
Pharmaceutical Chemistry Lecture
on
"PET Tracer Chemistry and Imaging in
Drug Discovery"

Dennis Hlasta

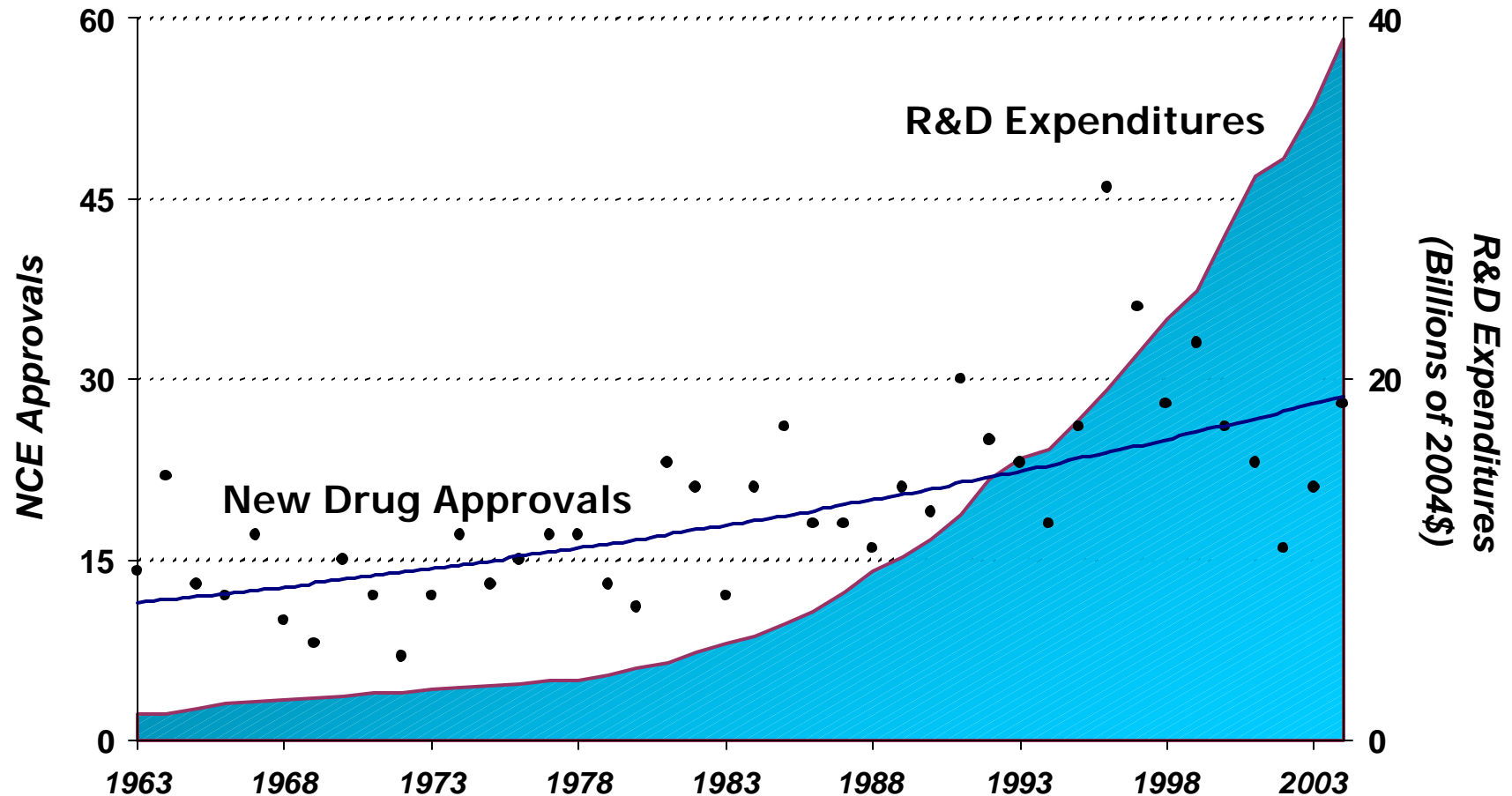
March 19, 2008

J&JPRD
East – Research & Early Development



New Drug Approvals

– Not Keeping Pace with Rising R&D Spending



Source: Tufts CSDD Approved NCE Database, PhRMA, 2005



Emerging Disciplines – a Historical Perspective

- that would “individually revolutionize” Drug Discovery

- Computer Aided Drug Design
- Structure-Based Design
- Molecular Biology
- Genomics / Bioinformatics
- High-Throughput Screening
- Combinatorial Chemistry
 - Large 20-30K Libraries or Mixtures
 - Diversity Enrichment Libraries
- Lab-on-a-Chip



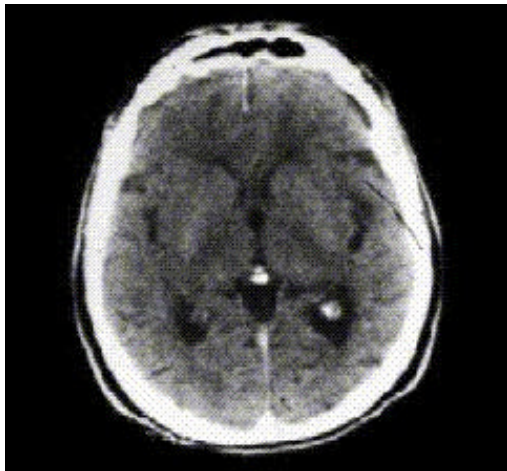
Comparison of Imaging Methods

	<i>Pros</i>	<i>Cons</i>
Positron emission tomography (PET)	Metabolic information Drug target info. - receptors	Radiation Dose, Cost
Computed tomography (CT)	Anatomy information, Bone density	No metabolic information, No drug target information, Poor soft tissue contrast, Radiation Dose
Magnetic Resonance (MRI)	Anatomy information, No Radiation, Soft Tissue information	Little metabolic information, No drug target information, Cost



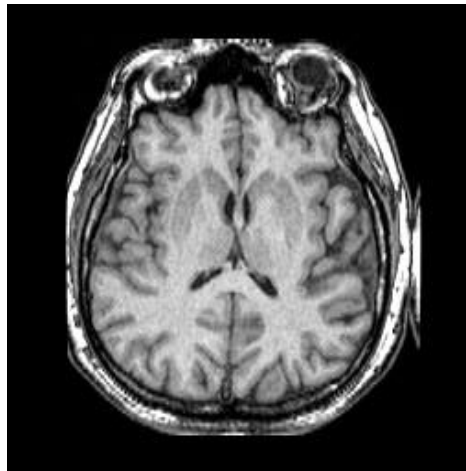
What is "functional molecular imaging"?

Diagnose this patient...



CT scan

X-ray imaging



MRI scan

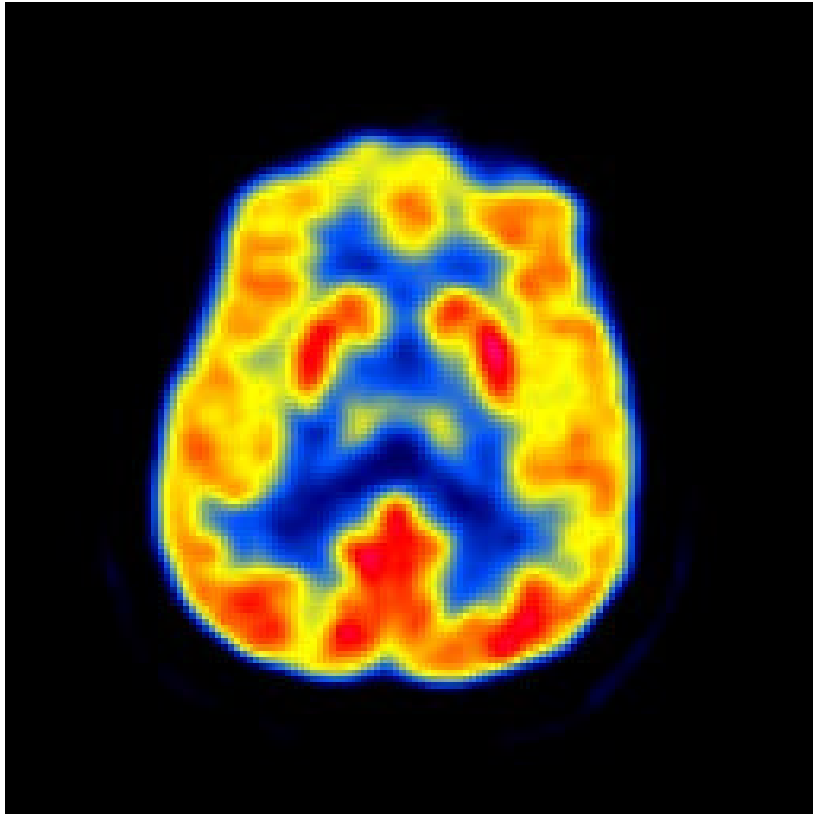
Images H-atom
relaxation (water)



