PET
Positron Emission Tomography

Review of FDA-Approved Agents & Promising Research Agents

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Objective

I. US FDA Approved PET Agents
II. Drug Development Process
III. Inst. RP Research Pathways
IV. Approved PET indications
V. PET RPs in Research

Assessment Question:
1. Of the 70% of investigational drugs that move to Phase I, what is the percentage of drugs that actually move to approval?
   a. 1%
   b. 10%
   c. 25%
   d. All of them, because we need them!
Assessment Question:

2. Xofigo® $^{223}$Ra dichloride is currently FDA approved for use in which of the following:

a. Prostate Cancer  
b. Breast Cancer  
c. Osteosarcoma  
d. Both a. and b.  
e. All of the above indications, because it’s awesome!

Assessment Question:

3. F-18 Flurpiridaz is an agent used for:

a. Beta amyloid imaging  
b. Tau protein imaging  
c. Myocardial perfusion imaging  
d. Bone imaging  
e. All of the above because it can do it all!

Assessment Question:

4. What are the characteristics of Cu-64? (circle the most correct answer)

a. Half-life = 12.7 hrs.  
b. Available via cyclotron  
c. Decays by positron emission  
d. Transitional metal, Z = 29  
e. All of the above because Cu-64 is an all-in-one radionuclide!
Assessment Question:
5. An example of theranostics of NETs is exhibited by use of which of the following:
   a. Ga-68/Lu-177
   b. Zr-89/Cu-64
   c. In-111/Ra-223
   d. All of the above because they all make a great team!

I. FDA Approved PET Agents

“Over the years, several THOUSANDS of PET tracers have been developed, yet FDG remains the primary agent.”
WHY?
"Yet, while PET is widely used in Europe, its benefits have not been widely available to American patients, mainly because of lack of reimbursement and inappropriate and costly regulations promulgated by the FDA."

(Source: Senate Report No. 43, 105th Congress, 1st Session)

Radiotracrer Approval Barriers:

- **Discovery/Development:**
  - Therapeutic: ~$850 million over 12.9 yrs.
  - Diagnostic: ~$100-200 million over 8-10 yrs.

- **New Drug Approval Cost (FDA.gov):**

<table>
<thead>
<tr>
<th>Application with Data</th>
<th>Application with Clinical Data</th>
<th>Application without Clinical Data</th>
<th>Product</th>
<th>Labeling and Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>$2,724,000</td>
<td>$1,187,500</td>
<td>$1,145,000</td>
<td>$14,875</td>
<td>$269,300</td>
</tr>
</tbody>
</table>


II. Drug Development Process

- **Drug Discovery**
  - Basic Research
  - Target ID

- **Pre-Clinical Development**
  - Candidate Selection

- **Clinical Research**
  - Phase I
  - Phase II
  - Phase III

- **Phase IV**

Overall, the clinical success rate for all drugs from Phase I to Approval is approximately 11%.

Clinical Research

Phase I → 70% drugs move to next phase

Phase II → 33% drugs move to next phase

Phase III → 25-30% drugs move to next phase

**Only 20-30% of drugs move to approval**

III. Institutional Research Process:

NM clinical protocols

1. Protocol
2. Reviewers
3. NMPRC
4. CRC
5. IRB
6. IND/RDRC

Role for a Nuclear Pharmacist
Drug Development Process

- IND Submission
  - 30 day FDA review of application
  - FDA approval, clinical trial begins
  - Researcher ends trials
  - Files marketing application
- NDA submission
- Approved Drug

IV. FDA Approved PET RPs

Sodium $^{18}$F Fluoride
Bone Imaging

Image Courtesy of Dr. Elba Etchebehere, MD/ACC
“Goal: Evaluate outcome after \( ^{223}\text{Ra} \) and the potential of fluoride PET/CT to determine whole-body skeletal tumor burden as a prognostic biomarker of survival in patients.”

**Radium-223**

**Bone Cancer Therapy**

**Xofigo\textsuperscript{®} \( ^{223}\text{Ra} \) dichloride**

- Alpha emission (95.3%)
- \( T_{1/2} = 11.4 \text{ days} \)
- Dose: 1.35 \( \mu \text{Ci/kg} \)
- Schedule: 4 week intervals X 6 doses
- Route: IV injection over 1 min
- Requirement: Blood counts, baseline
  - ANC > 1.5 \( \times 10^9 \)
  - Platelets > 100 \( \times 10^9 \)
  - Hemoglobin > 10 g/dL
  - & prior to subsequent txmt.
Xofigo® 223Ra dichloride

How it works:
Radium Targets Osteoblastic Bone Metastases by Acting as a Calcium Mimetic

Adverse Reaction:

