

Practical Challenges in Personalized Medicine Molecular Imaging



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Centre for Probe Development and
Commercialization



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Overview

- ❑ Molecular imaging
- ❑ Molecular imaging probes
- ❑ Challenges of probe development
- ❑ The future





Molecular Imaging Discovery

Molecular Imaging

- ❑ Reveals biology of disease processes at the molecular and cellular level
- ❑ Molecular Imaging probes provide:
 - Visualization
 - Characterization
 - Measurement
- ❑ Imaging Modalities:
 - Nuclear Medicine
 - MRI, MRS
 - Optical
 - US

Mankoff JNM 2007; 48: 18



Role of Molecular Imaging

Clinical Utility

- Prognostic, predictive information
- Monitor progress of interventions
- Early detection

Accelerates drug discovery and development

- Pharmacokinetics
- Pharmacodynamics



Novel Probe Discovery

Identify suitable biological target



Screen chemical structures for target affinity



Develop probe labelling strategies

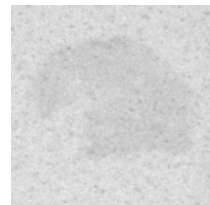
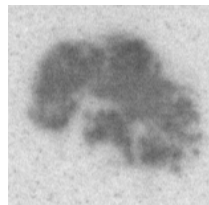


Validation in biological model systems

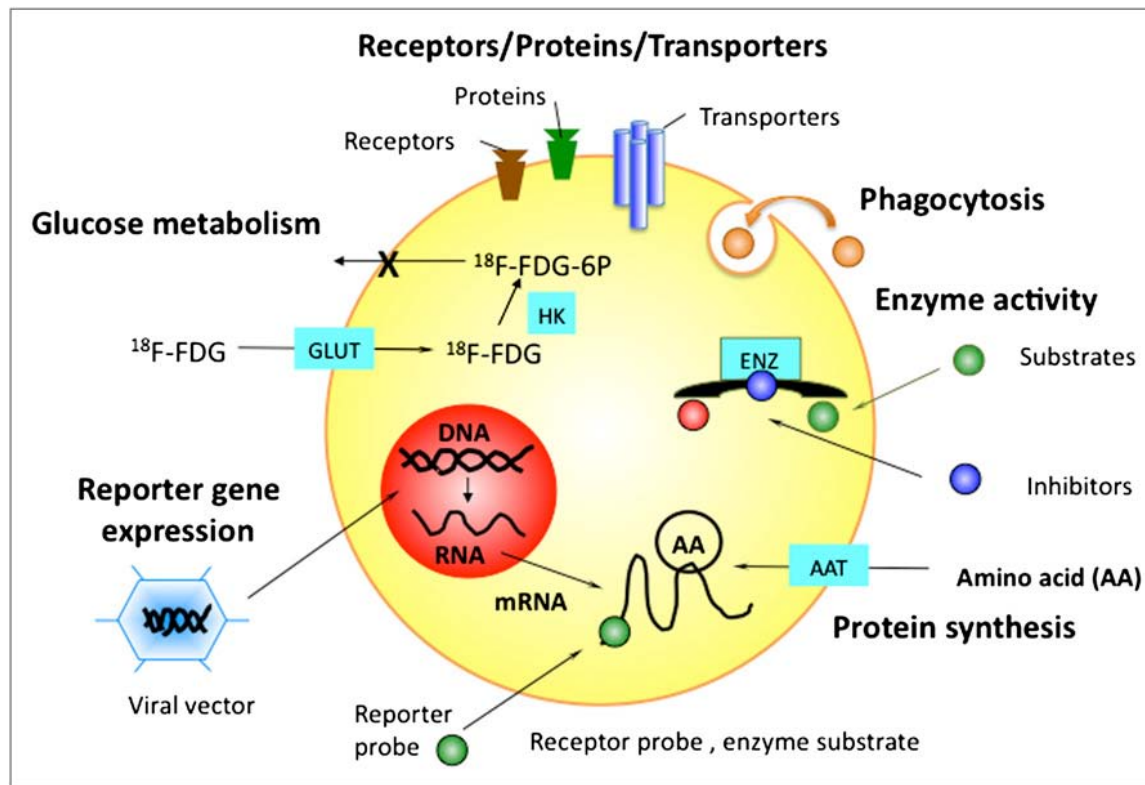


Target Characteristics

- ❑ Expression is a correlate of pathogenesis
- ❑ Clinical utility
- ❑ Target concentration
- ❑ Low expression in healthy tissue



