine compared to other radiotracers
  - F-18 Fluciclovine transport is primarily via ASCT2 and LAT1 amino-acid transporters[3]
  - F-18 Fluciclovine is not incorporated into newly synthesized proteins in malignant or normal cells



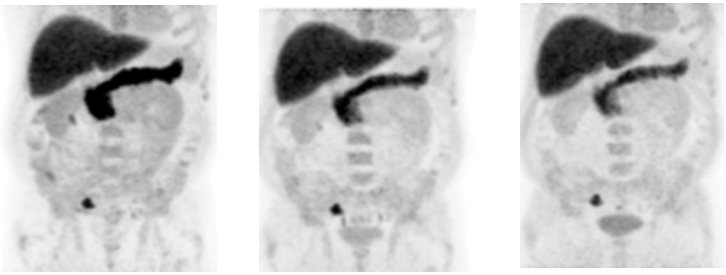
Radiotracers	Uptake amount (pmol/mg of protein) LNCaP cells	DU145 cells
anti-^{14}C-FACBC	105.9 ± 15.7	110.8 ± 14.5
^{14}C-Gln	88.6 ± 14.9	59.0 ± 6.2
^{14}C-Met	23.0 ± 1.6	56.7 ± 10.8
^{14}C-FDG	2.8 ± 0.7	1.9 ± 0.5
^{14}C-Choline	45.8 ± 12.4	15.6 ± 2.8
^{14}C-Acetate	14.1 ± 2.4	20.8 ± 3.8

1. Semin Cancer Biol. 2005;15(4):254-66
2. Okudaira et al. Mol Imaging Biol 2014;16:756-764
3. Oka S. et al. Nucl Med Biol. 2012;39:109-119
4. Okudaira et al.. J Nucl Med. 2011;52:822-829.

F-18 Fluciclovine(FACBC) Physiological Distribution

Biology:

- F-18 Fluciclovine: not metabolized; amino acid (A) transporters ubiquitous throughout body
- Pancreas and liver: AA metabolism & synthesis of plasma proteins
- Muscle hosts majority glutamine pool



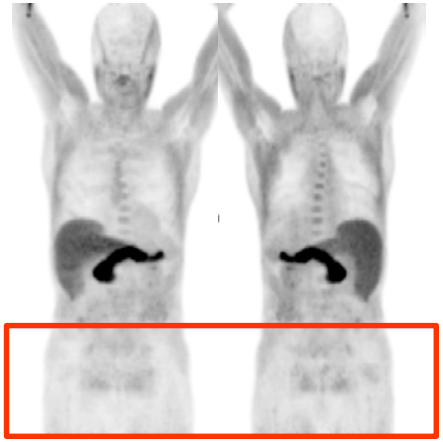
5-16 min- Pancreas > Liver

17-28 min: Pancreas = Liver

29-40 min: Pancreas < Liver

Whole body:

- Most intense physiologic uptake: liver and pancreas
- Moderate: salivary gland, pituitary
  - Muscle: ↑ with time
  - Marrow: heterogenous and ↓ with time
- Mild to none: brain and lung
- Variable: bowel
- Bladder <u>absent or mild on early imaging</u>
  and ↑ with time



1. Schuster, et al. J Nucl Med 2014

F-18 Fluciclovine (FACBC): Recent Updates

- New Drug Application (NDA)
  - Detection of recurrent prostate carcinoma accepted by U.S. FDA for priority review based on data from >700 prostate cancer patients imaged in the United States, Norway and Italy[1]
  - Granted Orphan Drug Designation diagnosis of glioma[2]

- LOCATE Trial:
  - Phase 3
  - Opening ~20 US sites (Q1/2016)
    - Determine effect of fluciclovine imaging on management of patients with biochemically recurrent prostate cancer. [3]

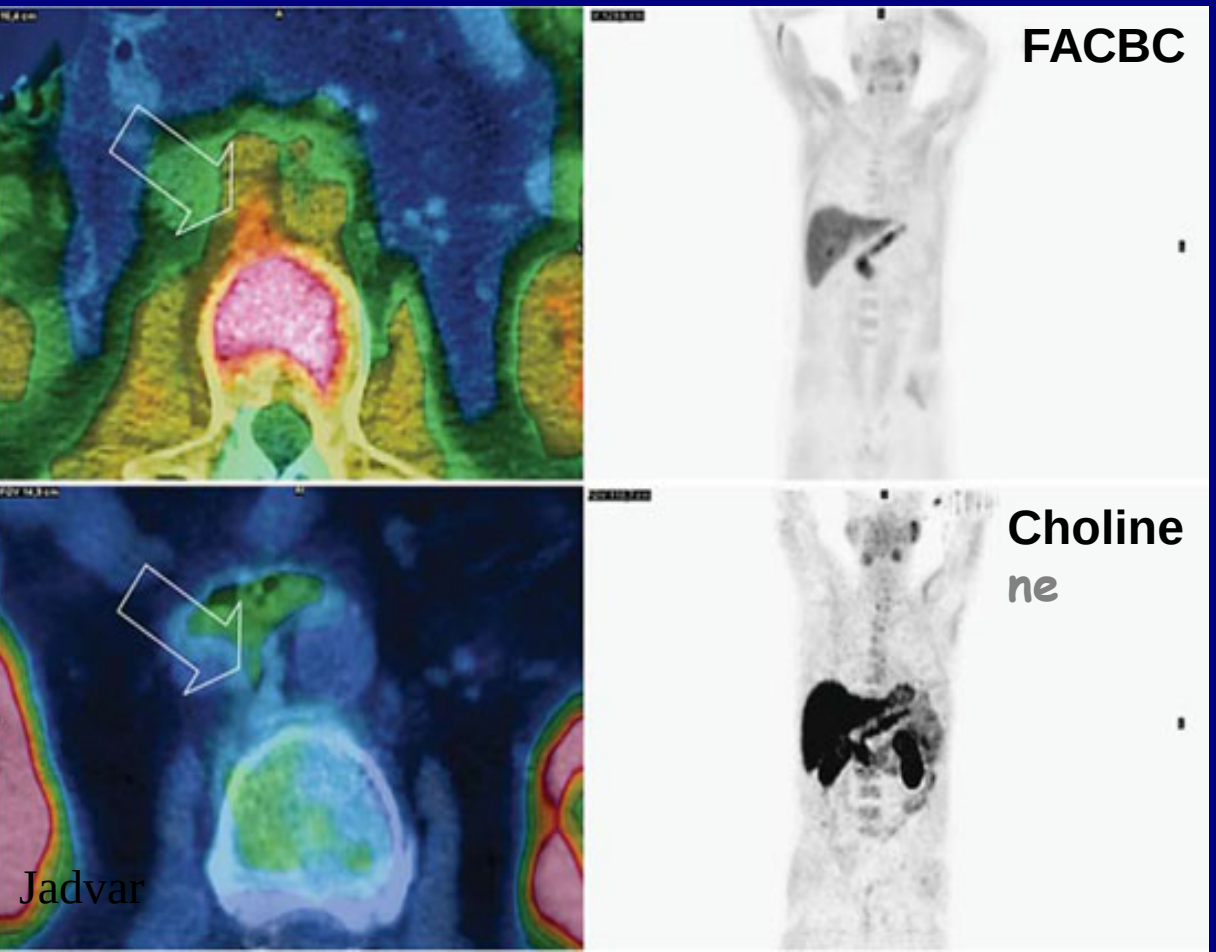
1. Press Release December 2015: http://www.blueearthdiagnostics.com/news/
2. Press Release April 2015: http://www.blueearthdiagnostics.com/news/
3. https://clinicaltrials.gov/ct2/show/NCT02680041?term=locate&rank=6