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>Peripheral edema (13%)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea (27%)</td>
</tr>
<tr>
<td></td>
<td>Nausea (20%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting (10%)</td>
</tr>
<tr>
<td></td>
<td>Anemia (3%)</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia (72%)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia (38%)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (31%)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia (18%)</td>
</tr>
<tr>
<td>1-10%</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>Injection site reactions (erythema, pain, swelling)</td>
</tr>
<tr>
<td></td>
<td>Aplastic anemia</td>
</tr>
</tbody>
</table>
Administration: Outpatient

Role for a Nuclear Pharmacist

Ra-223 Clinical Trials

Clinical Trials: Osteosarcoma, Breast Cancer & Multiple Myeloma

Role for a Nuclear Pharmacist
FDA Approved PET RPs

Rubidium-82
Heart Imaging

N-13 Ammonia
Heart Imaging
“The quality of images using the two radiopharmaceuticals (Rb-82 and N-13 ammonia) were comparable.”


Ideal Characteristics of MPI Agents

Criteria:
1. High cardiac uptake to run target ratio with minimal redistribution
2. Better image quality and ease of detection
3. Near linear myocardial uptake versus flow up to 5 ml/min (high first pass extraction)
4. Allow quantification of absolute myocardial flow
5. Effective with both exercise and pharmacologic stress
6. Appropriate safety profile
7. Available as unit dose (18F-labeled compound)


Seminars in Nuclear Medicine

Volume 41, Issue 4, July 2011, Pages 305-113
Positron Emission Tomography Radiopharmaceuticals: Current Status

The Next Generation of Cardiac Positron Emission Tomography Imaging Agents: Discovery of Flurpiridaz F-18 for Detection of Coronary Disease

Ming Yu, MD, PhD, Stephan G. Nikolaj, PhD, Markus Schwarzer, MD, Simon P. Robinson, PhD

DOI: 10.1053/j.semnuclmed.2011.02.004
Get rights and content
F-18 Flurpiridaz
Heart Imaging

18F Flurpiridaz

- Analog, Mitochondrial complex-1 inhibitor, pyridaben
- F-18 based, advantages over Rb-82/13N Ammonia

Lantheus MPI Pipeline
**Research Cardiac PET Agents**

<table>
<thead>
<tr>
<th>Imaging Agent</th>
<th>Target/Use</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CardioPET (18F FCPHA)</td>
<td>Myocardial perfusion/viability</td>
<td>Completed enrollment for Phase 1</td>
</tr>
<tr>
<td>VasoPET (18F AP4A)</td>
<td>Vulnerable plaque</td>
<td>Pre Clinical Studies completed</td>
</tr>
<tr>
<td>BFPET (18F TTP)</td>
<td>Myocardial perfusion</td>
<td>Completed Phase 1</td>
</tr>
</tbody>
</table>

**FDA Approved PET RPs**

- 2-[18F]fluoro-2-deoxyglucose or 18F-Fluoro-deoxy-glucose
- Similar in structure to glucose
- FDA approved indications: In 2000
  - Epileptic foci in the brain
  - Myocardial glucose metabolism
  - Tumor glucose metabolism
- In 2005
  - Alzheimer’s Disease and Fronto-temporal dementia

**18F-FDG**

- FDA approved indications:
  - In 2000
    - Epileptic foci in the brain
    - Myocardial glucose metabolism
    - Tumor glucose metabolism
  - In 2005
    - Alzheimer’s Disease and Fronto-temporal dementia
18F-FDG in Oncology

Clinical Trials: FDG

18F-FDG in Oncology

- Shortcoming: Not a specific tracer
  - targets glucose metabolism
  - inflammation vs tumor
  - high uptake areas: brain, bowel & excretion

- New RPs are needed → biomarkers
  - specific biological carriers
  - such as Mabs, affibodies, proteins, peptides

Modified from the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine (SNM)
Fluorothymidine

- An analog of thymidine
- Detect/Monitor tumor proliferation
- Marker for DNA synthesis
- Phosphorylated by thymidine kinase

Imaging Agent: [F-18] FLT

Human Studies
**F-18 Fluoromisonidazole**

**FMISO**
- 1H-1-[3-¹⁸F]-fluoro-2-hydroxy-propyl-2-nitroimidazole or [¹⁸F]-fluoromisonidazole
- Azomycin-based hypoxic cell sensitizer
- As a radiolabeled agent, used to image and quantitate tumor hypoxia
- Dose ≤ 10 mCi

**Nitroimidazole**

How Nitroimidazole works:
- Bind to oxygen-deprived cells covalently
- FMISO is trapped, provides image of hypoxia via PET
- Reversible in the presence of oxygen
- Renal elimination

**FDA Approved PET RPs**
C-11 Choline
Prostate Cancer

\[ ^{11} \text{C- Choline} \]

- \( T_{1/2} \): 20 min
- Indication: Prostate cancer recurrence and non-informative bone scan
- Dose: 10-20 mCi
- Route: IV