Molecular Imaging Targets



Anderson *et al.* J Nucl Med 2010; 51:3S

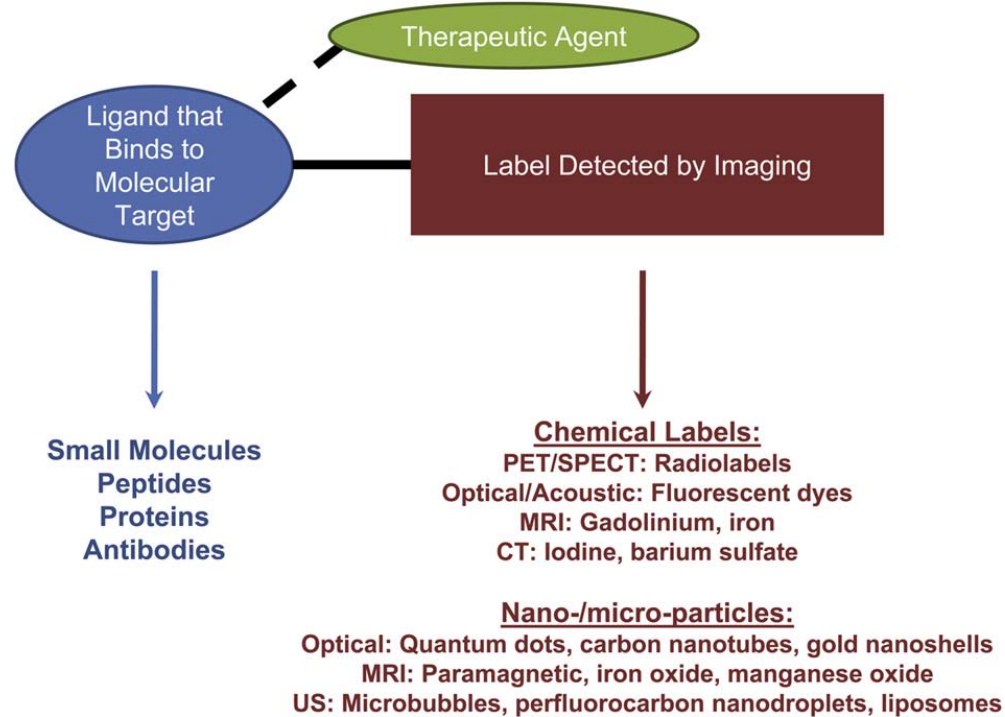


Probes

- ❑ High affinity and selectivity for target
- ❑ Low non-specific binding
- ❑ Amenable to radiolabelling
- ❑ Adaptable to GMP manufacturing
 - Reproducibility
 - Purity
 - Stability
- ❑ Acceptable safety profile



Probe Design



Pysz et al; Clinical Radiology 65 (2010) 500



Probe Validation

- ❑ Target affinity and specificity
- ❑ Contrast (Target: Background *in vivo*)
- ❑ *In vivo* distribution
- ❑ Metabolism - Low amounts of labelled metabolites in the ROI





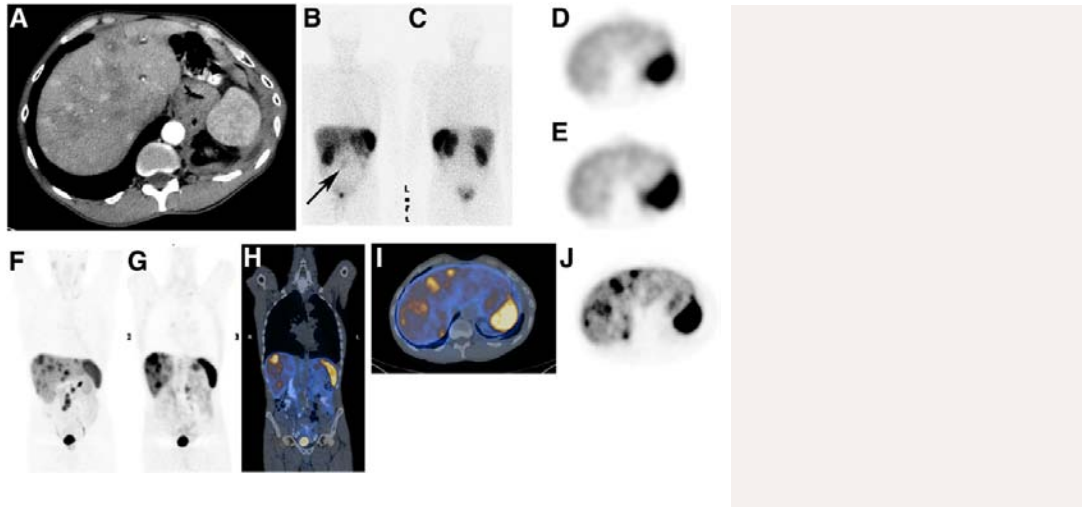
Molecular Imaging Probes Radiopharmaceuticals

Radioisotopes

- ❑ PET: Positron Emission Tomography
 - **Fluorine-18:** 110 min
 - Carbon-11: 20 min
 - Gallium-68: 68 min
 - Zirconium-89: 3.3 days
 - Iodine-124: 4.2 days
- ❑ SPECT: Single Photon Emission Computed Tomography
 - **Technetium-99m:** 6 h
 - Iodine-123: 13.2 h
 - Indium-111: 2.8 days



Neuroendocrine Tumour Imaging



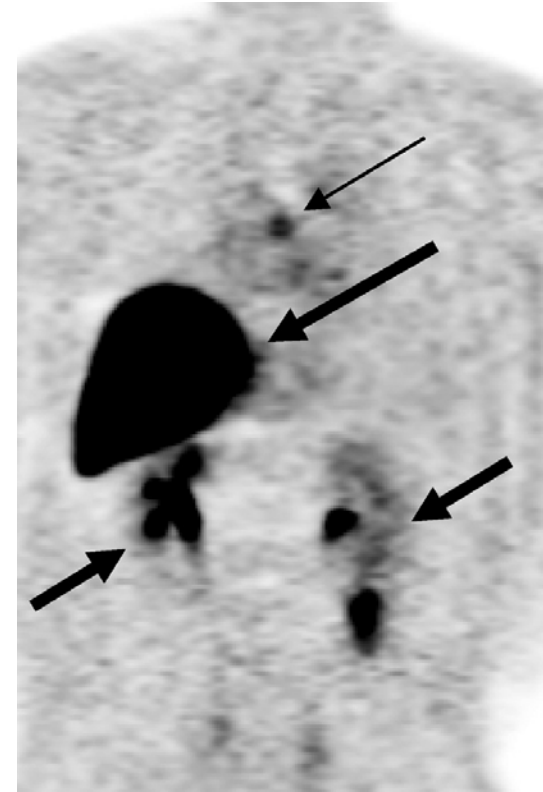
- In-111 pentetreotide (Octreoscan) is an agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.
- Used for staging disease, planning radiopharmaceutical therapy
- ^{68}Ga -DOTATATE PET changes the clinical management in 70.6% of patients