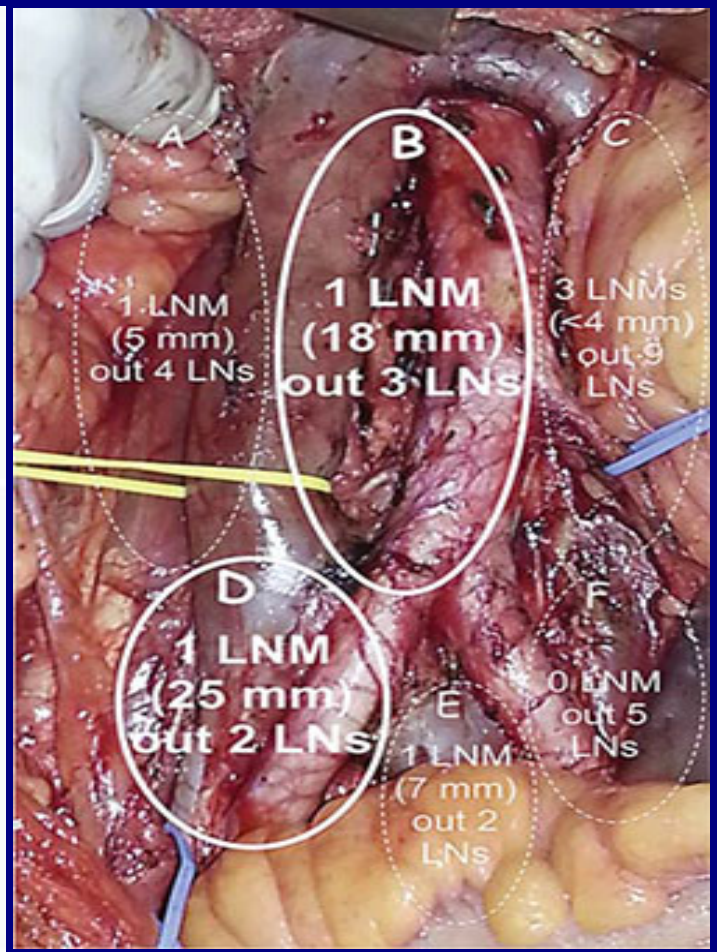
Prostate Cancer

F-18 FACBC vs C-11Choline

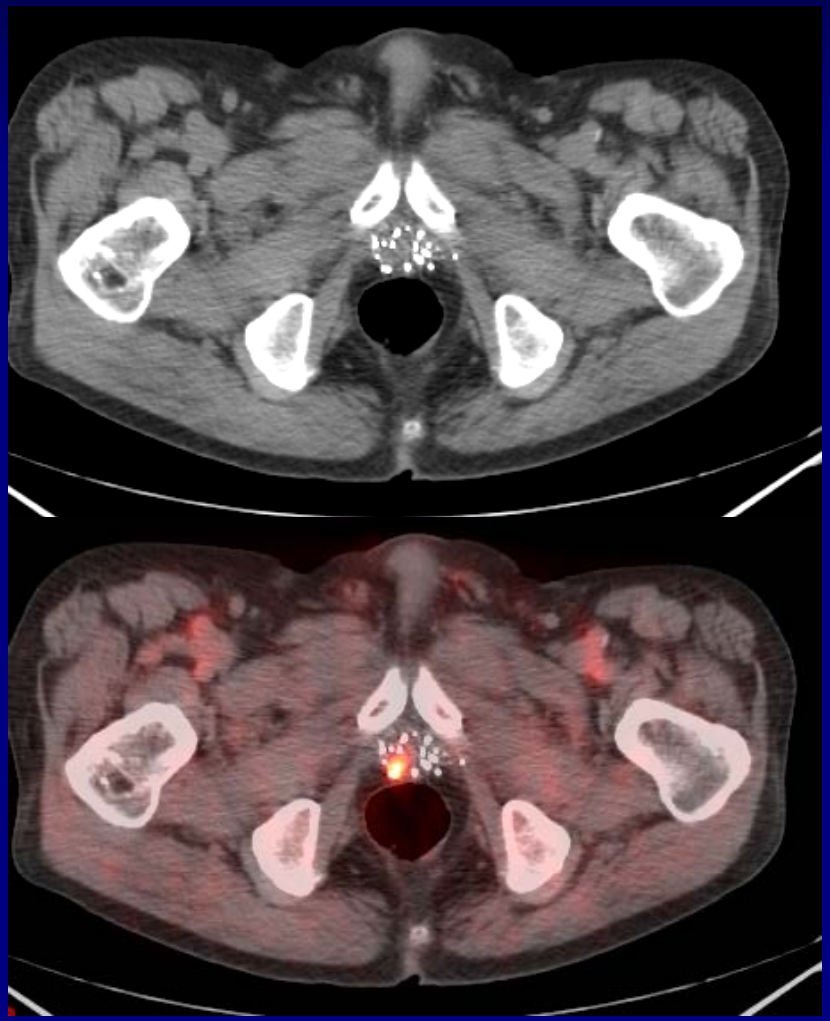
Schiavina R et al. *Urol Int* 2014; Nanni C et al. *Clin Genitourin Cancer* 2014

