Using Non-Human Primates to Build More Predictive Tools for Treating Cognitive Disorders

Jason Uslaner
Lack of Efficacy is the Leading Cause of Failure in Phase 2 and 3

- Potential causes for failure to demonstrate efficacy:
  - Preclinical measurements do not predict clinical efficacy
  - Mechanism of action not appropriately tested
    - Lack of good TE/PD biomarker (i.e. wrong dose)
  - Inability to reliably measure efficacy in clinic
Translational research attempts to connect basic research to patient care… it aims to move research results from "bench to bedside"
Preclinical Models
Traditional Approach: Rodent to Man

• Relatively Inexpensive
• Low compound requirement
• High Throughput
• Rich History
• More amenable to MOA studies

• Concerns
  – Complex Behavior
  – Tolerability
  – Translatable Biomarkers
Preclinical Models
Translational Approach: Rodent to NHP to Man

- Relatively Inexpensive
- Low compound requirement
- High Throughput
- Rich History
- More amenable to MOA studies

- Complex Behavior
- More comparable AEs
- Variety of Translatable Biomarkers

- Concerns
  - More expensive
  - High compound requirement
  - Lower Throughput
  - Short History
Increasing POS Through Convergence

### Efficacy across species and endpoint of interest

<table>
<thead>
<tr>
<th>Domain</th>
<th>Rodent</th>
<th>NHP</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Working Memory</td>
<td>✓</td>
<td>✓</td>
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</tr>
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<td>Episodic-like memory</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Executive Function</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</table>

### Relationship Between Biomarker and Efficacy

Data Convergence (or lack of) drives Go-No Go Decisions

Differentiation

We can’t only be efficacious, but need to be better than the competition!
An Example: Paired Associates Learning

- Test of *What* and *Where*
- Heavily dependent on hippocampus
- Predicts transition from MCI to AD
An Example: Paired Associates Learning

Paired-Associates Learning in Rhesus Monkeys
We can increase confidence in human translation and lower overall risk in our Discovery portfolio by:

1. Putting in place the most translatable and informative research operating plans.
2. Using and studying molecules/comparators having human data.
3. Understanding the assumptions and impact on translation.
4. Bridging gaps and integrating all PK-PD knowledge with quantitative/model-informed approaches.
**Pfizer Analysis: Application of TPKPD Increases Clinical POS**

<table>
<thead>
<tr>
<th>Exposure Confidence</th>
<th>Pharmacology Confidence</th>
<th>Pillars 1 and 2</th>
<th>Pillar 2 and 3</th>
<th>Pillar 1, 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>High</td>
<td>Exposure and Binding, No PD measure</td>
<td>Exposure and PD response, no direct measure of binding</td>
<td>Exposure, Binding, and PD</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>7 failed to test mechanism</td>
<td>1 failed to test mechanism</td>
<td>0 failed to test mechanism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 tested mechanism</td>
<td>5 tested mechanism</td>
<td>15 tested mechanism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 positive POC</td>
<td>6 failed in Phase 2</td>
<td>12 positive POC</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Total = 12</strong></td>
<td><strong>Total = 6</strong></td>
<td><strong>Total = 15</strong></td>
</tr>
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*•Morgan, Van der Graaf, et al. 2012*

- “3 pillars of survival”
  1. Exposure at target site of action over desired period of time
  2. Binding to the pharmacological target
  3. Expression of pharmacological activity
Examples Of How This Approach Has Been Implemented at Merck

• M1 positive allosteric modulator for Alzheimer’s disease
• PDE10 inhibitor for schizophrenia
• Dual Orexin Receptor Antagonist for insomnia
M1 Muscarinic Positive Allosteric Modulator

- AChEIs (acetylcholinesterase inhibitors): boost ACh (nonselectively) and indirectly increase muscarinic receptor activity

- Xanomeline (non-selective muscarinic agonist) showed efficacy in clinical studies
  - Poor PK and poor tolerability (only moderate selectivity)

- **Hypothesis**: a compound with high selectivity for M1 and modulatory mechanism predicted to result in improved efficacy with fewer side effects
  - Most cholinergic AE’s hypothesized to be mediated via M2 & M3
  - M1 (and M4) receptors largely restricted to brain while other muscarinic receptors present throughout periphery
PQCA is a selective M1 Positive Allosteric Modulator (PAM)

<table>
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<tr>
<th>Species</th>
<th>Potentiation IP* (nM)</th>
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<tr>
<td>Human</td>
<td>135</td>
</tr>
<tr>
<td>Rhesus</td>
<td>49</td>
</tr>
<tr>
<td>Dog</td>
<td>100</td>
</tr>
<tr>
<td>Rat</td>
<td>81</td>
</tr>
<tr>
<td>Mouse</td>
<td>69</td>
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</table>

>1000-fold selective over other Ms

No activity up to 30 μM in Panlabs

~30% free in plasma, not a PGP substrate

Similar Potencies across species
Convergence across assays and species at equivalent free drug concentrations...