*Koopmans et al. (2009) Critical Reviews in Oncology and Hematology ;71: 199
Octreoscan Package Insert*



[¹⁸F]-Fluoroestradiol

- ❑ ~ 70% breast cancers express ER (ER +)
- ❑ FES uptake: correlation with *in vitro* ER (r = 0.74)
- ❑ May help to address issues:
 - Heterogeneity/ tissue sampling
 - Loss of epitope/ loss of receptor function
- ❑ Level of FES uptake predicted response to tamoxifen (SUV threshold = 1)
- ❑ Responders (-55%) v non-responders (-19%): p = 0.0003



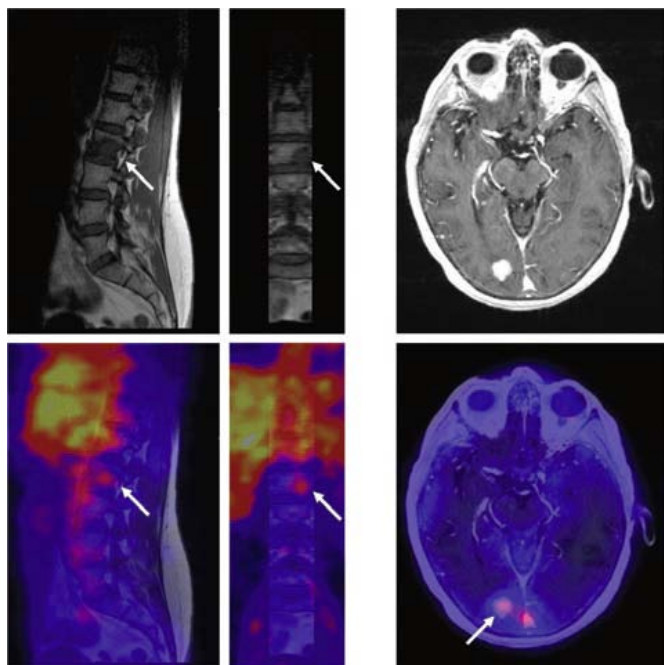
Sundararajan *et al.* (2007) *Semin Nucl Med*; 37: 470
Mortimer *et al.* (1996) *J Clin Oncol* 19:2797
Peterson *et al.* (2008) *J Nucl Med* 49: 367
Dunphy & Lewis (2009) *J Nucl Med* 50: 106S



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HER2



- ❑ Over-expression in 25 – 30% breast cancer
- ❑ Downregulation of ER \Rightarrow HER2 upregulation
- ❑ Trastuzumab used to treat HER2 +
- ❑ Many approaches with labelled antibodies, fragments, peptides
- ❑ In-111 Trastuzumab: id'd 45% of known lesions and new lesions in 13/ 15 patients