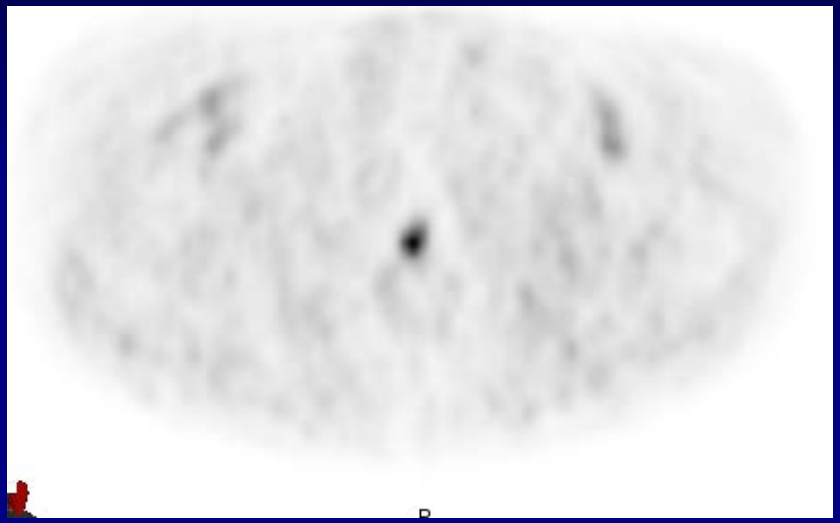
Early results in Biochemical Recurrance (BCR) post RP Improved detection rate: FACBC > Choline (by x factor of 2)





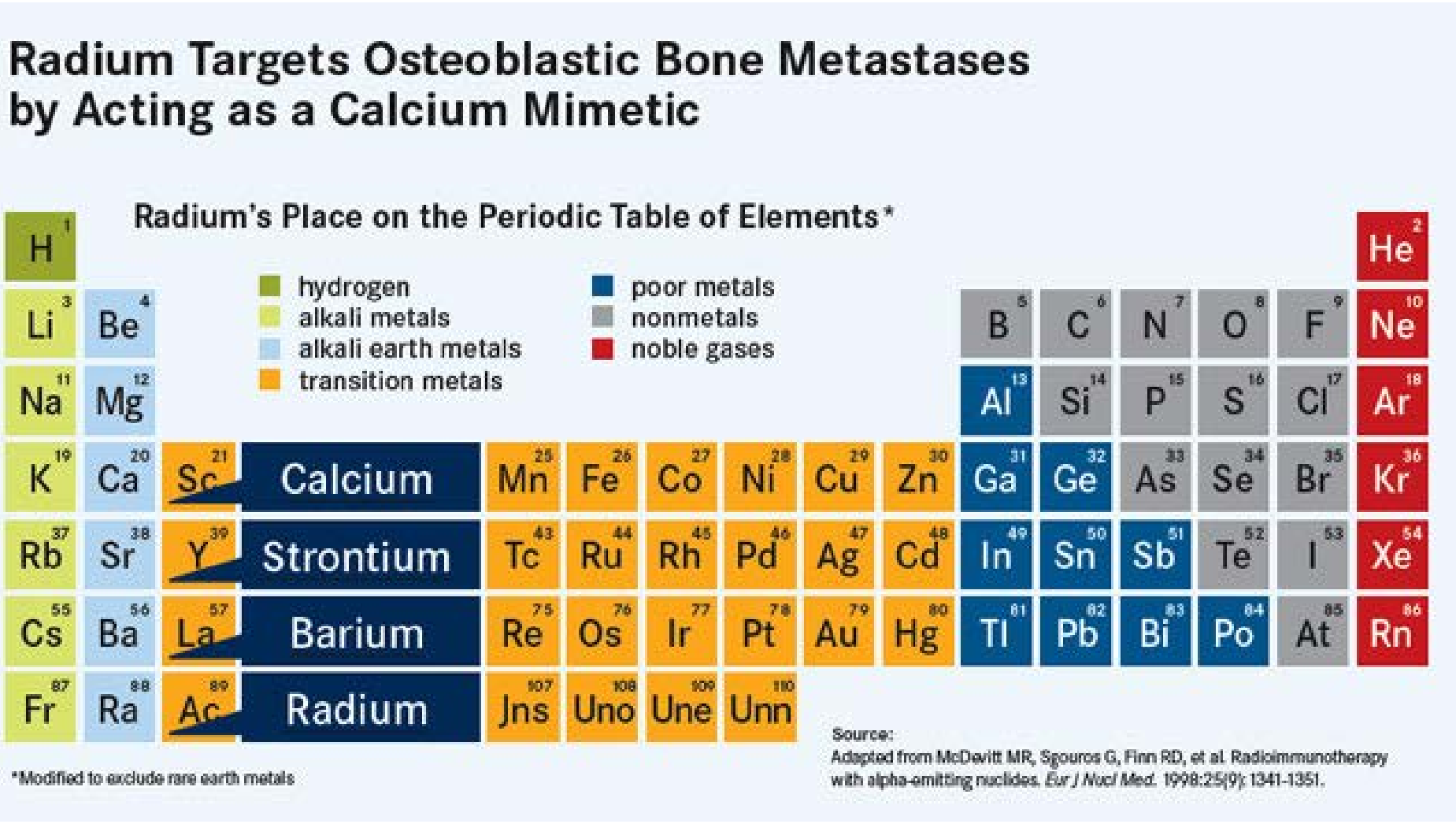
F-18 FACBC-PET/CT detection of local recurrence in the prostate bed





Slides courtesy of David Schuster MD, Emory University

Radium-223


Radium Targets Osteoblastic Bone Metastases by Acting as a Calcium Mimetic
Radium's Place on the Periodic Table of Elements*
hydrogen
alkali metals
alkali earth metals
transition metals
poor metals
nonmetals
noble gases
Calcium
Strontium
Barium
Radium
*Modified to exclude rare earth metals
Source:
Adapted from McDevitt MR, Sgouros G, Finn RD, et al. Radioimmunotherapy with alpha-emitting nuclides. Eur J Nucl Med. 1998;25(9):1341-1351.