Image presented by Dr. Val Lowe, APHA 2015

Research in Prostate Imaging

Abstract:

Comparison of PET imaging using sodium fluoride and 11C-choline/bone PET/CT for the diagnosis of pelvic bone metastases and comparison of 11C-choline/bone PET/CT with active skeleton in BMU. Results indicate that the sensitivity of 11C-choline/bone PET/CT was greater than 90% in patients with known bone metastases. The specificity of 11C-choline/bone PET/CT was also greater than 90% in patients with known bone metastases. These results suggest that 11C-choline/bone PET/CT may be a useful tool in the detection and differentiation of bone metastases. Additionally, 11C-choline/bone PET/CT may be a useful tool in the evaluation of bone metastases in patients with known bone metastases.
Gallium-68

- Decays by positron emission
- Half Life -> 68 minutes
- Stable 68Ga(3+) complexes
- Available via $^{68}$Ge-$^{68}$Ga generator

Research in Prostate Imaging

Copper-64

- Transitional metal, $Z = 29$
- Available via cyclotron
- Decays by positron emission
- Half Life -> 12.7 hr.
Normal Memory Loss OR Onset of AD?

**Normal Forgetfulness**
1. Parts of an experience.
2. Where the car is parked.
3. Where you left an object: car key.
4. A person's name, remembering later.

**Memory Loss with AD**
1. An entire experience.
2. How to drive a car or read a clock.
3. Recent events, such as forgetting you left the stove on.
4. Ever having known a particular person.

- 10-30% of AD patients lack AD pathology at autopsy¹
- PCP fail to diagnose 33% of mild dementias²
- 10% elderly have undetected dementias³


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Alzheimer’s Disease

**QUICK FACTS**

- Only 45% of people with Alzheimer's disease are employed.
- More than 90% of people with the disease are over 65.
- Only 10% of people with Alzheimer's disease report any difficulties.
- About 34,000 Americans die each year from Alzheimer's disease.
- About 25% of people over 65 have some degree of Alzheimer's.
- About 50,000 people under 65 have Alzheimer's disease.

Alzheimer Association
AD Definition

Alzheimer’s disease is a progressive, degenerative disorder that attacks the brain’s nerve cells, or neurons, resulting in loss of memory, thinking and language skills, and behavioral changes.

First FDA Approved PET Aβ Imaging Agent: AMYVid® (florbetapir)

- Prior, only sure diagnosis has been post-mortem
- Based on C-11 PIP
- PET images vs autopsy results
- Avid → Eli Lilly
- FDA approved in April, 2012

PET Aβ Imaging Agents

2013, Vizamyl® (flutemetamol) GE Healthcare
- 2014 Neuraceq® (florbetaben) Primal Imaging
Aβ imaging: Uncertain Utility:

*Does imaging/testing improve outcomes?*

- Debate: Meaning/Value of amyloid plaques presence
- Functionality: Does scan change patient management?
- Outcomes: Quantify improvements?

- 2013, CMS decision: “not reasonable or necessary”,
- CMS approved clinical trials

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**Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer’s Association**

1. Patients with persistent or progressive unexplained MCI
2. Patients satisfying core clinical criteria for probable AD because of unusual clinical presentation, either an unusual clinical course or an atypical clinical presentation
3. Patients with progressive dementia and atypically early age of onset (usually defined as ≤5 years in age)
4. Patients with core clinical criteria for probable AD with typical age of onset
5. To determine dementia severity
6. Based solely on a positive family history of dementia in presence of single positive P301L/P301S
7. Patients with a cognitive complaint that is unex- plained by clinical examination
8. As a means of genotyping for suspected monogenic mutations carriers
9. In asymptomatic individuals
10. Nonmedical use (e.g., legal, insurance coverage, or employment screening)

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The show must go on...

A test that can help to diagnose or predict onset of AD with certainty and improve health outcomes. CMS
Products in the Pipeline

F-18 NAV4694 (flutafuranol)

Navidea: We believe NAV4694 represents the potential to be the best-in-class PET amyloid imaging agent. Comparative studies like the one done by Dr. Christopher Bowe demonstrate that NAV4694 displays imaging characteristics nearly identical to those of [11C] PIB, the gold standard, but with a more practical distribution profile including the longer half-life of 185, making NAV4694 commercially feasible where [11C] PIB is not.

If approved, NAV4694 could certainly be used in clinical trials similar to the current Lilly trial (evaluating substantia nigra) to ensure subjects meet certain inclusion criteria. Moreover, in the case of disease modifying clinical trials with the secondary and late-stage markers binding NAV4694 may be able to be used to monitor disease progression.

Products in the Pipeline: Tau

Chemical structure of currently available tau tracers

FDA Approved PET RPs
Theranostics: Diagnosis & Treatment

Future Prospect of PET: nearly endless...

Role of a Nuclear Pharmacist: virtually boundless...

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