PET scan

Images the PET
radionuclide location

^{18}F FDG PET brain scan



PET scan

Images the PET
radionuclide location

- Radioactive analog of glucose
- Measures brain metabolism
- Changes in metabolism resulting from cognitive challenge or drug

What is “molecular imaging”?

- Probing biological processes at the molecular level.
- Image these biological processes in 3D.
- Most drugs are designed for a specific molecular target.
- Molecular changes nearly always occur long before improved clinical symptoms.



How do we do “functional molecular imaging”?

- Use a PET scanner
- Measure the three-dimensional distribution of a radioactively-labeled compound in the body
- Non-Invasive
- Animal studies first, then translate to Human study.
- Depends critically on radiochemistry



Positron Emission Tomography

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Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

Positron

Detects two gamma rays resulting
from decay of positron - 511 keV

Emission

Tomography



Photons emitted from inside
subject - as opposed to
“transmission” where they are
generated externally.

Positron

Emission

Tomography



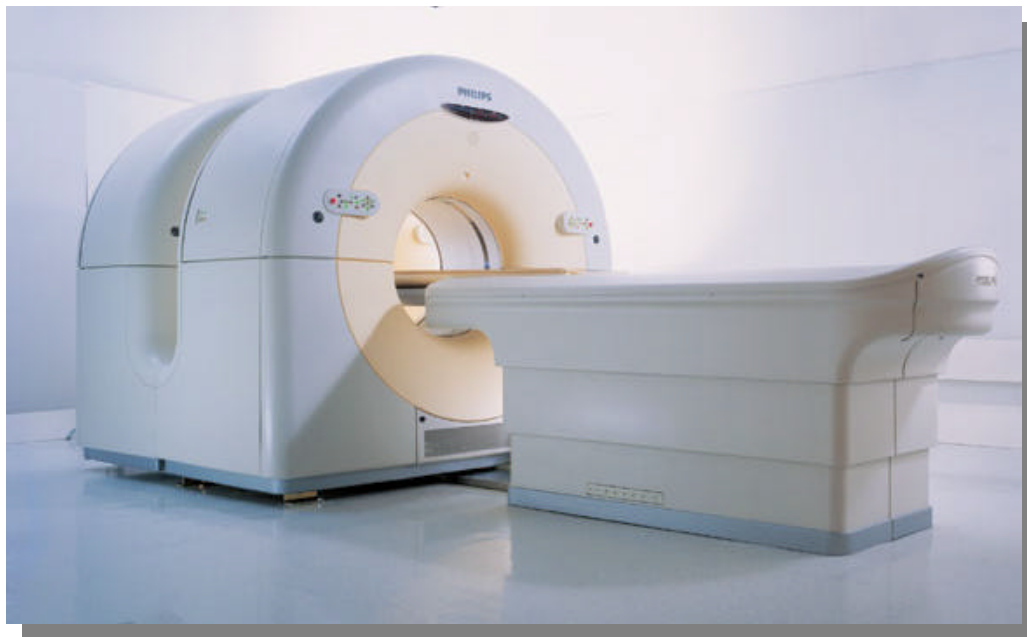
Positron Emission

Generates three-dimensional
maps of radioactivity
concentration - tomographic

Tomography

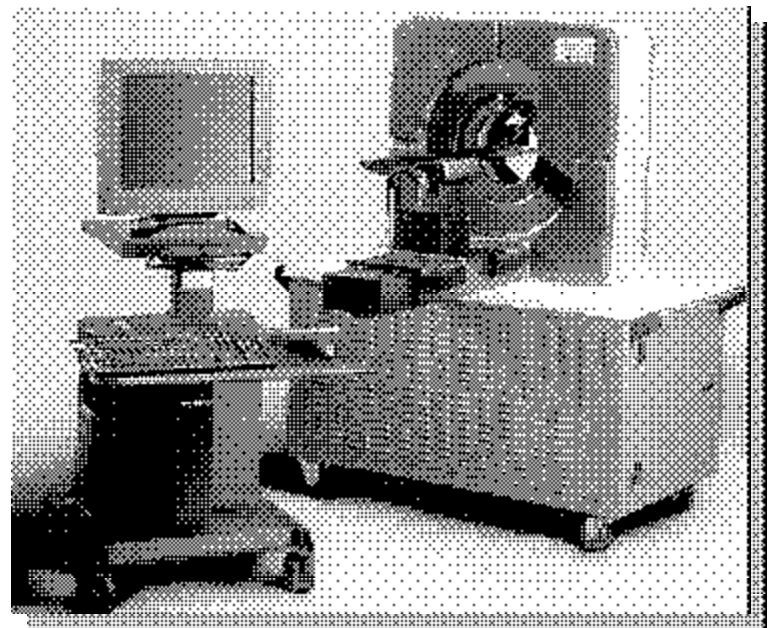


PET Scanners

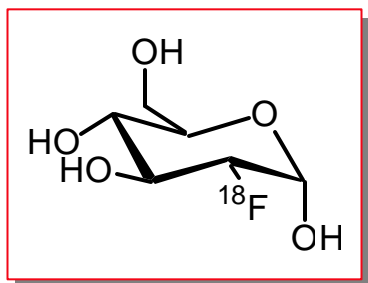


Clinical PET scanner

Animal PET scanner



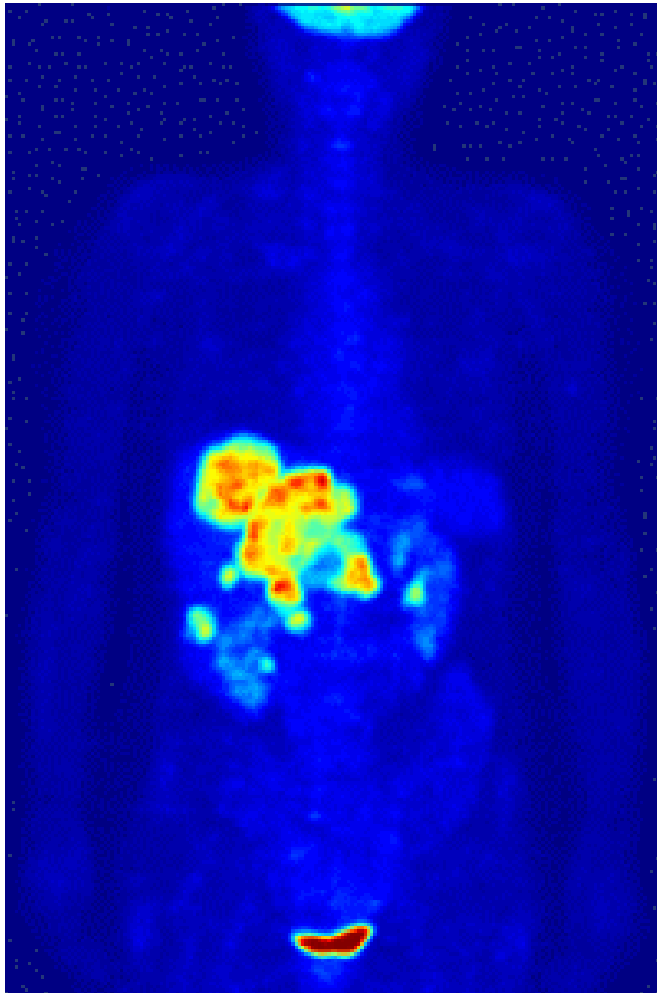
[¹⁸F]-Fluorodeoxyglucose (¹⁸F-FDG)



