The Role of Imaging in Pre-clinical Drug Development - an Industry Perspective
Focus on the Neurosciences

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Imaging Research, Merck and Co.,
West Point PA
Biomarkers: Experimental Medicine
Faster and Smarter Drug Development

• **Necessity:** Healthcare burden is increasing
  - Epidemics in diseases of aging - neurodegeneration, OA, cancer
  - Epidemics in metabolic disease - obesity, atherosclerosis, diabetes,
  - Inaccessibility of human brain - Psychiatry
  - Move to prognosis and use of disease modifying agents
  - Clinical outcome studies are long and expensive
  - Paradigm shift - early target and concept validation
    - Chemistry robotics/RAS - more molecules to study

• **Practicality:** Biomarker Discovery Toolbox
  - Experimental models - clinical pharmacology
  - Genomics - molecular expression profiling - metabol/proteomics
  - Fluid biomarkers
  - Imaging - non-invasive translational research technologies
Optimizing Drug Development

• Accelerate development
  - Faster identification of optimal molecules
  - Faster “lab to clinic”
  - Faster “first human dose” to “first patient dose”
  - Rapid proof of principle testing in Phase IA/IB

• Highly discriminating during development
  - Defining the optimal target population
  - Rapid Phase IIA efficacy assessment
  - Rigorous criteria for Phase IIB - dose selection
CNS Drugs - Where Are They?
## Spot the Difference

<table>
<thead>
<tr>
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<th>1977</th>
<th>2002</th>
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</table>
| **Depression**           | 5-HT+NE uptake inhibitors  
                          | MAO-inhibitors.  
                          | lithium                                                              | 5-HT uptake inhibitors  
                          | 5-HT+NE uptake inhibitors  
                          | lithium                                                              |
| **Bipolar Disorder**     |                                                                      |                                                                      |
| **Anxiety**              | benzodiazepines                                                      | benzodiazepines                                                      |
|                          |                                                                      | 5-HT uptake blockers                                                 |
| **Schizophrenia**        | D2 antagonists                                                       | D2 antagonists                                                       |
|                          | clozapine                                                            | DA/5-HT2 antagonists                                                 |
| **Alzheimer’s disease**  |                                                                      | (AChE inhibitors)                                                    |
| **Parkinson’s disease**  | L-DOPA/DDC inhibitors  
                          | D2 agonists                                                          | L-DOPA/DDC inhibitors  
                          | COMT inhibitors                                                     |
| **Sleep**                | barbiturates                                                         | Benzodiazepines, modafinil                                           |
|                          | benzodiazepines                                                      | GABA-Aα1 selective benzodiazepines                                   |
| **Acute brain/spinal cord injury and stroke** |                                                                      | (tPA)                                                                |
| **Epilepsia**            | hydantoins, barbiturates  
                          | benzodiazepines, succinimide                                         | hydantoins, benzodiazepines, succinimide,  
                          | valproic acid                                                       | valproic acid, gabapentin, lamotrigine  
                          |                                                                    | tiagabine                                                            |
| **Multiple sclerosis**   |                                                                      | interferon-β1                                                       |
| **Pain**                 | NSAIDs  
                          | opioid analgesics                                                    | NSAIDs, cox-2 inhibitors  
                          | opioid analgesics                                                   |
|                          |                                                                       | gabapentin                                                          |
| **Migraine**             | ergots alkaloids                                                     | 5-HT1D agonists                                                      |
The Drug Discovery Process

Key Challenge: Optimize Translational Research

Studies of Disease Mechanisms

Molecular Studies

Animal Studies
- knockout mice
- antagonists

Target
- receptor; - ion channel;
- transporter; - enzyme;

Lead Search
- robotic assay; - chemical diversity

Lead optimisation/Proof
- selectivity; - efficacy in animal models;
- pharmacokinetics

