Imaging in Early Drug Development

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The drug development process

- Discovery → Approval = 10-12 years
- >800 million dollars per registered drug
- Much actually associated with NMEs which fail to get to market
- The higher the attrition rate, the higher the cost of success
The drug development process

Yet conventional drugs still fail late in the life cycle due to:

- oral availability
- toxicity
- efficacy (at maximum tolerated dose)
PET and the drug development process

- For NMEs, PET can: confirm brain penetration
  confirm activity at site
  provide timecourse information

- PET can provide information on kinetics at the receptor or transporter

- PET can provide dose information for Phase II

- Need to define occupancy related to function

- Conclusion: PET can inform criteria for early development of lead compounds and thus reduce attrition at later stages
PET and the drug development process

Two possible approaches:

• Direct – radiolabel the compound under test
  - Difficult
  - Possibly lengthy
  - Costly

• Indirect – challenge binding of an existing PET ligand
  - If there is one

Problem:
PET is resource intensive and relatively expensive
What is PET?

When a positron meets an electron, they annihilate and release two gamma rays at 180° to each other.
**What is PET?**

A radiolabelled ligand or tracer is injected into the subject in the PET scanner.

Radioisotopes used are commonly:

- $^{18}$F – $T_{1/2} = 110$ min
- $^{11}$C – $T_{1/2} = 20$ min
What is PET?

Dynamic image sequence

Tissue tracer kinetics

Plasma tracer kinetics

Parameter estimates of:
• Delivery / Extraction
• Binding Potential - $k_3/k_4$
• Volumes of Distribution

TRACER KINETIC MODEL

Plasma

Free

Specific

$K_1$

$k_2$

$k_3$

$k_4$

What is PET?

Dynamic image sequence

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$K_1$

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$k_4$
The standard neuroreceptor ligand model

\[ C_t(t) = C_a(t) \otimes S a_i \exp(-b_i t) \quad (i=1,3) \]

\[ k3 = K_{on} \times B_{avail} \times f2 \]

\[ B_{avail} = B_{max} / [1 + \sum (F_i / K_i)] \]

k3 depends on the local Bmax of the receptor and the concentration and affinity of competing exogenous and endogenous ligands.
PET in drug development

• Pre-clinical imaging
  • Small animal PET
  • Primate PET

• Human imaging
  • Normal volunteers
  • Patients
PET in drug development

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Preclinical scanning

What can small animal PET offer?

A. Reduction in animal numbers
   e.g. biodistribution studies

B. Ligand/tracer kinetics in a single animal
   e.g. ligand evaluation –specificity and selectivity

C. Serial studies on a single animal
   e.g. lesion studies, transplantation studies, transgenics

D. Experimental studies similar to human PET
   e.g. ligand activation
Preclinical scanning

HIDAC
Oxford Positron Systems, Weston-on-the Green, UK: 1999

System Design
MultiWire Proportional Chamber with lead multilayer printed circuit cathodes
2 parallel-opposed detectors each with 6 modules
140 mm diameter
200 mm axial field of view
Detectors rotate through 180 degrees every 6 seconds
Data acquired in list mode.

Spatial Resolution
0.95 mm FWHM in 0.125 mm sinogram bins over whole FOV

Sensitivity
Dual-HIDAC ~0.4% efficiency
Quad-HIDAC ~1.2% efficiency
(4 banks of 8 detectors: imaging volume 160 x 160 x 250 mm)
A. Biodistribution Studies

Scanning enables: - 1. Description of location and relative size of signal; brain extraction etc. in a single animal

Putative ligand for the Adenosine A\textsubscript{2A} receptor \textit{in vivo} evaluation: rat

![Image of brain scans with indications of Heart and Striata]
B. Blocking Studies

Scanning enables:-

1. Acquisition of dynamic data to facilitate estimation of regional kinetic binding parameters.

2. Rapid testing of the regional selectivity of novel ligands (or derivation of the ED$_{50}$ for a competing drug)

Putative ligand for GABA$_A$ receptor, with possible subunit selectivity

*In vivo* evaluation:
Rat brain biodistribution

*In vivo* evaluation:
Signal block with compounds of known selectivity e.g. L-655,708 for the alpha-5 containing subtype
C. Serial Studies

Scanning enables:-

1. Multi-ligand studies and/or sequential scans over a period of time, to follow, for example, progression of graft function.

*In vivo* evaluation of dopaminergic receptor expression:
Striatal signal loss following unilateral lesioning in a rat model of Huntington’s disease, followed by functional recovery after striatal grafts.

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<table>
<thead>
<tr>
<th>Control</th>
<th>Lesioned</th>
<th>Transplant (1)</th>
<th>Transplant (2)</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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</tbody>
</table>

Expires: [AGAH/Club Phase 1 Joint Meeting, March 2005]

Ralph Myers, Director of Methodology Operations
Hammersmith Imanet, part of GE Healthcare
D. Studies Analogous to Human PET

Scanning enables:-

1. Setting up of animal models to investigate, for example, the effect of endogenous neurotransmitters on ligand binding (decrease in binding to D2 receptors as DA increases).