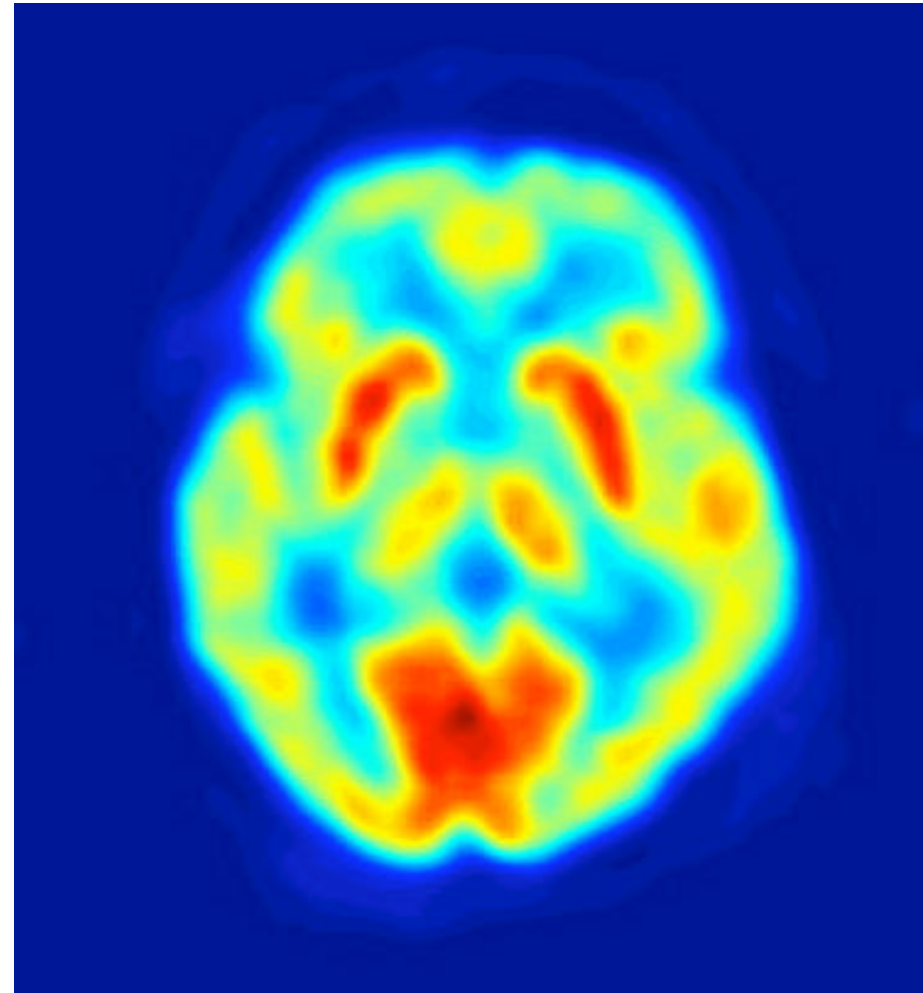
Hamacher K. *et al.* *J. Nucl. Med.* **1986**, 27, 235-238.

- Glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase.
- Mitochondrial hexokinase is greatly elevated in rapidly-growing cells.
- Because the oxygen atom (which is replaced by F-18) is required for the next step in glucose metabolism, no further reaction occurs on FDG.
- FDG is trapped in the cells.
- Results in intense radiolabelling of tissues with high glucose uptake.
- Imaging of Brain, Heart, and Tumors.

^{18}F FDG PET Images



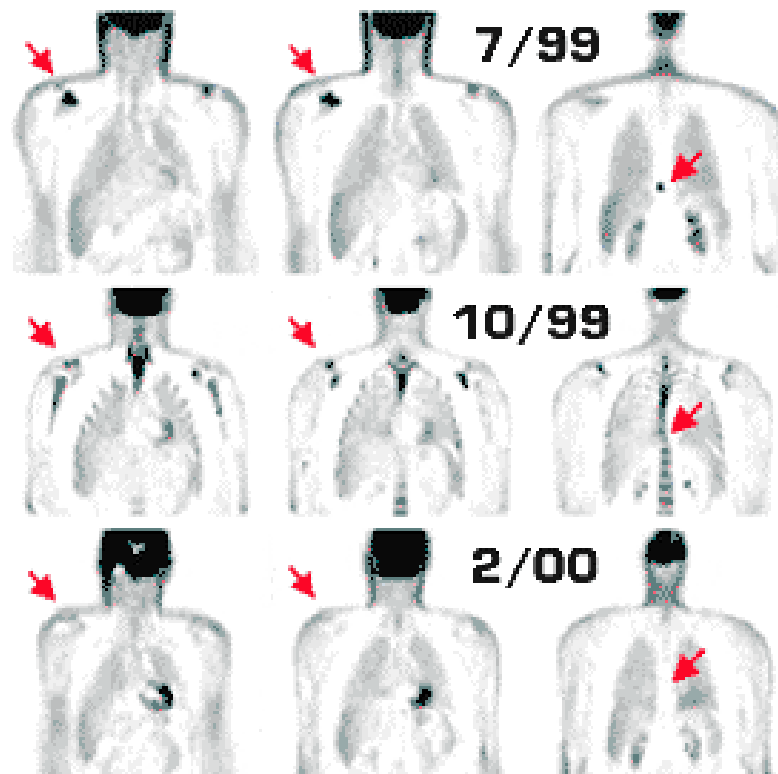
^{18}F -FDG whole body PET acquisition



A typical PET image of the brain examination in transaxial view. Red areas show more accumulated radioactivity and blue areas show where low to no activity was accumulated.

FDG PET in Hodgkin's or non-Hodgkin's lymphoma

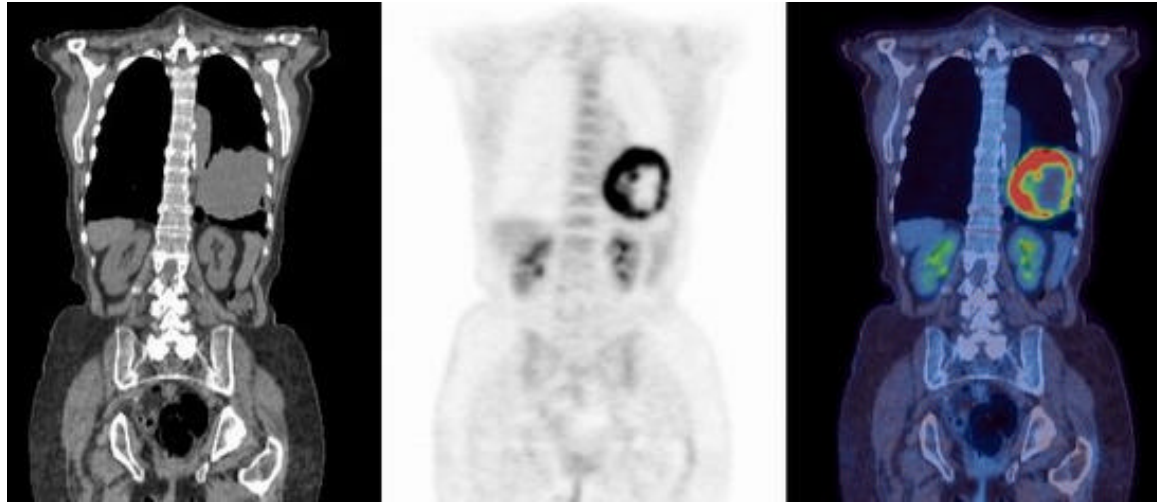
– *diagnosis and treatment*



PET scans trace the progress of this patient's recovery, showing that the chemotherapy is working.