Radiation Therapy: Xofigo®

Dose: 1.35 uCi / kg
4 week intervals x 6
Slow IV injection over 1 min

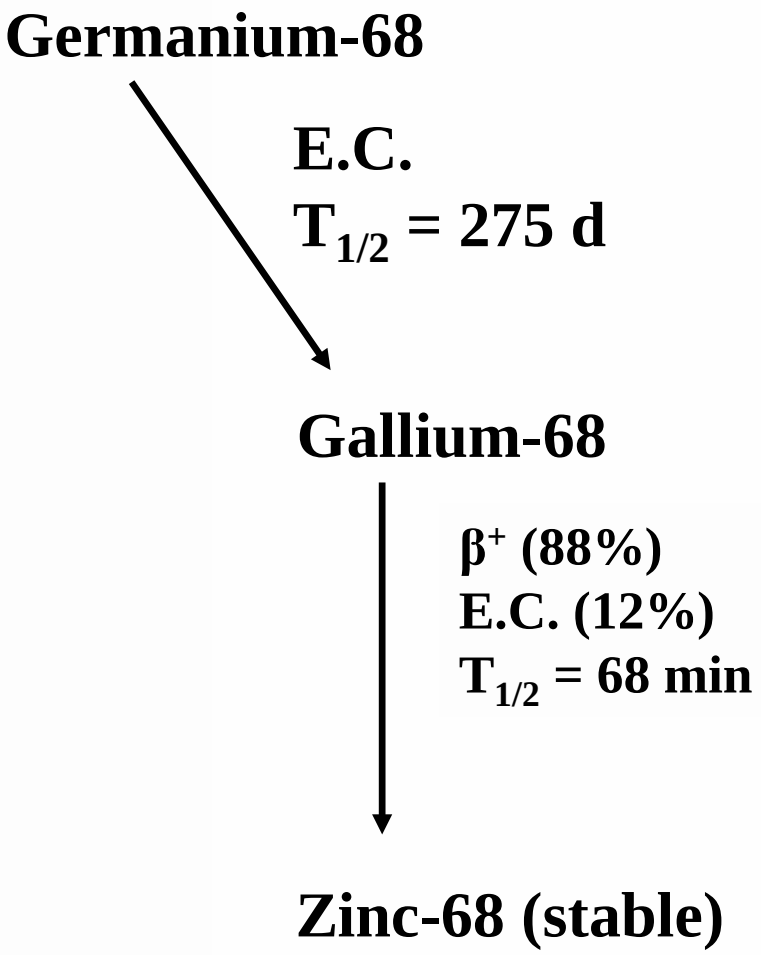
Check Blood Counts:
Baseline and prior to each dose
ANC > 1.5 x 10^9
Platelets >100 x 10^9
Hemoglobin >10 g/dL

Investigational Drugs

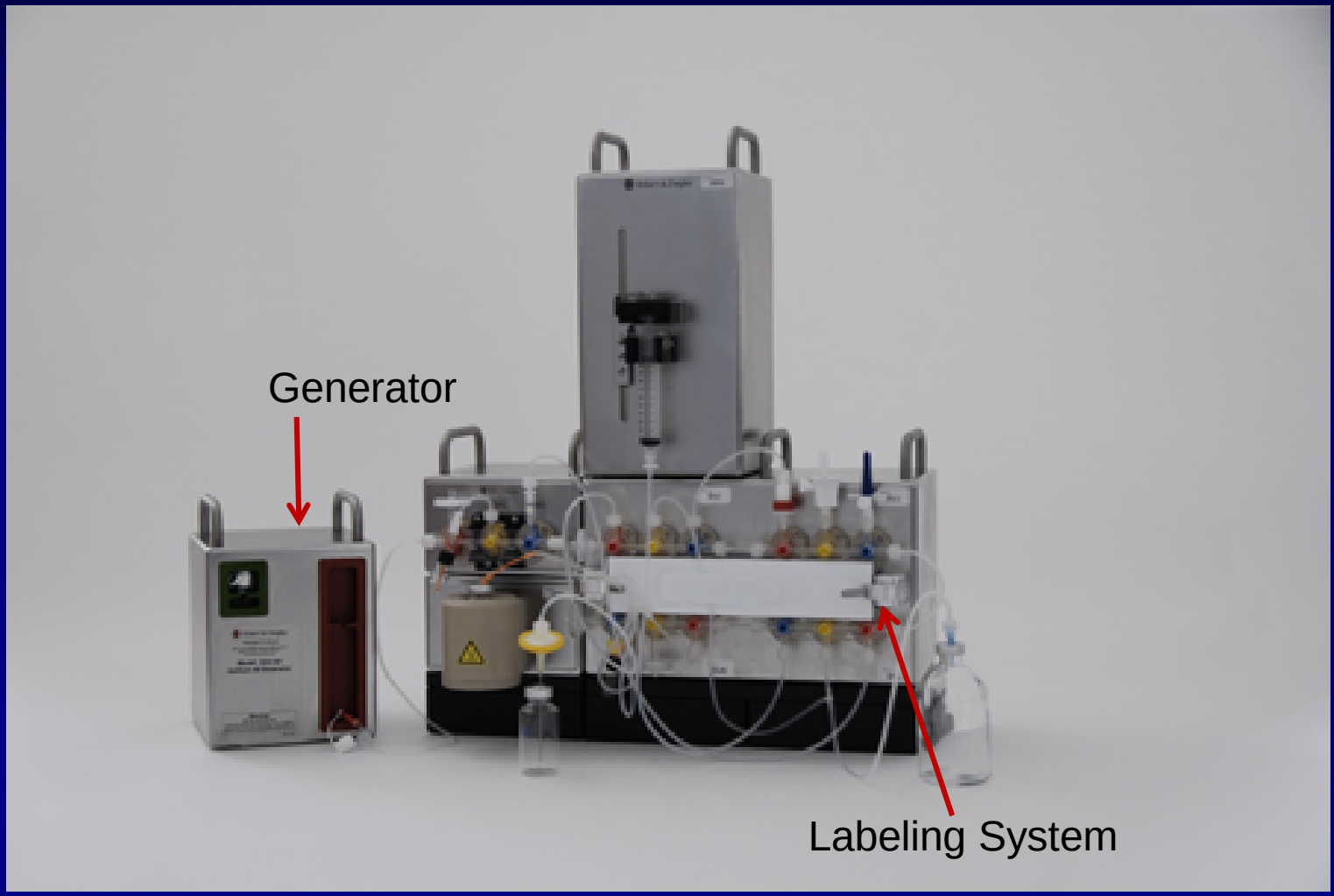
- Ga-68 DOTATOC
- Ga-68/Lu-177 PMSA
- Zr-90 Herceptin

Gallium-68 Generator

- Germanium-68 Parent
  - Cyclotron Produced
    - Zn-66 (a,2n) Ge-68
    - Ge-69 (p,2n) Ge-68
- Long lived parent
- Short lived daughter