2. Use of the model to inform clinical findings using experimental methodologies not feasible in man.
PET in drug development

• Pre-clinical imaging
  • Small animal PET
  • Primate PET

• Human imaging
  • Normal volunteers
  • Patients
PET in drug development

- Diagnosis
- Disease mechanisms
- Measurement of disease progression
- Effects of drug action
- Dose-response
$^{18}$F-FDG in a brain tumour
$^{18}$F-FDG PET
(resting glucose metabolism)

Normal

Alzheimer’s disease
18F-DOPA PET

Normal Subject

Parkinson’s Disease
Amyloid deposition: $^{11}$C-PIB

Normal subject

Alzheimer’s disease
PET in drug development

- Diagnosis
- Disease mechanisms
- Measurement of disease progression
- Effects of drug action
- Dose-response
**Microglia**

Microglia constitute 20% of all non-neuronal cells in the brain

In the healthy brain, microglia are in a resting state

Neuronal injury activates microglia

- expression of numerous proteins
- proliferation
- secretion of cytokines
- transformation into macrophages
PK11195 binding site

peripheral benzodiazepine binding site (PBBS)

$^{11}$C-PK11195
$^{11}$C-PK11195 in MS
PET and multiple sclerosis

Optic Neuritis with [11C]R-PK11195 and PET
PET in drug development

- Diagnosis
- Disease mechanisms
- Measurement of disease progression
- Effects of drug action
- Dose-response
$^{11}$C-PK11195 binding and atrophy in Alzheimer’s disease

MRI  Fused PK11195 BP and MRI  Subtraction MRI image

SAME DAY  16 MONTHS LATER
$^{18}$F-dopa PET: PD progression

Asymptomatic identical twin of PD patient

Control

Same subject symptomatic 5 years later
$^{18}$F-dopa PET before and after bilateral implantation of foetal dopaminergic cells in caudate and putamen
$^{11}$C-PK11195 PET in PD

Longitudinal development:

No significant change in microglial activation

PET 1

10 months

PET 2
PET in drug development

- Diagnosis
- Disease mechanisms
- Measurement of disease progression
- Effects of drug action
- Dose-response
The standard neuroreceptor ligand model

\[ Ct(t) = Ca(t) \otimes S \ a_i \ exp(-b_i \ t) \ (i=1,3) \]

\[ k3 = K_{on} \times B_{\text{avail}} \times f2 \]

\[ B_{\text{avail}} = B_{\text{max}} / \left[ 1 + \sum \left( F_i / K_i \right) \right] \]

k3 depends on the local Bmax of the receptor and the concentration and affinity of competing exogenous and endogenous ligands.
Two scan $^{11}$C-raclopride study

Scan 1: Baseline

- $^{11}$C-RAC
- D$_2$ Receptor
- Dopamine

Scan 2: Activation

$^{11}$C-rac

Graphs showing time against $^{11}$C-rac uptake in brain regions.
$^{11}$C-raclopride PET
Dopamine release after amphetamine

Normal volunteers

PD patients
PET in drug development

- Diagnosis
- Disease mechanisms
- Measurement of disease progression
- Effects of drug action
- Dose-response
Dose response curves

$^{11}$C-diprenorphine uptake

![Graph showing dose response curves for different brain regions with time in minutes and activity levels.](image-url)
Dose / receptor occupancy in humans determined with PET

Base-line

Dose 1

Dose 2

Dose (mg/kg) vs. Occupancy (%)

Ralph Myers, Director of Methodology Operations
Hammersmith Imanet, part of GE Healthcare
Dose / receptor occupancy in humans determined with PET

Baseline

Lowest dose

Highest dose
Dose / receptor occupancy in humans and rats determined with PET

**Human**

**Rat**

<table>
<thead>
<tr>
<th>Dose of flesinoxan (mg/kg)</th>
<th>Tissue : cerebellum ratio at 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001</td>
<td>15</td>
</tr>
<tr>
<td>0.001</td>
<td>10</td>
</tr>
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<td>5</td>
</tr>
<tr>
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<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

1 mg/kg flesinoxan iv dose
Plasma = 40 ng/ml at 60 min

0.012 mg/kg flesinoxan oral dose
Plasma = 6.4 ng/ml average over scan
Receptor occupancy and duration determined with PET

Baseline 4 hours 24 hours

Occupancy (%)

Time (hours)
Conclusions

PET can speed drug development by:

• Demonstrating drugs reach receptor targets
• Monitoring disease mechanisms and inflammation
• Objectively monitoring disease progression
• Elucidating the downstream effects of drug action
• Defining dose occupancy curves for phase I and phase II studies
Positron Emission Tomography in Drug Development

Ralph Myers
Hammersmith Imanet
Benzodiazepine sites
Normal human

$[^{11}\text{C}]$flumazenil
(non-selective)

$[^{11}\text{C}]$Ro15 4513
(a5 selective)
Reference Tissue Model

\[ R_I = \frac{K_1}{K'_1} \]

\[ BP = \frac{k_3}{k_4} \approx \frac{B_{\text{max}}}{k_d} \]
Glucose metabolism in dementia

Normal

Alzheimer's

Pick's

Normal

Multiple Infarct Dementia

Huntington's