Clinical Applications of Imaging to Drug Development
Novartis Research: Disease Areas

Massachusetts:
- Diabetes
- Infectious diseases
- Cardiovascular
- Oncology

New Jersey:
- Arthritis/Bone
- Cardiovascular

Great Britain:
- Chronic pain
- Respiratory

Switzerland:
- Arthritis/bone
- Nervous system
- Oncology
- Transplantation
- Ophthalmology
- GI Tract

Austria:
- Dermatology

Japan:
- Oncology
- Diabetes
- Cardiovascular
Novartis Research: Discovery Platforms

Massachusetts:
- Functional Genomics
- Discovery Technologies/HTS
- Pathways
- Animal Models
- Drug Discovery Chemistry
- Epigenetics
- IK@N

Switzerland:
- Functional Genomics
- Discovery Technologies/HTS
- Protease Platform
- Drug Discovery Chemistry
- IK@N
- GPCR

Vienna:
- Ik@N, in silico science
- Novel Assays
Drug Discovery Yesterday:

Fleming's discovery of penicillin: 1928
Drug Discovery Today: Target Identification

The Lewis and Clark Expedition of the 21st Century

Jim Borgman, The Cincinnati Enquirer, 12/17/99
Drug Discovery Today: Compound Development

- **Combinatorial Chemistry:**
  - “With the IRORI system we anticipate that 10,000 compounds will take about two months with one to two people…“ Czarnik

- **Rational Drug Design:**
  - Creation of large theoretical libraries

- **High Throughput Screening:**
  - “The acceleration of sample processing that results from this miniaturization leads to peak sampling rates in excess of $10^5$ per day” Pharmacopeia
Clinical Drug Development: Yesterday
Clinical Drug Development: Today
Phases of Drug Development

- **Preclinical**: Lead Selection, Biology, Tox, Formulation
- **I**: PK/PD, tolerability
- **II**: .02K-.1K patients
- **III**: 1K-5K patients
- **IV**: >10^5 K patients

**Costs**: 1.2 B USD

**Number of Compounds**

- 10^5
- 10^4
- 10^3
- 10^2
- 10^1

**Time (yrs)**

- 1
- 2
- 4
- 6
- 9
- 15

**Confirmed Safety and Efficacy**

- Rare side effects
- New indications

- Long term safety
Can Image Analysis Change the Economics of Drug Development?

Microarrays for Detecting Disease and Tailoring Therapy

Limits on Rational Drug Design
Application of Imaging in Drug Development

- Investigating pathophysiology
  - Multiple sclerosis: identifying surrogates of neurodegeneration
  - Alzheimer’s disease: measuring amyloid plaque load
  - Oncology: evaluating tumor metabolism, perfusion, hypoxia, cell proliferation

- Characterizing pharmacokinetics and pharmacodynamics
  - Distribution and kinetics of a drug candidate in target and non-target tissue
  - Interaction of the drug with the target: primary and downstream effects

- Defining a therapeutic endpoint:
  - Multiple sclerosis: identifying inflammatory lesions, following progression
  - Alzheimer’s disease: confirming diagnosis, following progression, and investigating tissue viability
  - Oncology: characterizing tumors, following treatment response
Selection of the Imaging Method: the ‘Pharmacological Audit Trail’

- Can we detect?  
  Expression of the target and/or activity of the pathway

- Are we achieving?  
  Potent target tissue exposure

- Can we observe?  
  Activity on the molecular target

- Can we measure?  
  Modulation of the desired biochemical pathway

- Can we demonstrate?  
  The desired biological effect

- Does all this translate?  
  To disease response
## Development and Selection of New Methods: Sensitivity

<table>
<thead>
<tr>
<th>Imaging instrument</th>
<th>Temporal resolution</th>
<th>Spatial resolution</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEG</td>
<td>1 msec</td>
<td>5 mm</td>
<td></td>
</tr>
<tr>
<td>EEG</td>
<td>1 msec</td>
<td>10–15 mm</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>3–5 sec</td>
<td>1.0–1.5 mm</td>
<td>$10^{-3}$ molar</td>
</tr>
<tr>
<td>PET</td>
<td>* 45 sec</td>
<td>4 mm</td>
<td>$10^{-12}$ molar</td>
</tr>
<tr>
<td>SPECT</td>
<td>&gt;60 sec</td>
<td>6–8 mm</td>
<td>$10^{-12}$ molar</td>
</tr>
</tbody>
</table>