http://www.petscan.org/frames_alzh.html

Lung Cancer



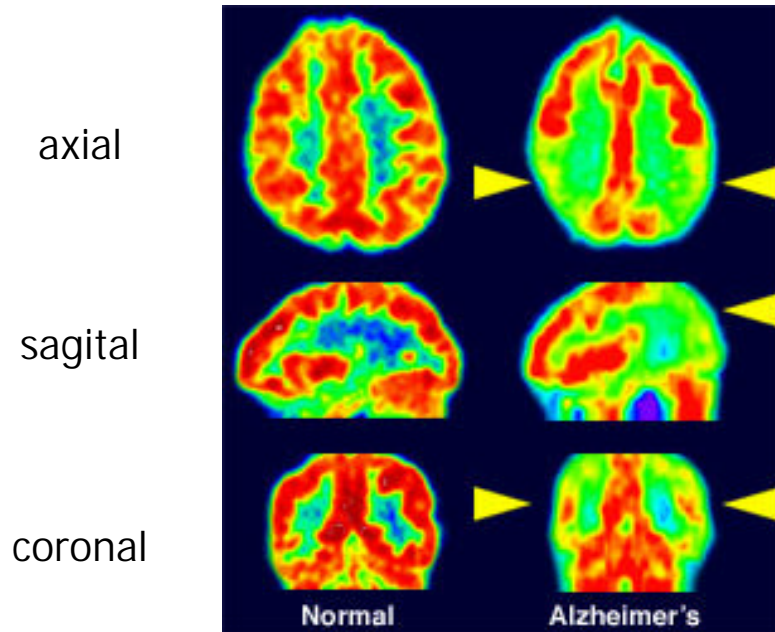
Clinical history: This patient was referred for assessment of a mass in the left lung.

Findings: There was high uptake of FDG consistent with lung cancer but no evidence of spread elsewhere. The mass was biopsied and shown to contain non-small cell lung cancer. The patient was treated with surgery.

Teaching points: PET/CT is used to determine the 'stage' of lung cancer (whether it has spread from the lung cancer elsewhere in the body). This helps to decide on the best treatment.

<http://howpetworks.com/>

Alzheimer's Disease Diagnosis

**Indication:**

The patient is a 77-year-old male with history of cognitive deficits.

Findings:

There is moderately severe biparietal hypometabolism, extending through the full extent of the parietal lobe. This most likely represents a variant of Alzheimer's disease.

Images courtesy of the Ahmanson Biological Imaging Clinic, UCLA.

http://www.petscan.org/frames_alzh.html

- Early drug therapy to slow the loss of the patient's ability to function.
- Future planning before loss of mental capacity.
- Positive and accurate diagnosis of other dementing processes, chronic depression, and normal aging.
- Help in the discovery and development of new therapies.

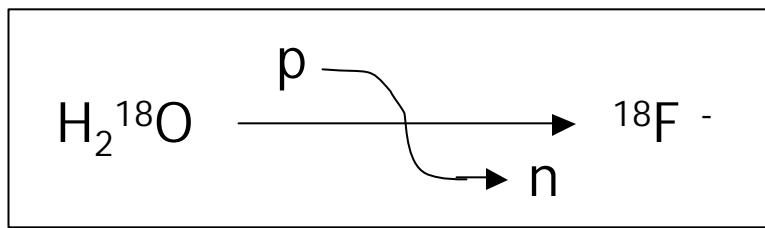


How are PET Radionuclides Produced?

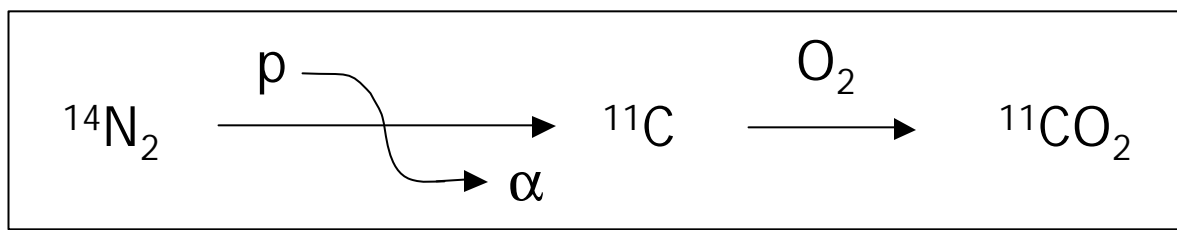
Radionuclide – An atom which is unstable, therefore undergoes radioactive decay



Cyclotron – produces PET Radionuclides



${}^{18}\text{F} \quad t_{1/2} = 110 \text{ min}$



${}^{11}\text{C} \quad t_{1/2} = 20 \text{ min}$



What is Positron Emission Tomography?

Where does the PET signal come from?



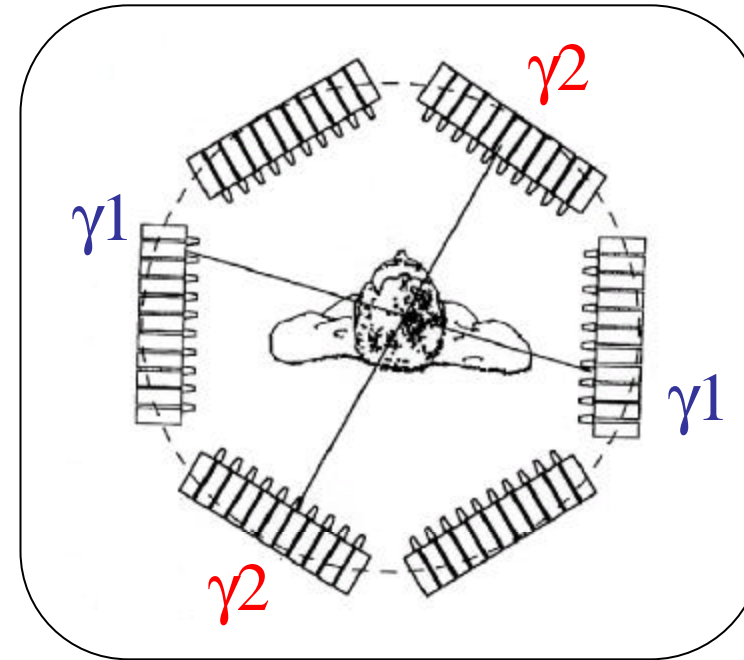
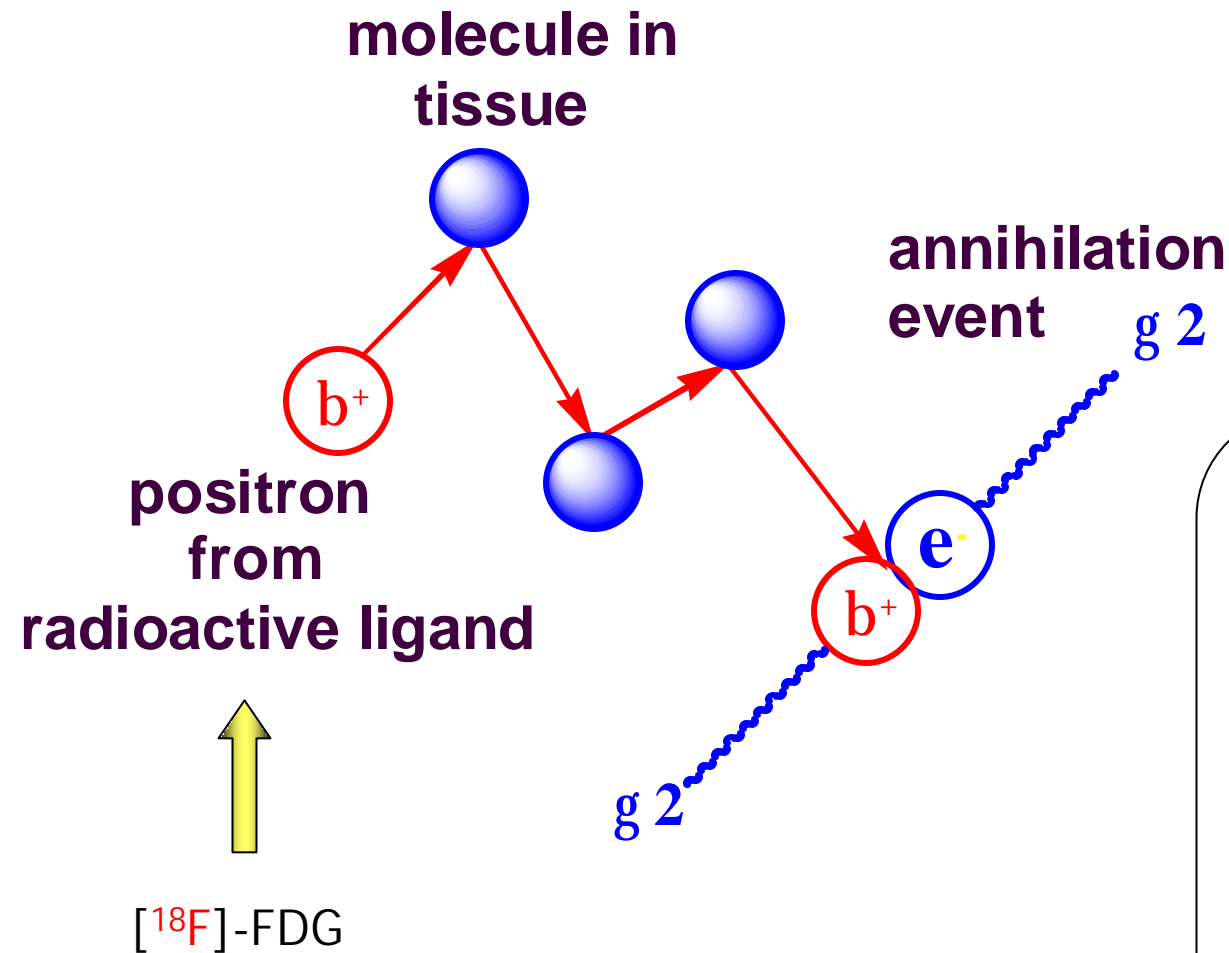
Matter – Antimatter Reaction