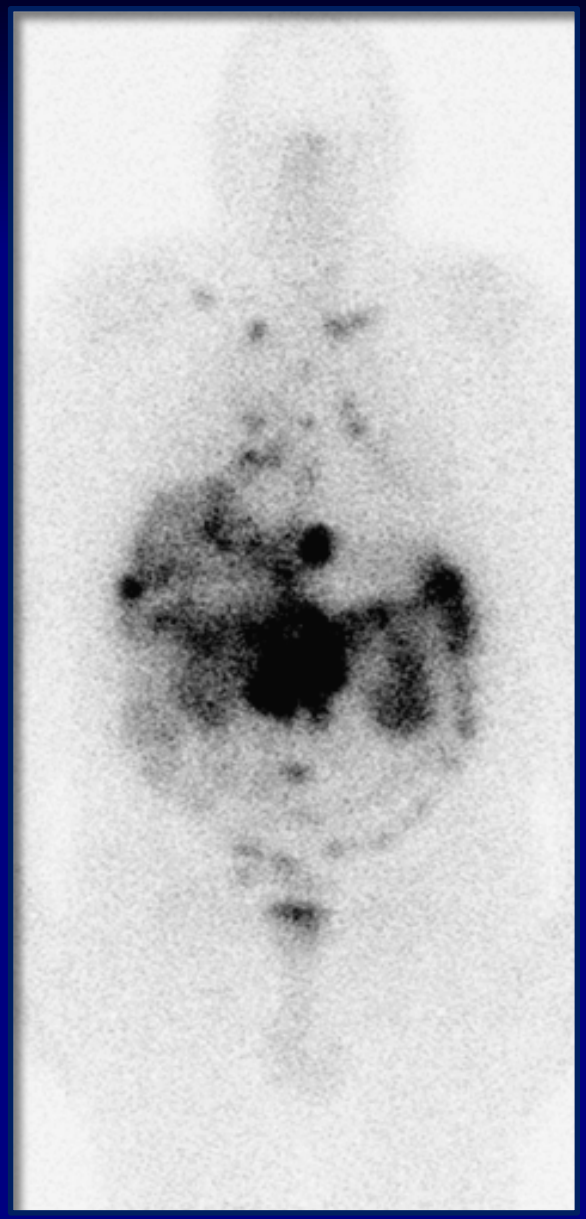


Ga-68 Modular-Lab System



Ga-68 DOTATOC Imaging

Octreoscan®
SPECT



Gallium-68
DOTATOC
PET

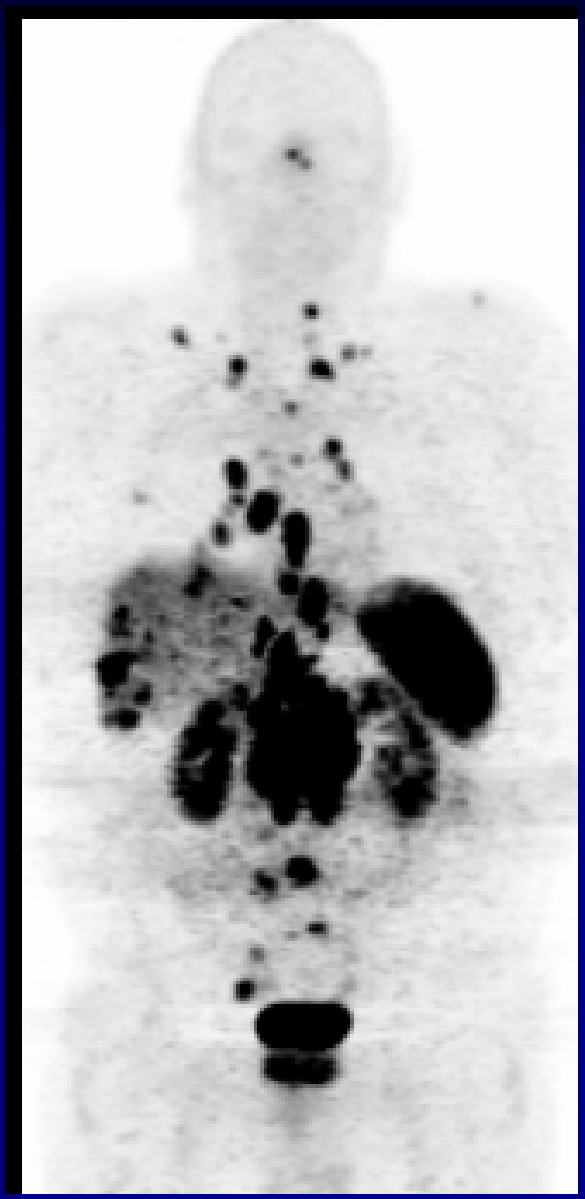


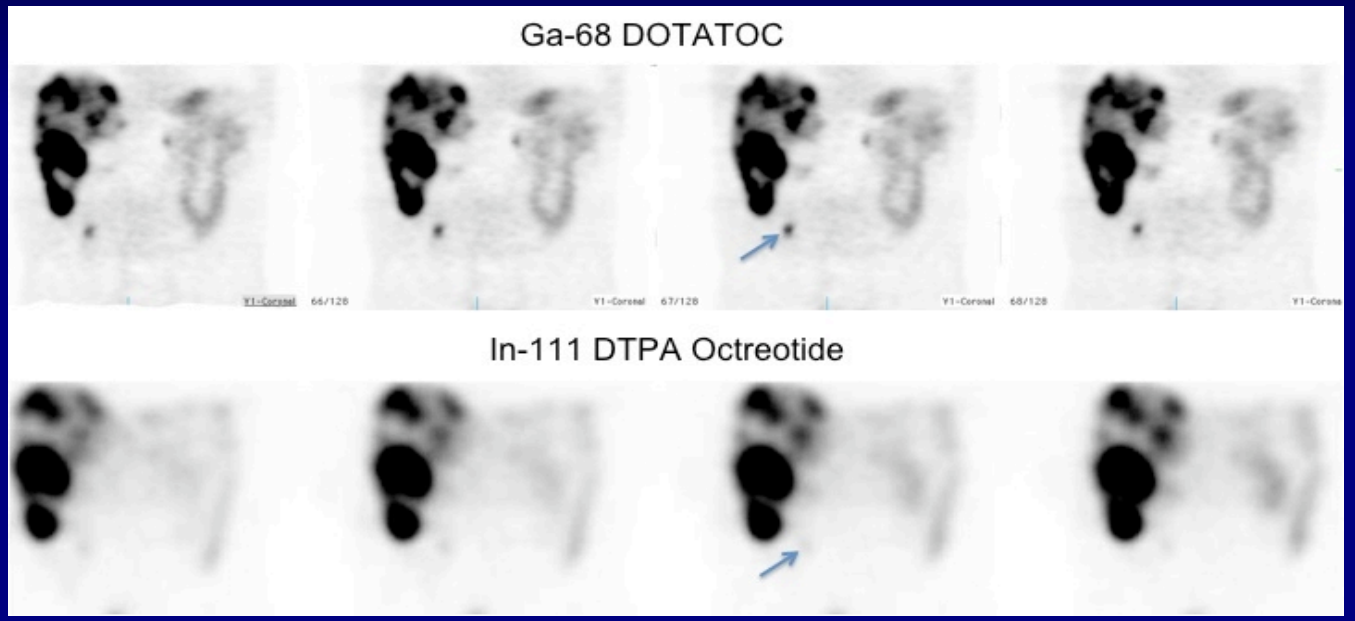
Image courtesy University of Iowa (M. Schultz)