**Paired Associates Learning**

- Vehicle
- Scopolamine
- 3.0 PQCA+Scop
- 10.0 PQCA+Scop
- 30.0 PQCA+Scop

**Object Retrieval Detour Task**

Scopolamine

**Continuous Performance Test**

- Vehicle
- 0
- 0.3
- 1.0

**Blood Flow**

- 3 mg/kg
- 1 mg/kg
- 0 mg/kg

Uslaner et al (2013)
M1 PAMs Can Be Combined With Standard of Care (SOC)

Rhesus PAL

Mouse NOR

Rhesus OR

M1 PAMs Demonstrate Improved Tolerability vs. SOC and Xanomeline

GI Tolerability

Main liability with SOC are profound GI effects, limiting dose

Increasing POS Through Convergence

**Efficacy across species and endpoint of interest**

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**Human Scopolamine Model**

Data Convergence (or lack of) drives Go-No Go Decisions

Cho et al., 2011
PDE10A is a Novel Therapeutic Target for Psychosis

- **Program Rationale:** PDE10A inhibition in the striatum will result in increased cAMP/cGMP signaling and striatal output, restoring behavioral inhibition that is impaired in schizophrenia.
THPP-1: Novel PDE10A Inhibitor

PDE10 $K_i = 1.0 \text{ nM}$

PDE selectivity:
- $>1000x$ PDEs 1-4, 7-9
- $\sim300x$ PDE 11
- $\sim100x$ PDE 5 & 6

Pharmacokinetics:

<table>
<thead>
<tr>
<th>Species</th>
<th>Plasma Protein Bound (%)</th>
<th>Clearance (mL/min/kg)</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rat</td>
<td>98.2</td>
<td>6</td>
<td>47</td>
</tr>
<tr>
<td>dog</td>
<td>97</td>
<td>3.8</td>
<td>79</td>
</tr>
<tr>
<td>rhesus</td>
<td>98.8</td>
<td>7.7</td>
<td>31</td>
</tr>
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</table>

Convergence across assays and species at equivalent free drug concentrations...

**Traditional Rodent Efficacy Assays**

- **MK-801 Induced Locomotor Activity (Acute)**
  - Distance Traveled (cm)
  - Veh, Veh, 1.5, 3, 4.5
  - THPP-1, MK-801

- **Conditioned Avoidance Responding**
  - % Avoidances
  - Veh, 1, 3
  - THPP-1 (mg/kg, po)

**Bridging Assay to NHP**

- Activity Counts
- THPP-1 (mg/kg)
  - v, v, 1, 3, 10, 30
- amph

**TE Biomarker: Receptor Occupancy**

- Striatum

**PD Biomarker: qEEG**

- **Gamma**
  - THPP-1 (1mg/kg), THPP-1 (3mg/kg), THPP-1 (10mg/kg), RSD (0.25)
  - Cox et al. (2015)
  - Smith*, Uslaner* et al., 2013
  - Vardigan et al (Submitted)
Additivity with SOC and differentiation

Leading therapies target GABA receptors which are widely distributed throughout various brain regions.

- Not only the parts that help you sleep, but also parts of the brain integral to cognition, motor control, etc.

In contrast, orexin neurons originate in one discrete area of the brain (LH), and selectively target the brain’s arousal system.

This targeted approach provides the potential to address liabilities of current therapies such as cognition disturbances, physical and psychological dependence, and motor deficits.

DORA-22 in vitro profile

hOX2R Ki = 0.62 nM  
hoX1R Ki = 10 nM  
hoX2R Fl = 11 nM  
hoX1R Fl = 32 nM
Similar across species. Data shown = human

Pgp: 0.6 (h), 0.8 (r)  
PPB: 4% (h), 3.5% (r)
Tests Used To Evaluate a Range of Cognitive Performance

**Novel Object Recognition**
- Dependent on hippocampus and perirhinal cortex
- Measure of long term memory

**Delay Match to Sample**
- Prefrontal /medial-temporal cortex-dependent task
- Measure of working memory
- Sample image presented and touched
- Delay Period (Variable)
- Monkey needs to remember image previously exposed to.