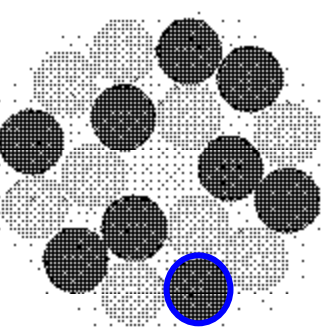
- Warp core – USS Enterprise / Star Trek
 - Fictional power plant based on matter–antimatter reaction.
 - **When matter and antimatter come into contact, they annihilate each other and release energy**
 - “dilithium crystals” are unreactive and regulate the reaction
 - Deuterium is the matter and antideuterium is the antimatter.
- PET Imaging
 - PET radionuclide decays and release a positron (antielectron).
 - When the positron collides with an electron in a matter–antimatter reaction, they annihilate each other and energy is released as 2 gamma rays.



Positron Emission Tomography (PET)

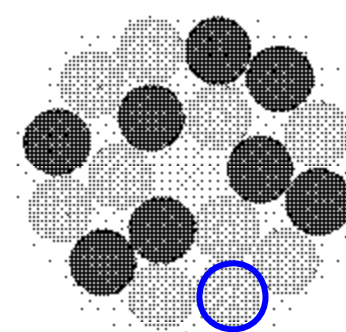


Positron Emission Tomography



Fluorine-18 nucleus containing 9 protons and 9 neutrons. This nucleus is unstable. It decays by positron (beta positive) emission.


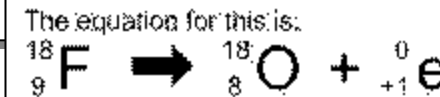
Fluorine-18 nucleus



Positron

Oxygen-18 nucleus


A proton has become a neutron, and a positron has been emitted. The Fluorine-18 nucleus has now become an Oxygen-18 nucleus.



The positron travels until it comes into contact with an electron. A positron is an anti-electron. The positron and electron therefore annihilate each other. Gamma rays are emitted at 180 degrees to each other.



The positron and electron have now annihilated each other. This caused gamma rays to be emitted at 180 degrees to each other. These continue to travel out of the body.



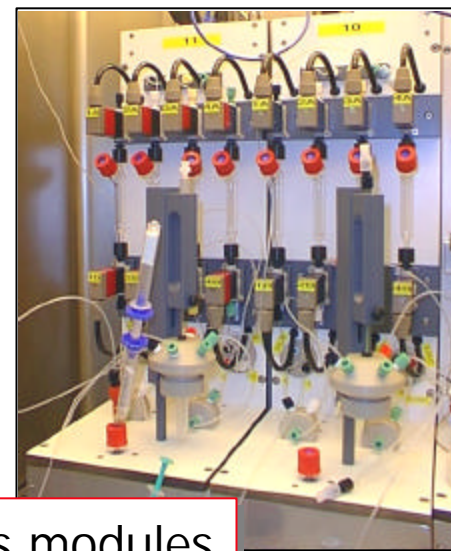
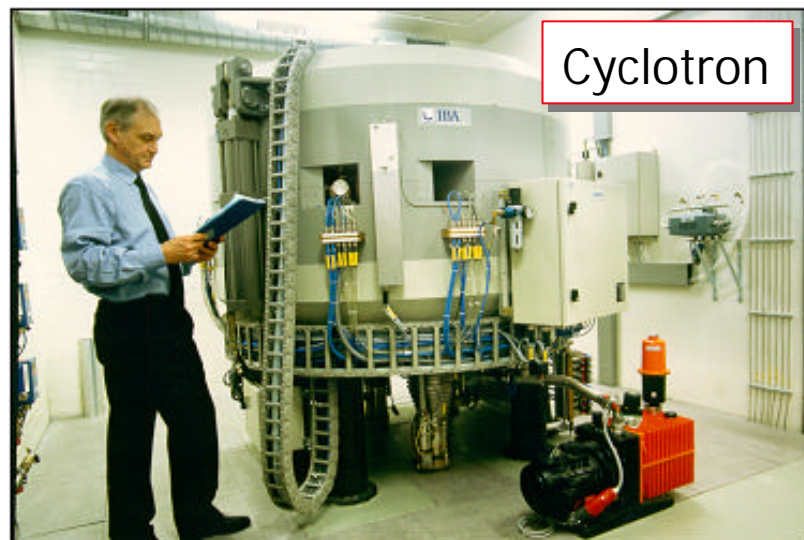
How are PET Tracers Synthesized?

Tracer – molecule that is labeled with a radionuclide and used in molecular imaging. Given at extreme low dose levels in animal and human studies at 2-5 mCi or ~5 ug.