*For PET, 45 sec corresponds to that obtained when using $\text{H}_2^{15}\text{O}$ to measure cerebral blood flow; otherwise, for dynamic studies measures can be made at 15- to 30-sec intervals*
How Imaging can fit with Drug Development

<table>
<thead>
<tr>
<th>Number of Compounds</th>
<th>Preclinical</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tbody>
<tr>
<td>10^5</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

- **Time (yrs)**: 2 4 6 9 15
- **Number of Compounds**
  - Lead Selection
  - Biology, Tox, Formulation
  - PK/PD, tolerability
  - Safety and Efficacy Learned
  - Safety and EfficacyConfirmed
  - 1K-5K patients
  - >10^5 K patients

**Imaging goals**
- Target validation
- PK, PD, Dose
- Surrogate markers and endpoints
- Theranostics
- Product differentiation

**Costs**
- <1.2 B $!
Pharmacokinetics: Regional Distribution in the Target Tissue

Accumulated radioactivity of $^{11}$C-drug in transverse, coronal, and sagittal planes 0-5 minutes

Accumulated radioactivity of $^{11}$C-drug in transverse, coronal, and sagittal planes 10-90 minutes
Pharmacokinetics:
Rate of Distribution into the Target Tissue

![Graph showing the rate of distribution into different brain regions over time.](image)
Receptor Occupancy Theory

- AJ Clarke developed the theory for quantitation of drug action (1933)
  - Drugs can act by binding to a receptor
  - Binding is a function of concentration of drug and receptor (at equilibrium)
  - For drugs with reversible binding and a finite number of receptors:
    \[
    [L] + [R] \overset{k_1}{\underset{k_2}{\rightleftharpoons}} [LR]
    \]
- The effect on the receptor is a function of extent of occupancy
Value of Occupancy Studies

- Confirms the target *in vivo*
- Confirms drug reaching the target *in vivo*
- Confirms that the hypothesis can be tested
- May permit target specific kinetics
- May provide critical thresholds for adverse events
- Can support clinical dose decisions
  - Reduces the expense of Phase 2 (~1 Mi USD per dose arm in depression)
  - Supports registration dose and pricing claims
- May help to differentiate from other agents
Dose dependent occupancy of the Serotonin 5HT1a Receptor

Rabiner et al Neuropsychopharmacology 2000
Dose dependent occupancy of the Neurokinin NK-1 Receptor by Aprepitant

Hamill et al AMI 2004
Drug target specific radiotracers: the challenges

- Historically developed by academic centers using commercially available ligands
  - Several companies now have in-house programs
- New ligand development:
  - Requires chemistry, biology, analysis resources similar to clinical compounds
  - Requires high affinity for target and low affinity for non-target
  - Robust, stable labeling
  - Clinical testing requires GMP-like production
Pharmacodynamics: Central Effects of Drugs using FDG PET
Predicting the Outcome of Drug Treatment

Baseline  24 hours  7 days  2 months  5.5 months

Reduction in FDG uptake predicts long-term outcome. This effect can be seen as early as 24 hours after starting treatment.
Assessing Disease Progression: Dementia

• Dementia: progressive and gradual decline in cognitive skills
  • loss of memory
  • problems with reasoning or judgment
  • disorientation
  • difficulty in learning
  • loss of language skills
  • decline in the ability to perform routine tasks.

• Changes in personality and behaviour (agitation, anxiety, delusions, hallucinations)

• Multiple causes of dementia
  • Alzheimer’s is the most common
Time Course of Alzheimer’s Dementia

Initiation factors
- Genetic?
- Immunology?
- Head trauma?

Risk factors
- Age
- Genetic?
- Sex?
- Environment?
- Education?
- Depression?
- CV risk factors?
- Oxidants?

Cognition
- Symptoms
- Diagnosis

Brain Pathology
- Loss of independence

‘Prodromal’ Phase

‘Clinical’ Phase

0-20 yrs 20-50 yrs 50-70 yrs 70-80 yrs
Alzheimer’s is Currently Confirmed only at Autopsy

Cortical atrophy

Enlarged ventricles
However: Atrophy is readily observed \textit{in vivo} in probable Alzheimer’s Disease

Average annual loss in gray matter compared to healthy elderly (LUT: blue to red = 0 to 15\%)  
Thompson et al 2003
And Brain Glucose Metabolism is significantly altered in probable Alzheimer’s Disease