Drug Candidate
- safety testing

Human Studies
- Phase I, II, III

Approved Drug

MSD
Most projects turn out to be conceptually flawed.
CNS Disorders
Many Targets : Difficult Selection

• Current number of targets
  - Psychiatry and Neurology = 15

• Potential number of targets > 400
  - > 100 neurotransmitter and neuropeptide receptors
  - > 50 ion channels expressed by nerve cells
  - > 200 orphan GCPRs in brain
  - > 50 CNS specific enzymes and transporters

• How to choose?
  - Maximize probability of success - use a biomarker
  - If going to fail need to fail fast
  - And....... Fail cheaply !!
Neurosciences

- Preclinical model predictability is weak
  - tests often biased towards known mechanisms
- Chronic indications - cognition, depression, anxiety
- Clinical studies are long, complex and expensive
- Rating scale read-outs are subjective and sub-optimal
- Early target/concept validation?
  - Experimental Medicine approaches

Alternative Trial Methodologies: Imaging
Animal Models of Psychiatry
Integrated Neurophysiology - Yes

How to recognize the moods of an Irish setter
One of the Problems!!
Placebo Response in Psychiatric Disorders

Meta-analysis of CNS trials

% Change

<table>
<thead>
<tr>
<th>Disorder</th>
<th>(n=)</th>
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<tbody>
<tr>
<td>Psychosis</td>
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<td>OCD</td>
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<td>GAD</td>
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<td>Depression</td>
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<td>PTSD</td>
<td>4</td>
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<tr>
<td>Panic</td>
<td>12</td>
</tr>
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Arif Shah with permission
PHARMA Biomarker Activities Cover Discrete Applications

Drug Activity Biomarkers
PK/PD, MOA, Dose, POC
PROXIMAL
Translational

Patient Biomarkers

Pharmacogenomics
Responders
Enrich POC

Disease Biomarkers

Diagnosis
Prognosis
Stratification

Toxicity Biomarkers

Variation in Drug Metabolizing Enzymes

“Dirty” Compounds

BIOIMAGING

Adapted from Biomarkers: Cambridge Healthtech Advisors 2004
Key Decision Points when Making a Drug

- Translating and Interpreting preclinical data
- Providing early concept validation
- Choosing and validating the right dose

Phases where Imaging can help
What Can Neuroimaging Do?

1. Neuroreceptor mapping - PET
2. Metabolic mapping: ‘CNS Fingerprinting’
   - Glucose metabolism \([^{18}\text{FDG PET}]\)
   - Cerebral blood flow (PET and MRI)
   - MR Spectroscopy
3. Structural Imaging - MRI
4. Functional mapping - Proof of Concept
   - Response neuropharmacology: fMRI and phMRI
PET Radiotracer Imaging

- Unique bridge from laboratory to clinic
  - ONLY way to measure receptor (pM to nM) pharmacology quantitatively in vivo in animals and humans - minimally invasive

- Tracers are radiolabeled antagonist drugs ($^{11}$C and $^{18}$F)
  - agonists, partial agonist and inverse agonists complex
  - mass dosed very low (< 50 ng/kg) - pharmacologically inactive

- Monitor drug delivery to CNS targets
  - Establish [plasma] occupancy relationships

- Preclinical non-terminal - all minimally invasive imaging
  - important with higher species
  - three R's reduction, refinement, replacement
MRI detection is \( \mu \text{M} \)
- PET and SPECT \( \text{pM} \) to \( \text{nM} \)
- PET/SPECT drug exposures are < 10 ug total dose
- MRI Gd chelates - 4 to 12 grams per patient

**Gd Chelates** - human serum albumin, fibrin and charge
- High concentrations - low toxicity of binding
- Blood vessel leakage, tumor imaging, cartilage

**Targeted MR contrast agents** -
- Attractive concept: Few examples

**MRI (fMRI)** - supreme anatomical and temporal resolution
**MRS** detects endogenous substrates present at mM
PET and CNS Proof of Concept (POC)