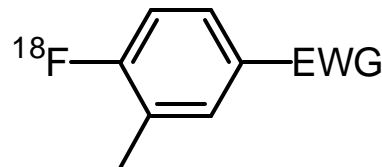
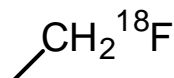
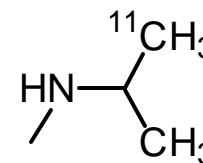
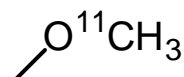
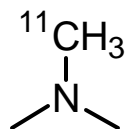
PET Radiochemistry and Cyclotron

- Cyclotron
 - F-18 & C-11 precursors
- Radiochemistry lab
 - Hot cells
 - Synthesis modules
 - QC analytical lab

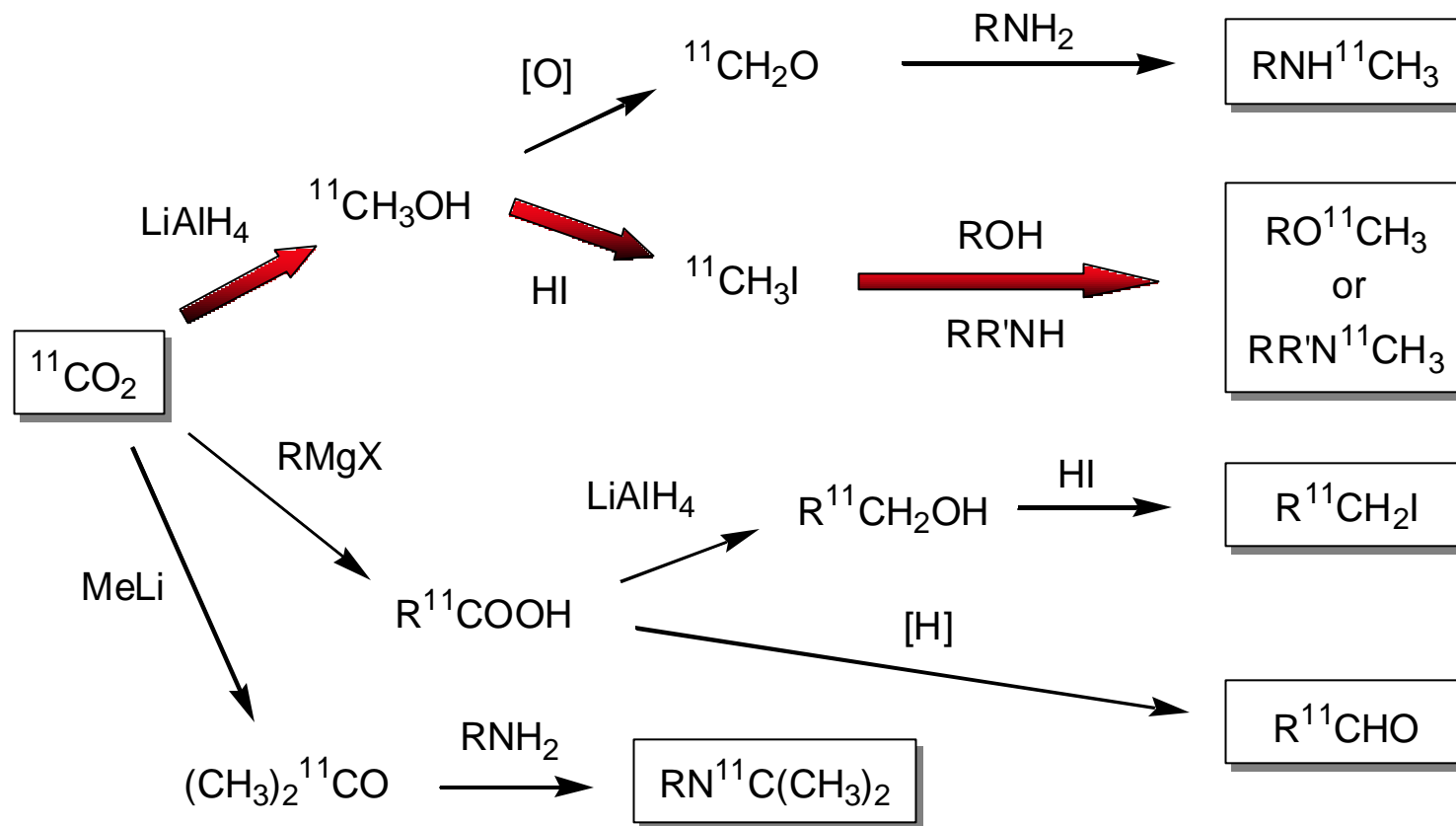


PET Tracer Selection

- Design drug molecules with C-11 and F-18 labeling in mind for future imaging studies.



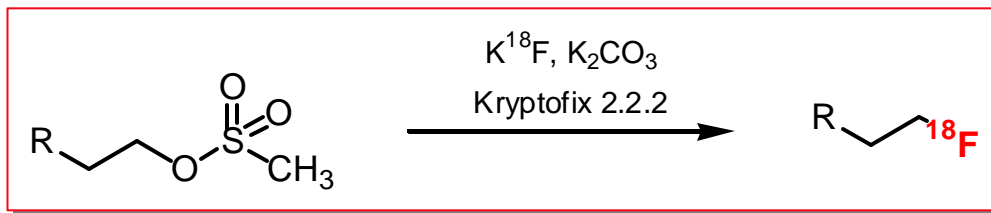
$^{11}\text{CO}_2$ Chemistry



¹⁸F Chemistry

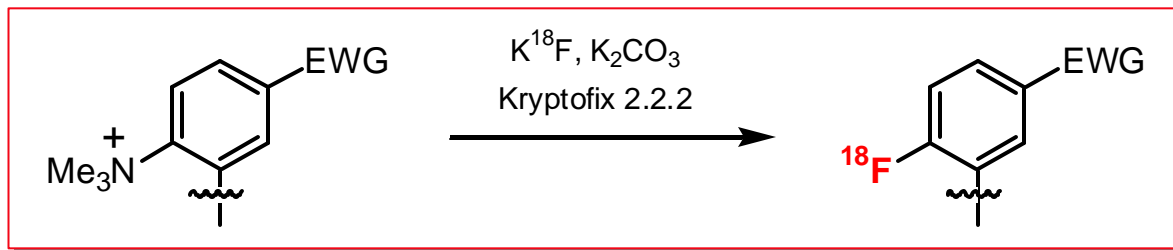
Nucleophilic Displacements:

- By far the largest body of F-18 fluorination experience is nucleophilic.
- F⁻ displacement of halogens on alkyl-halides
- Tosylates, mesylates, triflates (most common pathway)



Nucleophilic Aromatic Substitution (S_NAr):

- Nucleophilic reactions with diazoniums don't work well (Sandmeyer Rxn).
- Substitution of activated aromatic nitro or iodide provides moderate yields in uncomplicated structures.
- Preferred method is substitution of EWG activated, aromatic-trimethylammonium salts with fluoride.

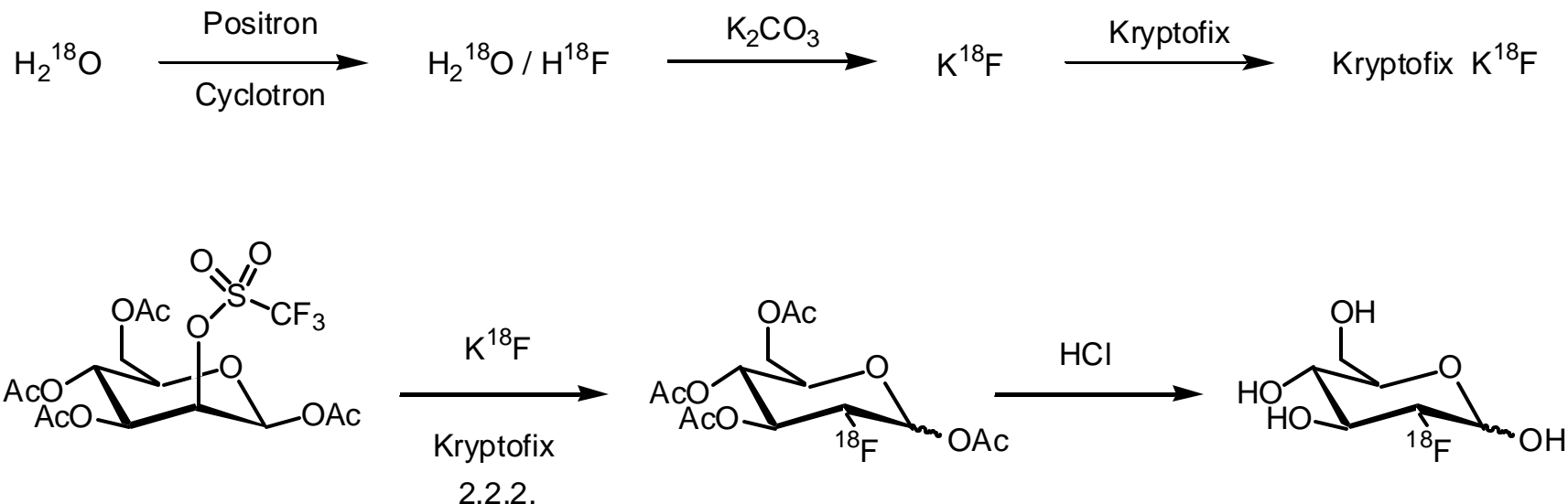


EWG = -SO₂NH₂; -COR; -CN; etc.