Zr-89-Trastuzumab: Fusion with MRI

Dijkers et al (2010) Clin Pharmacol Ther. 87:586

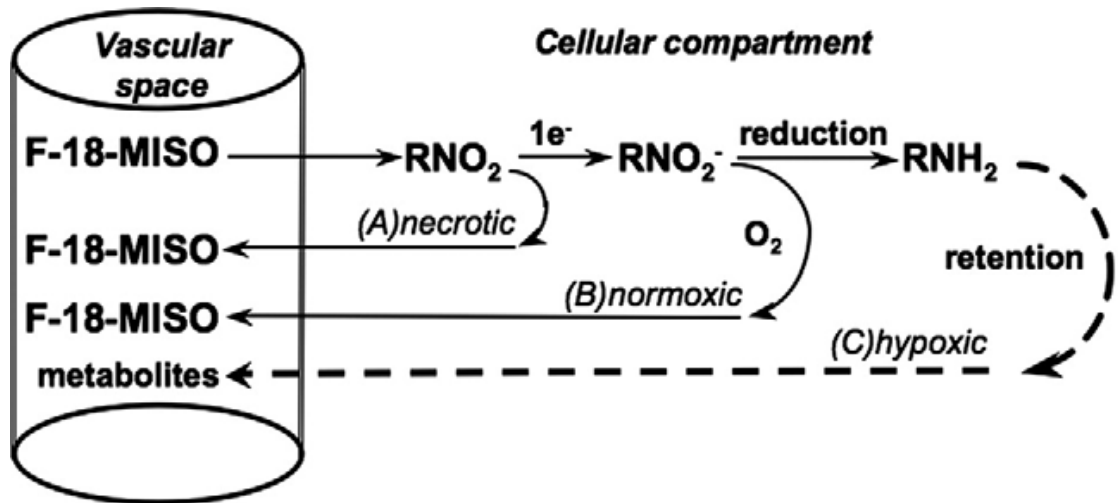


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Hypoxia – [F-18]-FMISO

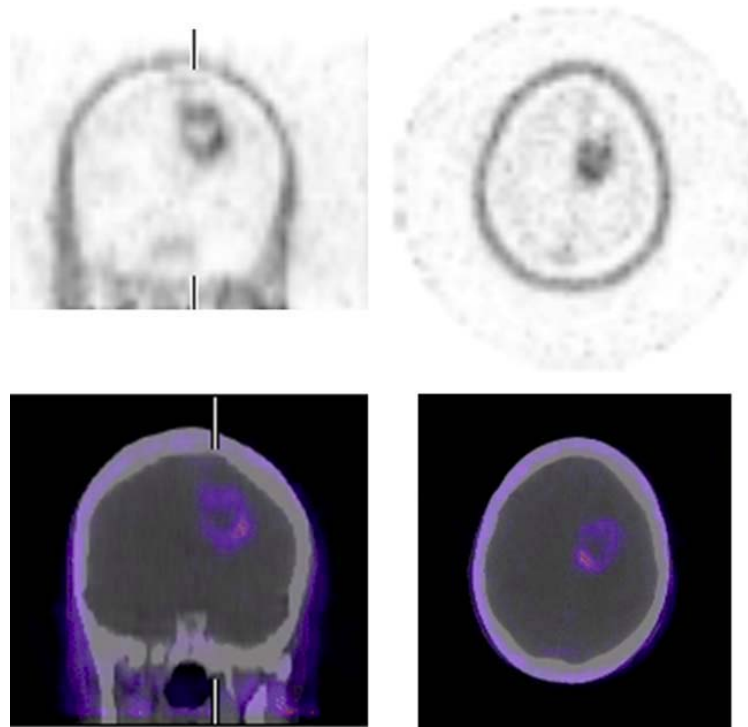
Hypoxia \Rightarrow high degree of invasiveness and resistance to chemoradiation \Rightarrow poor prognosis



- Inverse correlation with pO_2
- Independent prognostic factor in H & N; NSCLC
- Radiation painting, tirapazamine

Lee & Scott (2007) Semin Nucl Med; 37:451

[F-18]-FAZA



Postema et al; Eur J Nucl Med Mol Imaging (2009) 36:1565



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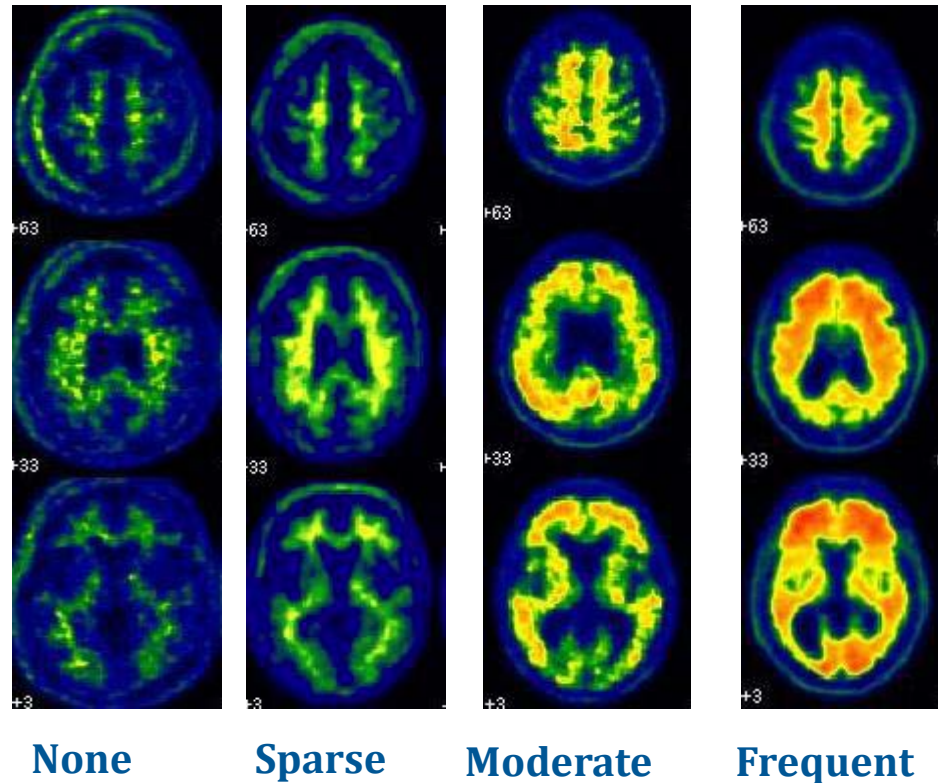
[¹⁸F]-Florbetapir

Correlation between uptake on PET image and cortical β -amyloid levels.

(Spearman's rho ($\rho = 0.78$, $P < 0.0001$; 95% Confidence Interval [CI], 0.58 to 0.89)

Proposed Indication:

“.....imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β -amyloid in the brain.”



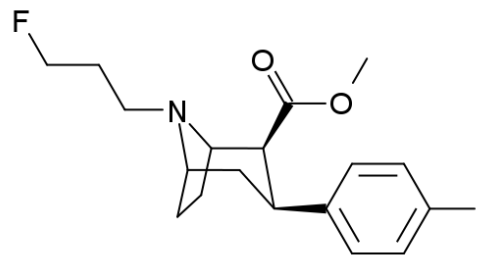
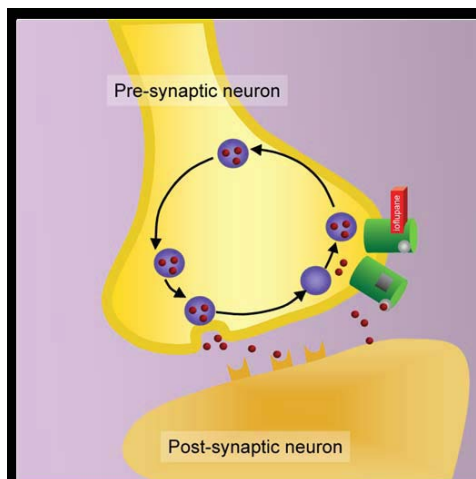
FDA Advisory Committee Briefing Document; NDA #202-008
Advisory Committee Meeting of January 20, 2011