Brain areas with significant decline in metabolism at 1-Year follow-up in 14 patients with Alzheimer’s Disease

Alexander et al, AJP May 2002
β-Amyloid protein deposition is accelerated in Alzheimer’s

Two abnormal structures in the brain associated with AD

- Extracellular amyloid plaques (primarily β-amyloid peptides)
- Intracellular neurofibrillary tangles (hyperphosphorylated tau)
And might be estimated with β-amyloid Targeting Tracers

- $[^{11}\text{C}]-\text{PIB}$ brain distribution has been tested at several sites and in young and old healthy controls, Alzheimer's disease, and Mild Cognitive Impairment
- Distribution of the ligand distinguishes strongly between AD patients and controls
- Test-retest variability: 5-10%
Integration of Imaging in measuring Progression

Prodromal Phase

Cognition and behavior

Brain Atrophy: MRI

Clinical Phase

Symptoms

Diagnosis

Loss of independence

Brain β Amyloid?

Brain Metabolism: FDG PET

Initiation factors
Genetic
Environment
Others

Promoting factors
Age
CV risk factors
Others

Initiation factors
Genetic
Environment
Others

Promoting factors
Age
CV risk factors
Others

Brain β Amyloid?
Multi-modality Imaging in Clinical Drug Trials for Alzheimer’s Disease

- Each method measures the target organ for the disease and treatment
- Each method measures different aspects of the disease
- Imaging methods are less variable compared to clinical measures
- Amyloid imaging may directly measure the treatment target

<table>
<thead>
<tr>
<th></th>
<th>Mini Mental State Examination</th>
<th>Glucose Metabolism in Posterior Cingulate (FDG PET)</th>
<th>Hippocampal Volume atrophy (MRI)</th>
<th>PET Amyloid tracer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group size</td>
<td>100 *</td>
<td>60 *</td>
<td>40 *</td>
<td>?</td>
</tr>
</tbody>
</table>

* from Jack et al 2003, Alexander et al 2002
Goals:

- *identify* the best neuroimaging methods, brain physiological parameters, biological markers, clinical and cognitive information for following aging and disease progression over a 3 year period
- *standardize* methods of data collection
- *develop* a public reference dataset and repository of clinical material
- *provide* information for early identification of patients at risk, to permit early intervention
- *assess* ability to use neuroimaging parameters as a surrogate endpoint in MCI/AD trials
ADNI Study Design

- MCI (n = 400): assessed at 0, 6, 12, 18, 24, 30, 36 months
- Mild AD (n = 200): assessed at 0, 6, 12, 18, 24 months
- Controls (n = 200): assessed at 0, 6, 12, 24, 36 months
- 1.5 T MRI for clinical and volumetrics for all subjects:
  - MCI - All except 30 months
  - AD - All except 18 months
  - NL - Baseline, 6 months, then yearly
- 3.0 T MRI at same timepoints in a 25% subset
- FDG PET at same timepoints in a 50% subset
- \(^{11}\)C-PIB at ~10 sites (proposed)
- Blood and urine at Baseline then at same intervals as imaging for biomarkers
- Immortalized cell lines at baseline
- CSF at Baseline and yr 1 in a 20-50% subset
In summary, Imaging is Increasing in Drug R&D but varies with Stage of Development

- Early drug development:
  - Target/compound specific
  - New probe/methods development
  - Collaboration with limited number of imaging centers
  - Small preclinical and clinical studies for decision making

- Full/late drug development:
  - Disease/indication specific
  - Established methods
  - Multi-site trials with imaging CROs
  - Standardization of acquisition, data management, and analysis
  - Regulatory compliance especially FDA and EMEA
Challenges for Pharma Industry

- **New method/probe development**
  - Internal or external?
  - Intellectual property issues with external partners
  - Capacity at academic PET centers
  - GMP for radiopharmaceuticals

- **Established method application**
  - Serial measurements in multi-center trials
  - Developing and standardizing acquisition protocols
  - Robust (but sensitive) analysis methods
  - Limited longitudinal and interventional data
  - Identification of imaging endpoints that qualify as biomarkers and surrogate endpoints
DICOM is and will be the ‘coin of the realm’ for image data management for drug development

- Establishment of standards for the field are essential and much appreciated!
- Harmonization with HIPAA and health regulatory standards
- Flexibility in the header for attachment of study specific information

Acquisition parameters are key for data QC and audit trail

- Managing human error: can header data entry be further automated?

Continuing standardization between vendors in the header