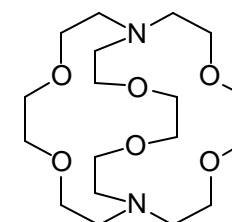
Examples of PET Tracer Syntheses and Imaging



[¹⁸F]-Fluorodeoxyglucose (¹⁸FDG)



Hamacher K. *et al. J. Nucl. Med.* **1986**, 27, 235-238.



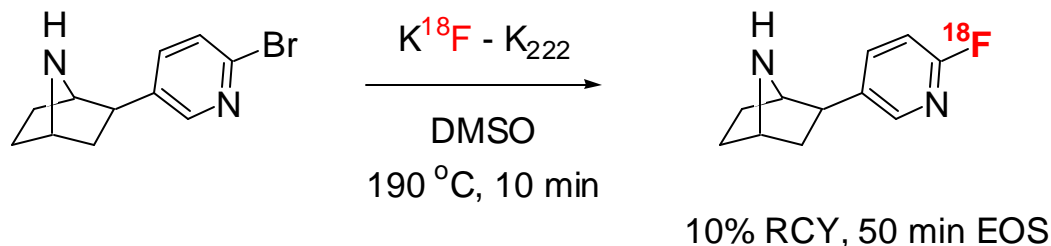
Kryptofix 2.2.2.

crown ether

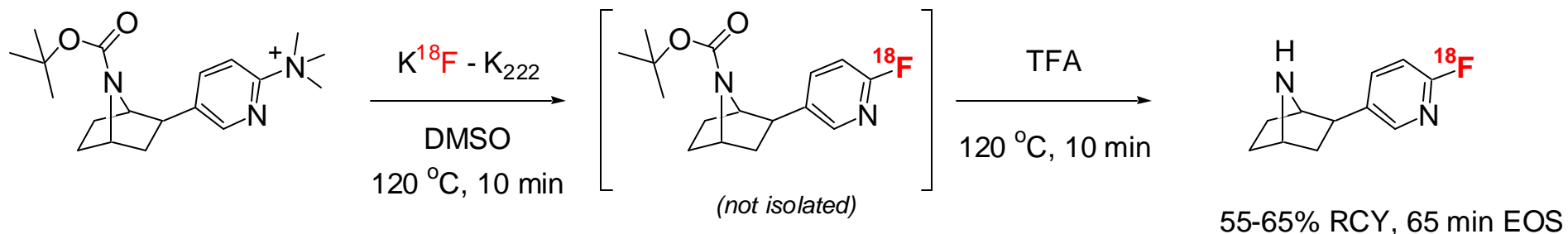


Nicotinic **a4b2** tracer

– Epibatidine an analgesic natural product

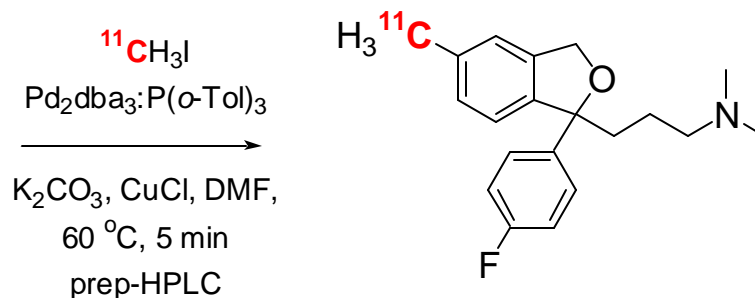
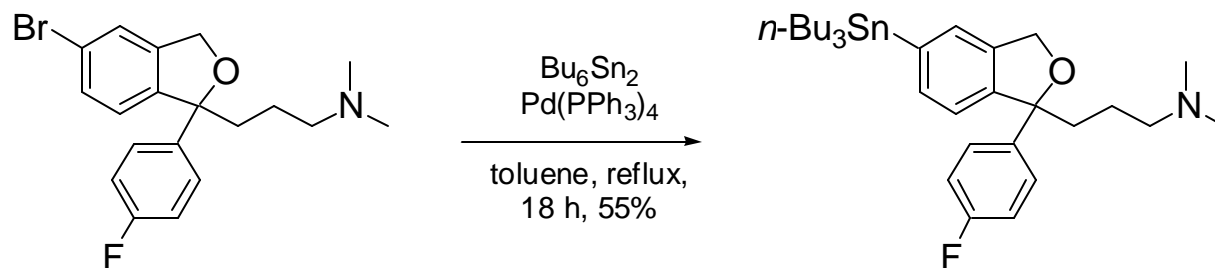


Horti AG, et al. *J. Label Compds Radiopharm* **1996**, 28, 355-365.
Horti AG, et al. *J. Nucl. Med.* **1997**, 38, 1260-1265.



Ding YS, et al. *Synapse* **1996**, 24, 403-407.
Ding YS, et al. *J. Label Compds Radiopharm* **1997**, 39, 828-832.

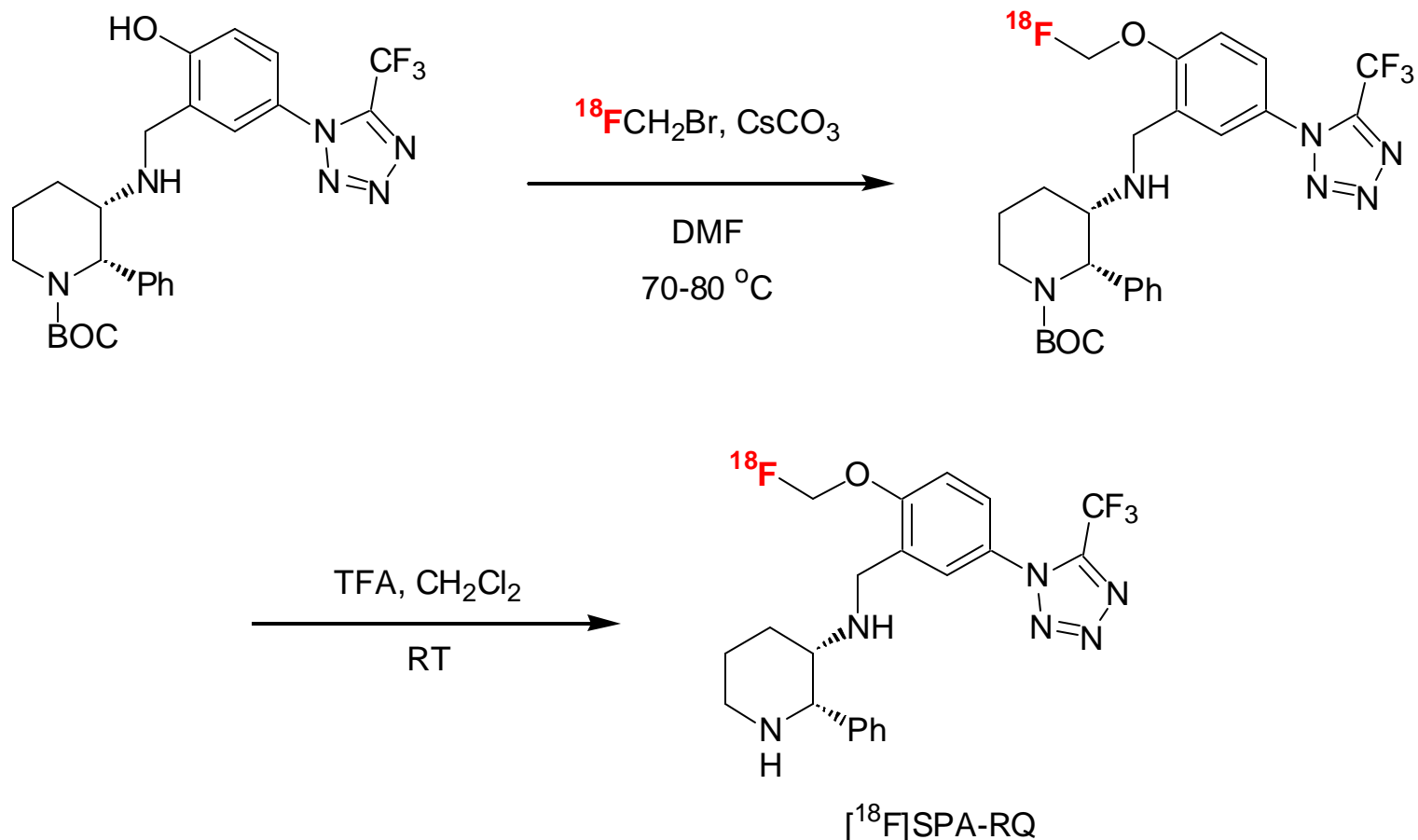
Citalopram – Tracer for the Serotonin Transporter