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DaTSCAN ([¹²³I]- Ioflupane)



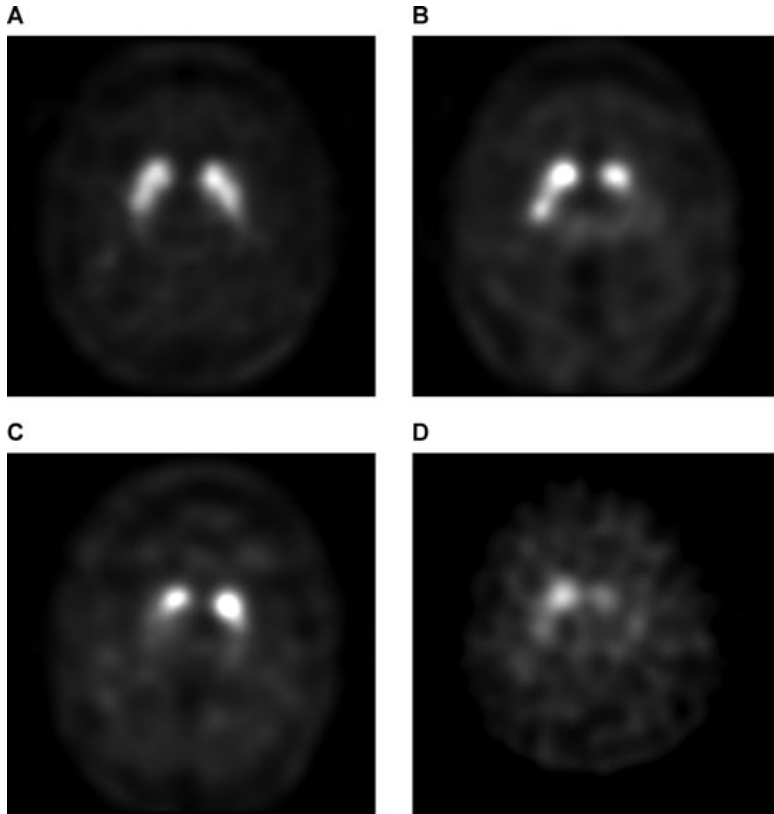
<http://en.wikipedia.org/wiki/DaTSCAN>

- Ioflupane is a cocaine analogue (< 0.325 µg/ dose)
- Binds to dopamine transporter (K_i = 0.623 nM)
- Marker to examine the integrity of the dopaminergic nigrostriatal neurons.

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM186404.pdf>



DaTSCAN



A: Normal
B - D: Abnormal

Hauser and Grossett (2011) Mar 16 J Neuroimaging 1552

Indication (EU):

Detection of loss of functional dopaminergic neuron terminals in the striatum:

- Differentiate Essential Tremor from Parkinsonian Syndromes
- Differentiate probable dementia with Lewy bodies from Alzheimer's disease.

DaTScan Product Characteristics; GE Healthcare 2010

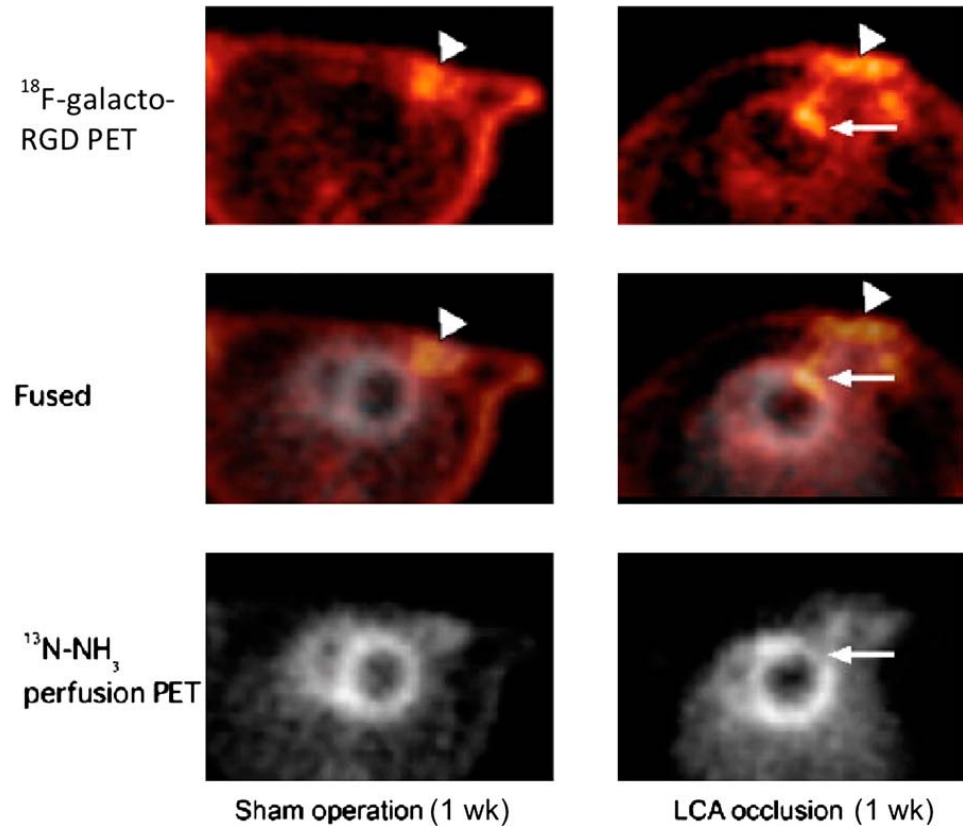


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Molecular Imaging: Cardiovascular