Ga-68 DOTATOC Imaging

Identifying unknown primary tumor

Ga-68 DOTATOC PET

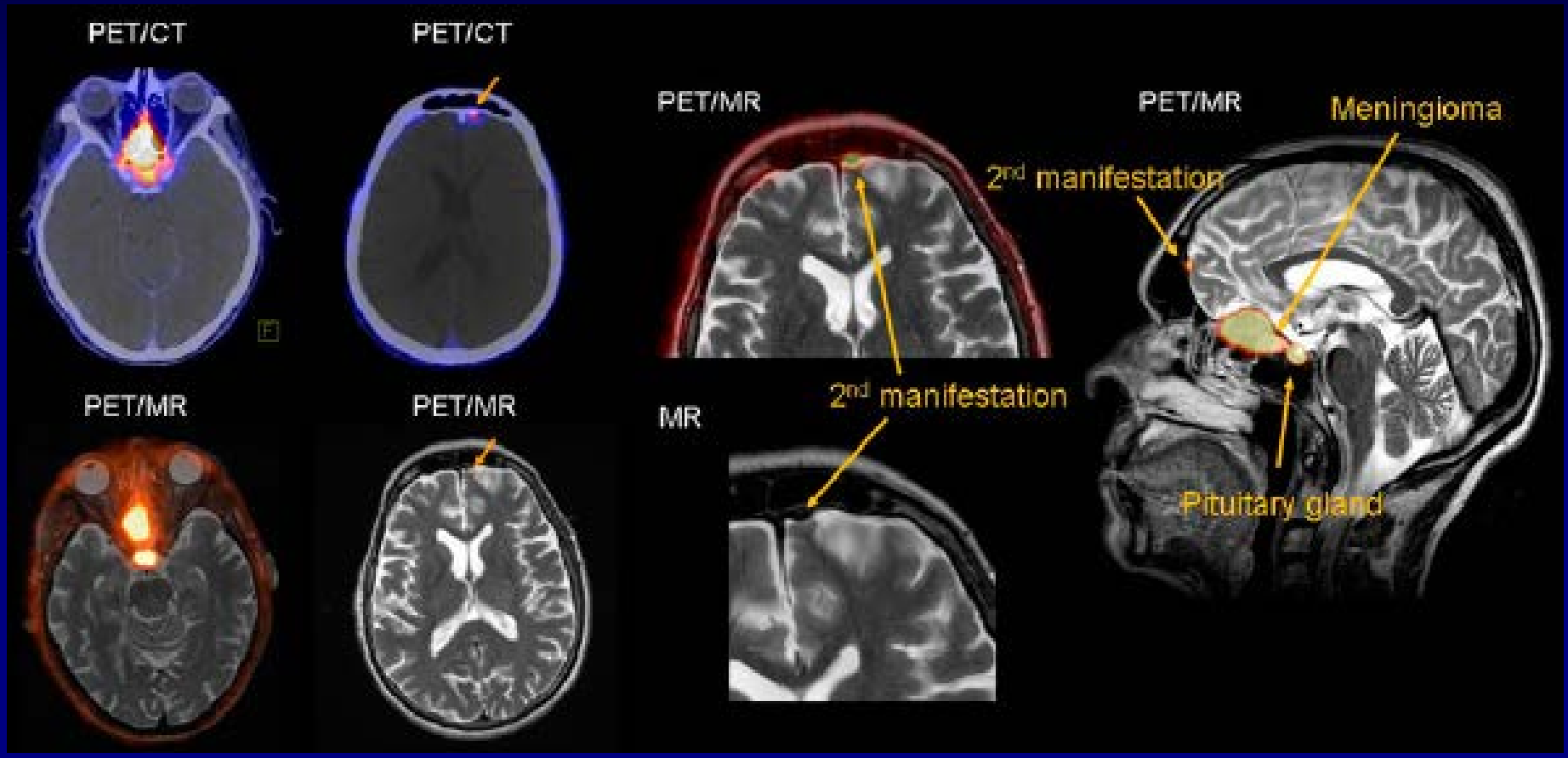
Octreoscan® SPECT



- Not identifiable by Octreoscan® (SPECT)
- Ga-68 DOTATOC, primary could be identified
- Received Orphan Drug status by FDA

Image courtesy University of Iowa (M. Schultz)

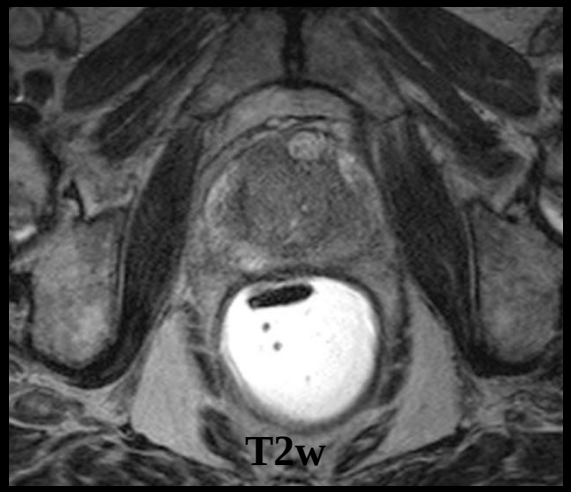
Ga-68 DOTATOC PET: PET-MRI
Meningioma

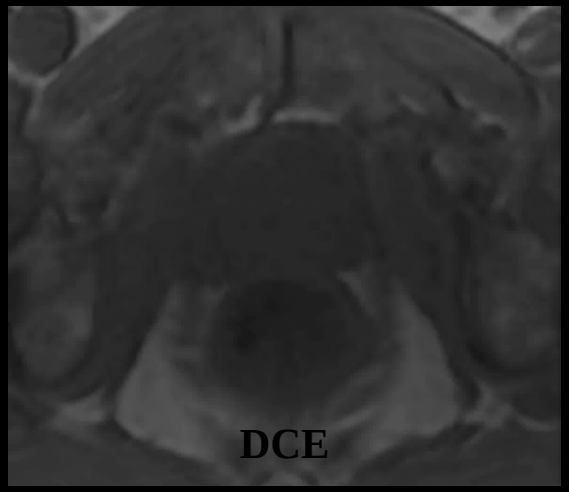


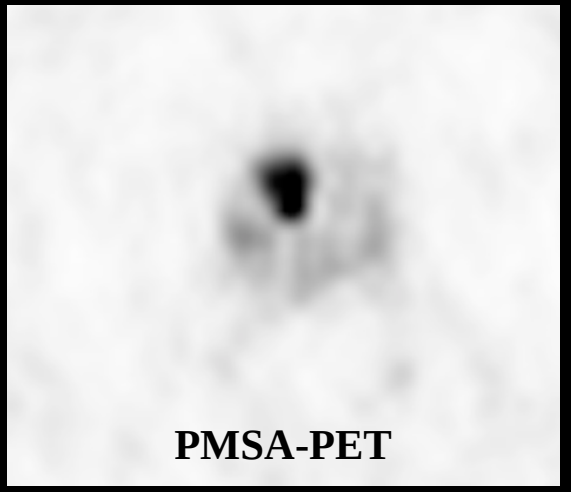
Ga-68 DOTA-TOC: somatostatin receptor imaging of meningioma