65-90% RCY, 45 min EOS
>98% radiochemical purity

J. Madsen, et al. *Bioorg Med Chem* **2003**, 11, 3447-3456.

Aprepitant – NK1 Radiotracer [¹⁸F]SPA-RQ

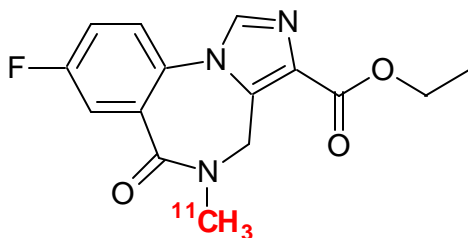


Bergstrom, Hargreaves, Burns, Goldberg, Sciberras et al *Biol Psychiatry* 2004, (55) 1007



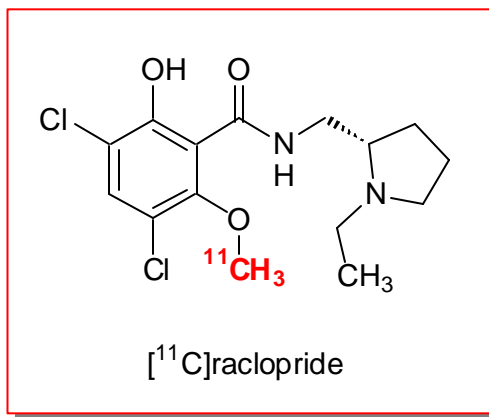
Alkylations with $[^{11}\text{C}] \text{MeI}$ and $[^{11}\text{C}] \text{MeOTf}$

^{11}C -labeled radiopharmaceuticals prepared via N-, O- and S-methylation reactions



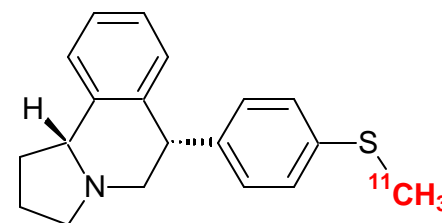
$[^{11}\text{C}]$ flumazenil

Zhang et al. *Nucl Med Biol* **2002**, 29, 233-241.



$[^{11}\text{C}]$ raclopride

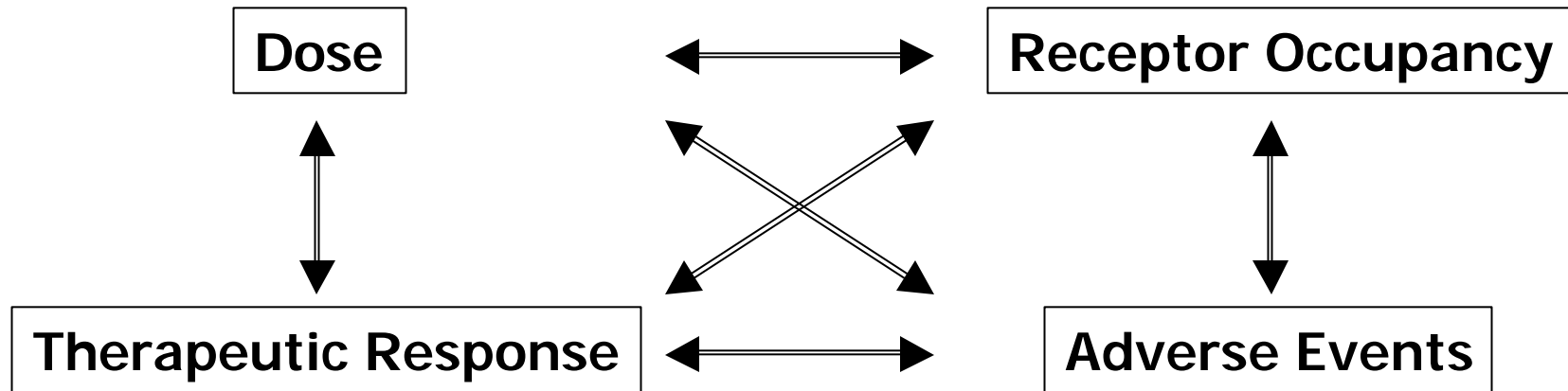
Wilson et al. *Nucl Med Biol* **2000**, 27, 529-32
Iwata et al. *Appl Radio Isot* **2001**, 55, 17-22



$[^{11}\text{C}]$ McN-5652

$[^{11}\text{C}]$ raclopride is a selective radiotracer for the D_2 dopamine receptor

What value does a PET Tracer deliver?



- PET tracer used to quantitate the drug receptor occupancy.
- Allows a direct correlation of dose, receptor occupancy and therapeutic response.
- Key deliverable of a PET tracer is to set the dose for phase III human studies.

Imaging in drug discovery

- Proof of target
 - Is drug getting to target?
- Proof of mechanism
 - Is drug having an effect?
- Proof of efficacy
 - Is drug affecting disease?



Impact of Molecular Imaging on Drug Development

- Improve selection of Development compounds
 - Enhances the quality of molecules as well as enhances their probability of success.
- Eliminate failures early
- Can allow the early selection of the right clinical dose.
- People are heterogeneous, therefore finding the lowest dose of a drug that is effective for all is very difficult
- Find the right dose for clinical efficacy
 - Optimizes the therapeutic index.
 - Therapeutic index is the ratio of adverse event dosage to the lowest therapeutic dosage.



Quotes by chemists

"People are growing up with no idea that science is actually different from political punditry, different from people spouting opinions. Science actually tells you things that are true, not just things that are somebody's opinion,"

Theodore Gray, Popular Science columnist (C&Enews, Nov. 26, 2007 p 50)

"It's important to put our faces on chemistry and for us to feel proud to talk about what we do as chemists and how many alternative careers there are for chemistry."

ACS President Catherine Hunt, (C&Enews, Dec. 17, 2007 p 36)



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1. R. A. Frank, et al. *J. Label Compds Radiopharm* **2007**, 50, 746-769.
2. Gary J. Kelloff, et al. *Clin Cancer Res* **2005**, 11, 7967-7985.
3. <http://howpetworks.com/>
4. http://www.petscan.org/frames_alzh.html
5. http://depts.washington.edu/nucmed/IRL/pet_intro/toc.html
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3. Mason and Mathis *Neuroimag Clin N Am* **2003**, 13, 671.
4. H.D. Burns *Annual Reports in Med Chem* **2001**, 36, 267.
5. Lee and Farde *TRENDS in Pharmacol Sci* **2006**, 27, 310.
6. J. Wang and L Maurer *Current Topics in Medicinal Chemistry* **2005**, 5, 1053-1075.