- ❑ [^{18}F]-FDG (glucose analogue)
 - Viability
 - Inflammation - atherosclerosis
- ❑ [$^{99\text{m}}\text{Tc}$]-Annexin/ [^{18}F]-Annexin
 - Apoptosis - ischemia
- ❑ [^{123}I]-MIBG
 - Sympathetic Innervation
- ❑ Radiolabelled RGD peptides
 - Angiogenesis



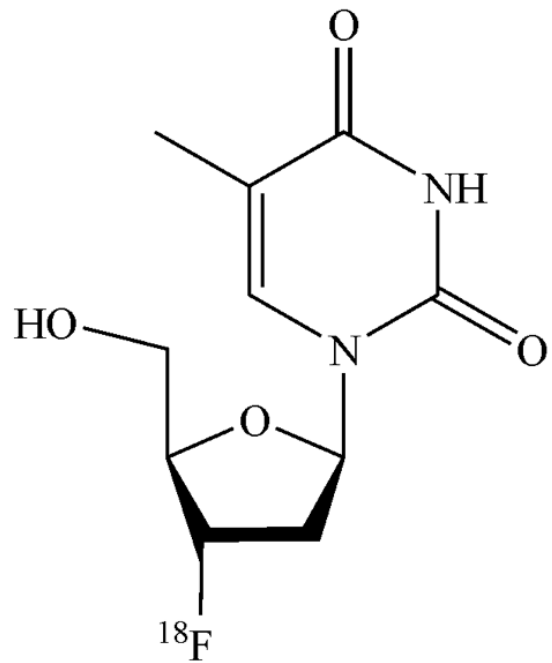
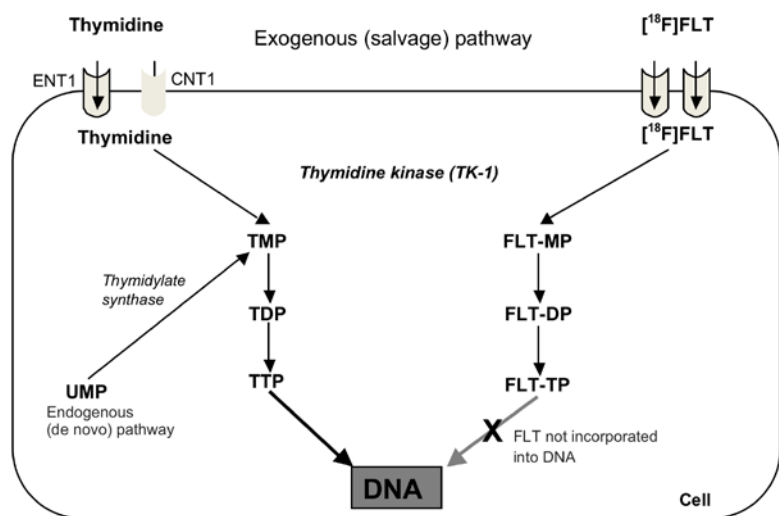
Higuchi *et al.* Cardiovascular Research (2008) 78, 395