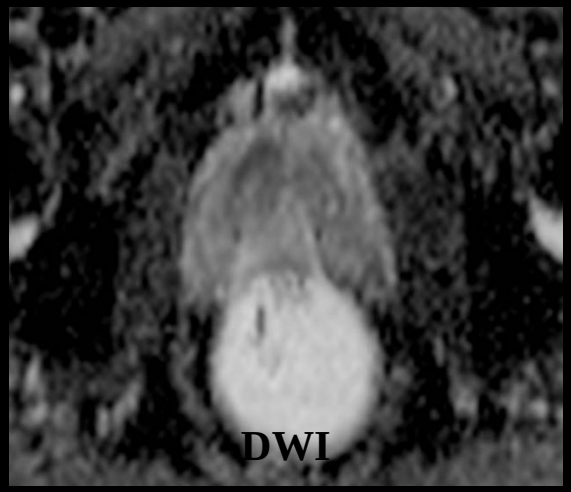
Pichler, JNM 2010

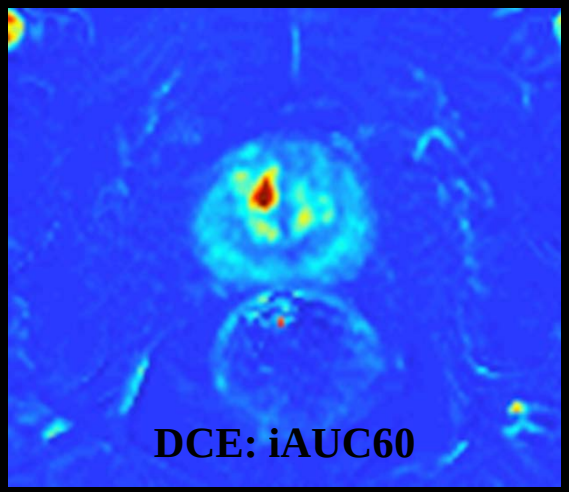
Ga-68 PSMA PET/MR in biopsy negative prostate cancer PET/MRI

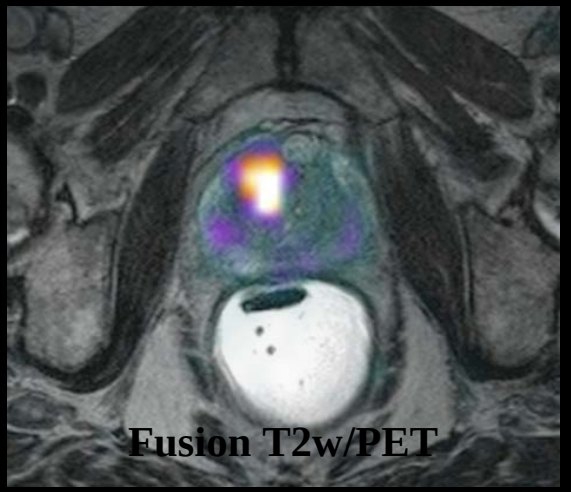












Slide courtesy of Ambros Beer MD, PhD and Matthias Eiber, MD, TUM/LMU Munich

Why Immuno-PET?
Radiolabeled Antibodies

- Antibodies (intact or fragments) are very selective targeting agents
- A wide variety of antibody based therapeutics have been developed in the last 2 decades
- Immuno-PET offers the potential to:
  - Stratify patients that may benefit from antibody therapy
  - Monitor the course of therapy
  - Pave the way for next generation targeted radiotherapeutics

Trastuzumab (Herceptin)

- FDA approved antibody
- Indication: treatment of metastatic breast cancer whose tumors overexpress HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease
- Herceptin imaging agent may be useful for predicting response to Herceptin therapy and determining dosing strategies

Zr-89Trastuzumab Clinical Trial (IND)
Assessment of HER2 Receptors in Breast Carcinoma

Zr-89 Trastuzumab

1. Zr-89: $T_{½}$ = 3.27 days
   - Useful for pharmacokinetic study of intact MAbs
   - Production Method: Y-89 (*p*,*n*) Zr-89
2. Conjugate DFO to Trastuzumab (MAb); then complex Zr-89 to conjugate
3. Evaluate HER2 Positive lesion detection and safety
4. Perform human dosimetry and safety evaluation