- PET receptor occupancy can focus POC studies
  - especially when no surrogate end-points - CNS drugs
- Achieve sufficient occupancy at well tolerated doses
  - reproduce preclinical - is it worthwhile testing efficacy?
- Helps dose selection for pivotal efficacy trials
- A valid POC requires adequate receptor occupancy
- No occupancy - no efficacy - not surprising
  - new molecule needed
- Full occupancy - no efficacy - concept flawed
  - do something else
Translational Research

Neural Systems Breakdown

<table>
<thead>
<tr>
<th>Distributed Neural Groups/Circuits</th>
<th>Distributed Neural Groups/Circuits</th>
<th>Neurons Molecules &amp; Genes,</th>
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<tbody>
<tr>
<td>1 2</td>
<td>3 4</td>
<td>5 6</td>
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Breaking the Barrier - Animal-Human Drug Evaluation

1 Clinical Conditions

2 Human Neuroimaging

3 Animal Pharmacology

4 Animal Neuroimaging

5 Cell Biology

6 Molecular Biology & Genetics

Translational Research: Preclinical to Clinical

Of Mice and Men”

• Optimal efficacy requires high levels of receptor blockade
• Valid proof of concept requires high levels of receptor occupancy round the clock
• Long clinical efficacy read-out
• High safety margin
• Dose-selection critical

Use PET to Determine Clinical Occupancies
Open and Define the Therapeutic Window

Predicted C120 hr

Occupancy (%)

Mean C24 hr ± SE

No Go Zone

- DIO mice (Ex-Vivo)
- Lean mice (Ex-Vivo)
- Lean mice (Ex-Vivo)
- Rhesus (PET)
- Rhesus (PET), predicted [drug]
- Human (PET)
Interpretation of Key Preclinical Data

Classical Benzodiazepines are anxiolytic, sedative and have abuse liability

GABA-A $\alpha_2/\alpha_3$ functional subtype selective agonists are anxiolytic, non-sedating

? abuse potential?
Self-Administration Studies

test drugs ability to be a reinforcer

Blue light on:
Injection available

Food Hopper

Drug Lever
Food Lever
FR 160
FR 30

Food available 24 hrs/day (green light).

IV Drug (or Vehicle) available 24 hrs/day with a 3-hour timeout after each injection. Max = 8 inj/day

Cocaine baseline
Test doses for 15 days.

With permission Nancy Ator JHU
Self-Administration of Lorazepam

With permission Nancy Ator JHU
Self-Administration of Lorazepam, TPA123 or TPA023

Mean Injections Days 11-15

- Lorazepam
- TPA023

Dose (mg/kg, i.v.)

With permission Nancy Ator JHU
TPA023 Occupancy Studies

$[^{11}C] $ Flumazenil - BZ site of $\text{GABA}_A$ receptors

Baseline: 0.0032 mg/kg, 0.032 mg/kg, 0.32 mg/kg

Occupancy:
- No detectable (±10%)
- 74%
- 100%

$[^{11}C] $ Flumazenil
Staging the Lesion: Refining the model

MPTP: Parkinson’s Disease

- Opportunity to test therapeutic strategies with potential utility at different stages of the disease
Choosing the Best Compound

Substance P (NK₁) receptor antagonists: Rhesus Monkey

- Optimizes compound Selection
- Optimizes therapeutic window
Milestones
Substance P NK₁ Receptor Antagonists

REDUCTION OF CISPLATIN-INDUCED EMESIS BY A SELECTIVE NEUROKININ-1-RECEPTOR ANTAGONIST

Rudolph M. Navari, M.D., Rick R. Reinhardt, M.D., Ph.D., Richard J. Gralla, M.D., Mark G. Kris, M.D.,
Paul J. Hesketh, M.D., Ali Khojasteh, M.D., Hedy Kindler, M.D., Thomas H. Grote, M.D.,
Kelly Pendergrass, M.D., Steven M. Grunberg, M.D., Alexandra D. Carides, Ph.D.,
and Barry J. Gertz, M.D., Ph.D., for the L-754,030 Antiemetic Trials Group*