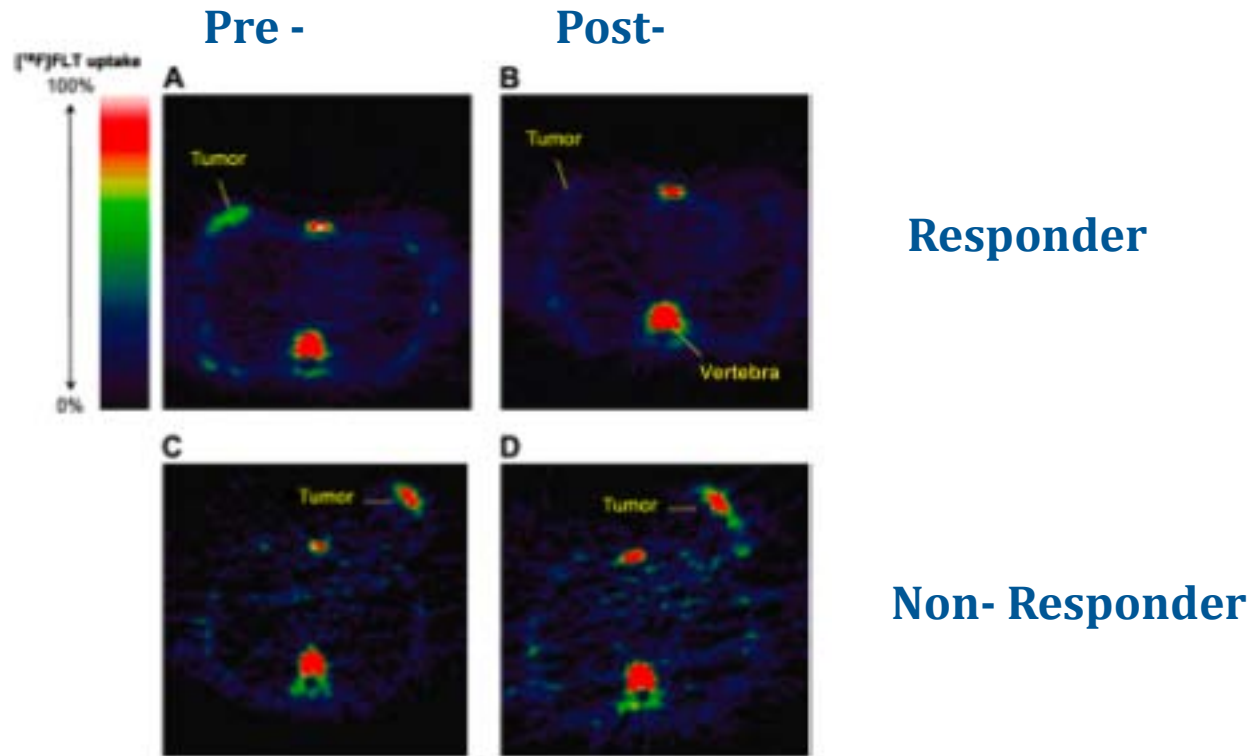
Molecular Imaging Drug Development

[¹⁸F]-FLT



Vallabhajosula S Semin Nucl Med. 2007; 37: 400

Breast Cancer: Response to Therapy



Tumour response assessed 1 week after initiation of treatment with 5-fluorouracil, epirubicin and cyclophosphamide. Clinical response assessed at 60 days.

Decrease in uptake discriminated between clinical response and stable disease ($p = 0.022$)

Kenny *et al.* *Eur J Nucl Med Mol Imaging.* 2007; 34: 1339





PET Probe Development

Just in Time Probe Manufacturing



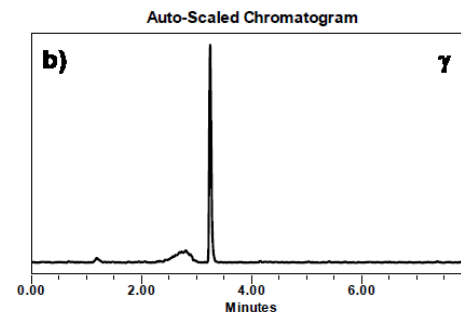
Raw material
Production



^{18}F



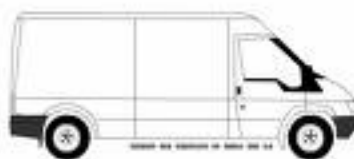
Probe
Manufacturing



Quality testing



Dispensing and packaging



Shipping



Administration and imaging



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CPDC Quality System

- Design Control
- Material Controls
- Equipment Controls
- Facility Controls
- Document Control
- Change Control
- Training
- CAPA
- Auditing and Inspections

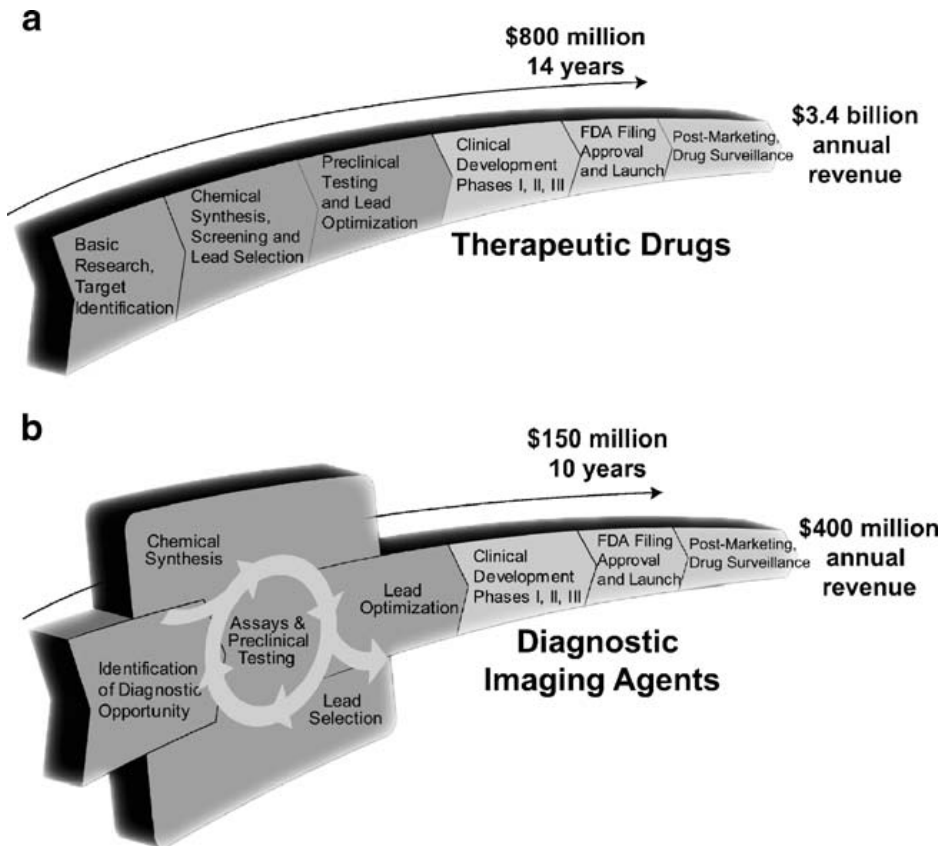


Current Challenges

- ❑ Discovery
 - Identify and validate targets
 - Design and validate probes
- ❑ Clinical validation
 - Correlation with histopathology
 - Reproducibility
 - Impact on clinical outcomes
- ❑ Standardization:
 - Production
 - Imaging
- ❑ Costs of development; production; imaging