**Serial Choice Reaction**
- Prefrontal cortex-dependent task
- Measure of sustained divided attention
- Centering response required until cue of variable duration (0.4-4 sec) presented.
- Monkey needs to touch cued location to receive reward.
50% Recognition is equal to chance; S = scopolamine 1 mg/kg; * indicates significantly lower than vehicle.
Delayed Match To Sample

DORA-22

Percent Correct

Retention Interval

Diazepam

Eszopiclone

Zolpidem

Uslaner et al. (2013)
Index of Therapeutic vs. Adverse Cognitive Effects in Rat and NHP models

- DORAs:
  - Eszopiclone
  - Zolpidem
  - Diazepam

Rat:
- Cognitive impairing Dose
- Minimum effect Sleep Dose

NHP:
- Positive Therapeutic Range
- Negative Therapeutic Range

Dose (mg/kg):
1 2 3 4 5 10 15 20 25 28 30

- = Minimum effect Sleep Dose
- = Cognitive impairing Dose
Summary

- Translational methodologies in NHPs and TPKPD best practices have been employed Merck neuroscience to improve POS in the clinic
- Merck continues to invest in order to establish novel translatable biomarkers to increase POS in various other CNS disease areas
  - Psychosis
  - Pain
  - Movement Disorders
  - Disease Modifiers
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Richard Hargreaves
John Hunter
Brief muscarinic review

- Selective targeting of M1 muscarinic receptor could provide additional benefit in improving cognition in AD without substantially increasing adverse effects from nonspecific cholinergic stimulation
- M1 expression in periphery relatively limited

<table>
<thead>
<tr>
<th>What</th>
<th>mAChR's involved</th>
<th>Implication for M1-selective SAMM</th>
</tr>
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<tbody>
<tr>
<td>Peptic ulcer</td>
<td>M3 &gt; M5 → acid secretion</td>
<td>SAMM should not increase gastric acid</td>
</tr>
<tr>
<td>GI motility</td>
<td>M2 and M3 → increased GI motility</td>
<td>SAMM should not have an effect on GI motility</td>
</tr>
<tr>
<td>Salivation</td>
<td>M3 &gt; M1 stimulate salivation</td>
<td>SAMM may increase salivation, although not as much as nonselective muscarinic agonist</td>
</tr>
<tr>
<td>Overactive bladder</td>
<td>M3 inhibition helps incontinence</td>
<td>SAMM should not worsen incontinence</td>
</tr>
<tr>
<td>COPD/bronchial asthma</td>
<td>M3 &gt; M2 → bronchoconstriction</td>
<td>SAMM should not worsen COPD or asthma</td>
</tr>
<tr>
<td></td>
<td>M1 → bronchodilation</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>M2 → vagal bradycardia</td>
<td>SAMM should not cause bradycardia</td>
</tr>
</tbody>
</table>

Data from mouse KO studies
The Conundrum Of Drug Development For CNS Diseases Translation From Lab To Clinic

Novel Drug Targets

Translational Efforts

Preclinical
Target Validation Lead Optimization

Experimental Medicine

Clinical Neuroscience

Performance

Dose

PCC

Note: These curves are hypothetical!
Cellular Evidence That Supports Cognitive Effects:
DORA-22, Eszopiclone, Diazepam, And Zolpidem Reduce Arc Protein Levels In Hippocampus Of Rat At Doses Which Impair Cognition

![Graphs showing the effect of different drugs on Arc protein levels in the hippocampus of rats.](image-url)
Additivity with SOC and differentiation

Compounds Matched for Sleep Time in Rat

Uslaner et al, (2013)
Compounds Matched for Sleep Time in NHP

DORA-22

Mean Decrease in Active Wake

1 3 10 30 mg/kg PO

Eszopiclone

Mean Decrease in Active Wake

1 3 10 mg/kg PO

Diazepam

Mean Decrease in Active Wake

1 5 10 mg/kg PO

Zolpidem

Mean Decrease in Active Wake

1 3 mg/kg IM

Uslaner et al, (2013)
Compounds Matched for Sleep Time in Rat

DOR-A-22

Eszopiclone

Diazepam

Zolpidem

Uslaner et al, (2013)
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Compounds Matched for Sleep Time in NHP

Uslaner et al, (2013)
Alzheimer’s: an area of critical unmet need

- Most common form of dementia, affecting 1 out of every 8 people >65 years of age
- Acetylcholinesterase inhibitors (current lead therapy class) and NMDA antagonists only modestly effective
  - AChEIs exhibit tolerability issues related to non-specific cholinergic activity
- Current Market is Symptomatic Treatments Only:
  - Acetylcholinesterase inhibitors (AChEIs) are the leading class with 69% of sales, and NMDA receptor antagonists capture the remaining 31%
- Three approved AD therapies reached blockbuster status despite modest efficacy
  - ARICEPT (donepezil/AChEI/Pfizer): $4.4B peak sales
  - NAMENDA (memantine/NMDA/Forest): $1.4B 2012 sales, 75% concomitant use with AChEIs
  - EXELON (rivastigmine/AChEI/Novartis): $1.1B 2012 sales

$6.4 B Global Market

- US, $2.6 B
- EUCAN, $1.7 B
- Japan, $1.3 B
- Other, $0.8 B

Source: N7D Anti-Alzheimer’s Products IMS Sales Data MAT 2Q13