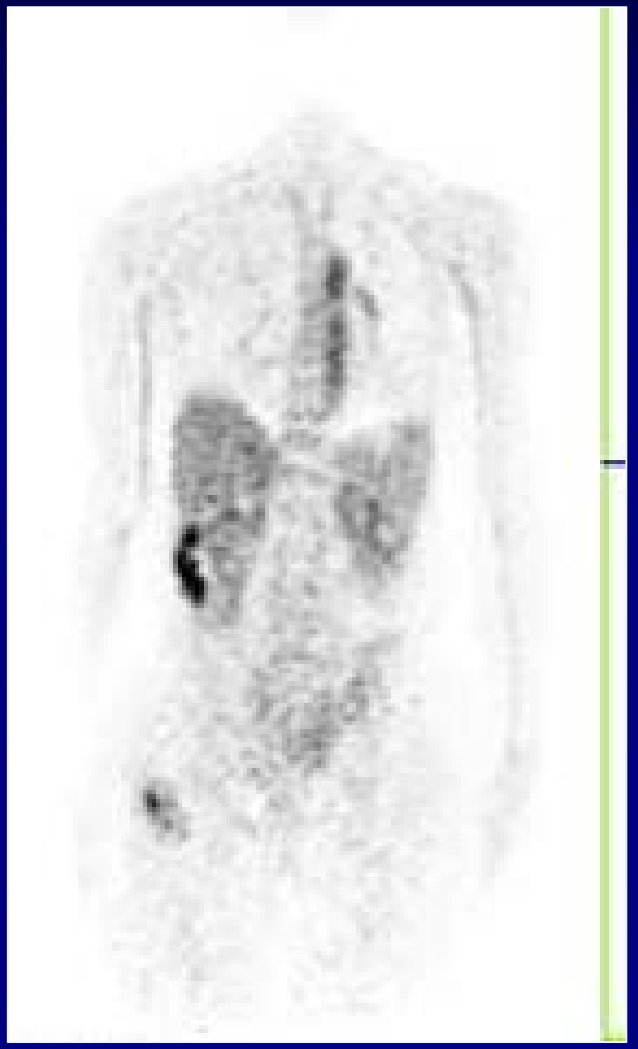
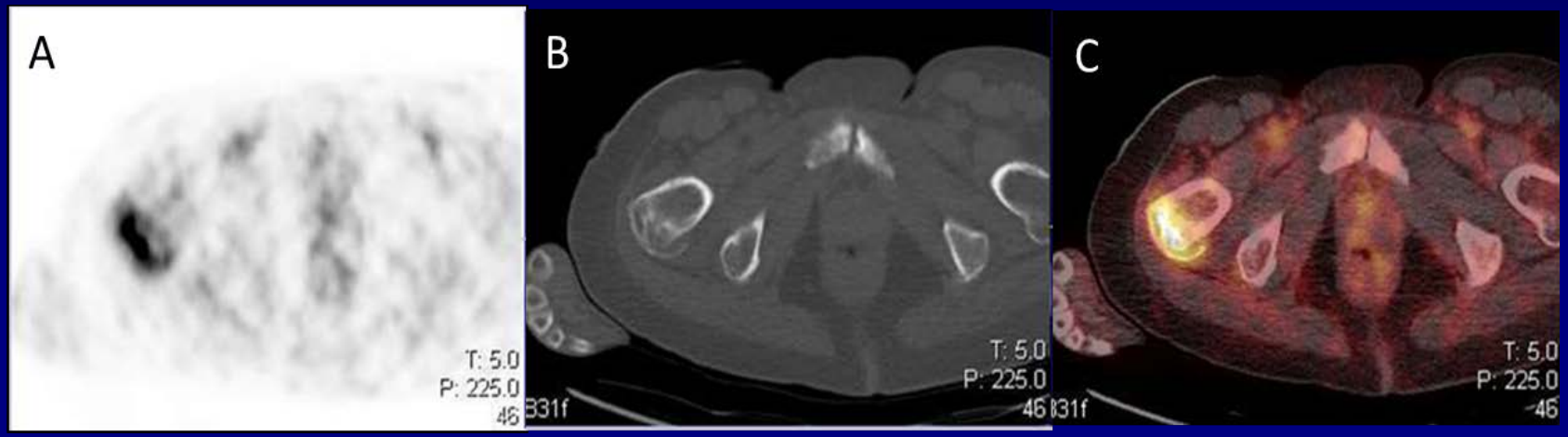


Image courtesy of F. Dehdashti, MD Washington University School of Medicine

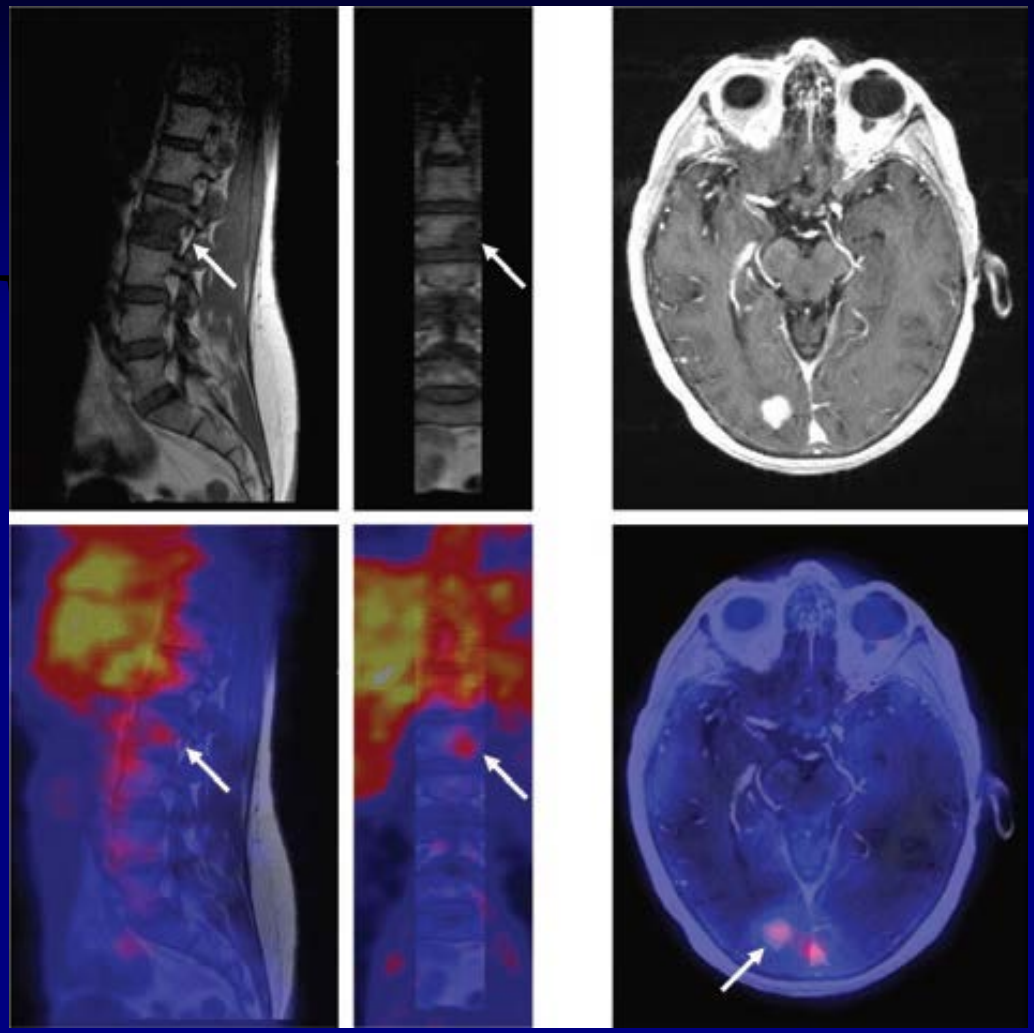
Zr-89-Trastuzumab Clinical Trial



Axial Zr-89-DFO-trastuzumab images in a patient with metastatic HER2 positive disease with a known femur lesion. PET (A), CT (B) Fusion (C)

(a) A vertebral metastasis seen on MRI was unapproachable for biopsy. HER2 status was determined by Zr-89 trastuzumab PET image

(b) HER2-positive brain lesion undetected by conventional CT. Lesion identified using Zr-89 trastuzumab PET, subsequently confirmed by MRI.



Dijkers et al *Clinical Pharm and Therapeutics* May 2010

What will be next to market?