Probe Development



Agdeppa & Spilker (2009) AAPS J; 11: 286



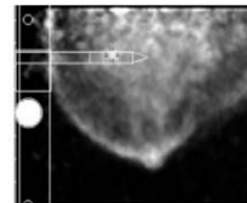
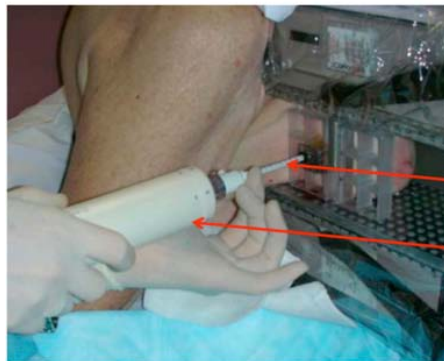


Molecular Imaging

The future

The Future: Probes

- ❑ Organ-specific imaging cameras, eg breast-specific cameras (SPECT and PET):
 - Improved sensitivity
 - Facilitates image-guided biopsy
 - Molecular targetting (eg Her-2 and ER) could improve biopsy sampling for treatment planning



Needle Cannula

Biopsy Tool

Courtesy: Naviscan Inc

Tissue sample analysis

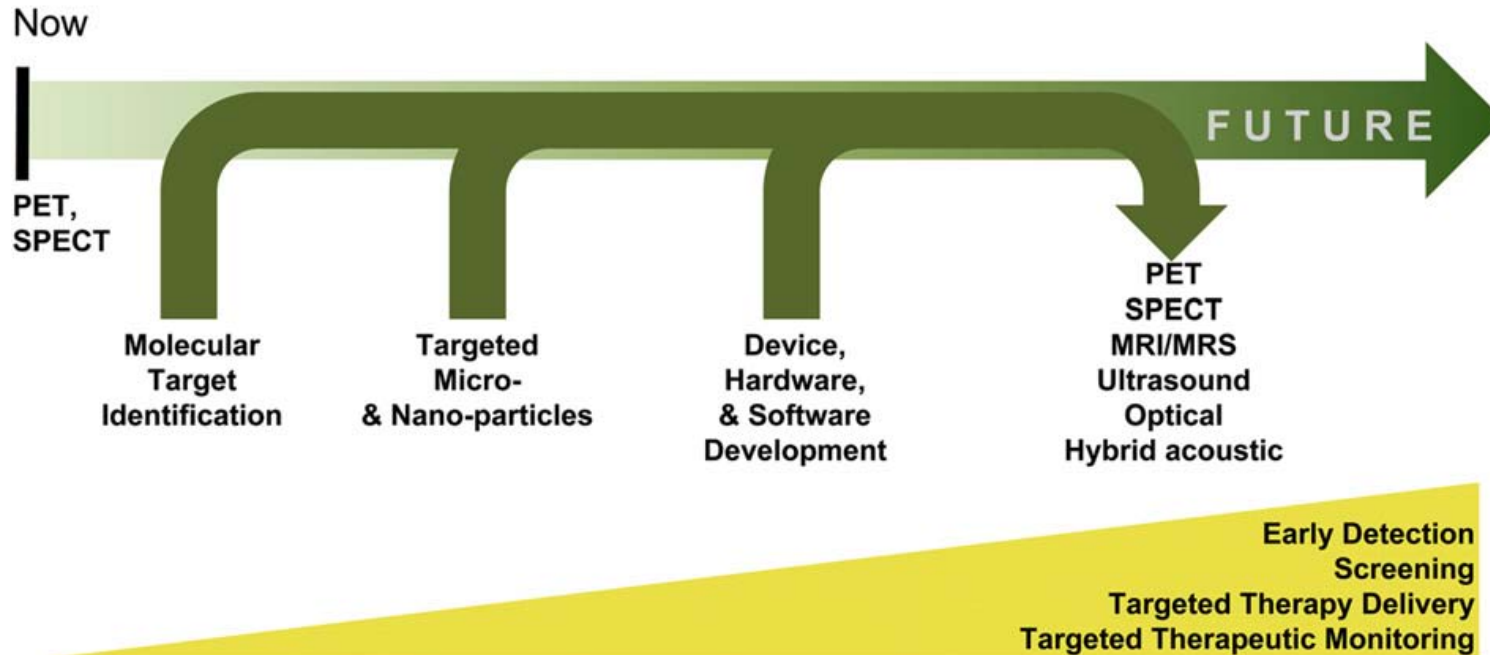
- ❑ Combine radiolabelled prosthetic group with fluorophore
- ❑ Imaging and histology
- ❑ Ideal to have identical prosthetic structures:
 - SAACQ chelator: Tc-99m and Re analogs
 - SAACQ \Rightarrow fluorescence
 - Potential demonstrated with probes for A- β Plaque and HIV1-Tat basic domain (neural stem cell uptake)

Stephenson *et al.* (2008) *Bioconjug Chem* 19; 1087; Schaffer *et al.* (2008) *Nuc Med Biol* 35; 159



Future of Molecular Imaging

Progression Trends in Clinical Molecular Imaging



Pysz et al; Clinical Radiology 65 (2010) 500



Conclusions

- ❑ Genomics and proteomics have led to increased targetting opportunities
- ❑ Molecular imaging can provide diagnostic information assisting in targetted therapy
 - Whole body imaging
 - Avoids sampling errors
 - Repeated scanning
- ❑ Advances in imaging technology and radiochemistry will expand the scope of molecular imaging



Acknowledgements

- John Valliant
- Karin Stephenson
- Travis Besanger
- John Forbes
- Sally Adams
- Karen Gulenchyn, HHS



Our Partners

Canada 

Centre for Probe Development and Commercialization (CPDC) is supported by the Government of Canada through the Networks of Centres of Excellence (NCE) Program.



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Thank You



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