The New England Journal of Medicine

Distinct Mechanism for Antidepressant Activity by Blockade of Central Substance P Receptors

Mark S. Kramer,* Neal Cutler, John Feighner, Ram Shrivastava,
John Carman, John J. Sramek, Scott A. Reines, Guanghan Liu,
Substance P (NK$_1$) Receptor PET Studies

[18F] SPA-RQ Before Drug

[18F] SPA-RQ After Drug

[18F]SPA-RQ
hNK$_1$ IC$_{50}$ 0.067 nM
Aprepitant - Clinical Occupancy Study

Occupancy 24h Trough - key to once a day drugs


Plasma Drug Conc.

Scan 1 for 4 h
Baseline Radiotracer Injection 1
T = day 1 cold drug dosing start

Scan 2 for 4 h
T = 24 h after last dose on day 15: Radiotracer Injection 2

14 days of dosing 24h later
Aprepitant PET occupancy study

[18F] SPA-RQ as tracer

Data obtained 1-4 hours, normalized to CBL

Ascending doses of Aprepitant

Placebo

Pre-Rx

Post-Rx 14 day trough
Dose Related Blockade of Brain NK₁ Receptors by Aprepitant

Binding of PET tracer to NK₁ receptors

Blockade of NK₁ receptors after aprepitant dosing

Aprepitant: CINV Dose Finding Study

Time to First Emesis or Rescue

Percent of Patients with Complete Response

- APR 125/80
- APR 375/250
- APR 40/25
- Control

Justifying the Dose of Aprepitant


Binding of PET tracer to NK<sub>1</sub> receptors

Blockade of NK<sub>1</sub> receptors after aprepitant dosing

Mean (± SE) Plasma Trough Concentrations of the Aprepitant 3-Day Regimen

Brain NK<sub>1</sub> Receptor Occupancy (%)

Tracer Binding

Low

High
Substance P Antagonists and Depression

Mean Change in HAM-D17 (+ SE)

MK-0869 300 mg (n = 66)
paroxetine 20 mg (n = 68)
placebo (n = 64)

p = 0.051
p = 0.009
p = 0.001
p = 0.004
p = 0.005

hyp.

Week

1
2
4
6
Aprepitant : PET Simulations

Anti-depression occupancy index

CINV Efficacy

Aprepitant 160 mg Phase III

MK-0869 mean trough plasma level

% Occupancy by MK-0869

0 10 20 30 40 50 60 70 80 90 100

40 mg 125 mg 375 mg

MK-0869 mean trough plasma level
## Summary of Week 8 LOCF Efficacy

Data 160 mg vs Placebo (⁺: p<.050, ▬: p>.050)

<table>
<thead>
<tr>
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<th>HAMD (Primary)</th>
<th>CGI-I</th>
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K Ranga Krishnan American Psychiatric Association New York May 2nd 2004
Too near the bone!!

"Find out who set up this experiment. It seems that half of the patients were given a placebo, and the other half were given a different placebo."
Key Decision Points when Making a Drug

- Translating and Interpreting preclinical data
- Providing early concept validation
- Choosing and validating the right dose

Phases Where Imaging Can Help
Integrate imaging approaches to provide a bridge to genomics from the clinic and back
NIHROADMAP Initiative
(nihroadmap.nih.gov)
New Pathways to Discovery: Toolbox for Biomedical Research

• Speed development of new drugs
• Molecular Libraries and Molecular Imaging
• Accelerate validation of new targets for drug therapy
  - NIH molecular imaging probe development center
    • early detection and treatment of disease
    • monitor and help development of effective therapeutics
• Enabled by advances in genetics, chemistry, robotics and minimally/non-invasive imaging
Wayne Gretsky

'Skate to where the puck is gonna be'

'You miss 100% of the shots you never take'