We will start momentarily at 2pm ET

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Session 5

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Session 4: Lead Optimization – Building Efficacy & Safety

Dr. Craig Lindsley
Editor, ACS Chemical Neuroscience
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Assistant Director of Industry
Member Programs, ACS

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Lead Optimization – Building Efficacy & Safety

Craig W. Lindsley
William K. Warren, Jr. Chair in Medicine
Professor of Pharmacology and Chemistry
VCNDD Co-Director, Director, Medicinal Chemistry
Editor-in-Chief, ACS Chemical Neuroscience

ACS Webinar
May 29, 2014

Drug Discovery Phases and Timelines

Small molecules have a 20% success rate from IND to NDA
Criteria for Lead Selection

Compound Series
- Reproducible activity
- Dose responsive
- Confirmed structural identity
- Purity established
- No evidence of class instability
- Tractable synthetic route established
- Favorable IP position and competitive assessment for class
- Demonstrable exploitable SAR
- Support for interaction with molecular target
- Selectivity/Profile established
- Assessment of 'drugability' (in vivo profile)
- Secondary Assay Funnel Validated

Chemical Attributes

Biochemical Attributes

Pharmacology Attributes

Intellectual Property Position

Solid IP

Poor IP

Chemotype Frequency

Lead Optimization— an iterative process of compound synthesis, testing, and design

Library Design → Med Chem → Purification/analytical chemistry

Screening “Hit” → Compound design and synthesis → Biological Assays

Sample Handling Delivery to Biologists

Activity at target potency, efficacy, affinity

Off target activity Related targets, other identified problem targets

In Vitro ADMET hERG, CYPs, PXR, metabolic stability, pgp, permeability, protein binding, etc.

In Vivo/In Situ In situ efficacy in vivo animal models, in vivo DMPK, human predictive PK

Requires Medicinal Chemists to KNOW Pharmacology
An Overview of $M_1$ mAChR Signaling – Signal Bias

Receptor Reserve: Excess Receptors Beyond Those Necessary for a Maximal Response

- High Receptor Reserve: Potency < Affinity
- Low Receptor Reserve: Potency ≈ Affinity
- In vivo there is a large range of mAChR receptor reserve levels
- In a given cell, mAChR coupling to distinct pathways can have different receptor reserves
Receptor Reserve – Weak Partial Agonist Considerations

- Weak partial agonists can have increased efficacy and potency in high receptor reserve
- Weak partial agonists can look like antagonists in low receptor reserve
- High receptor reserve systems set the highest bar for identifying antagonists
- This is critical for an antagonist program as it is the safest way to identify true antagonists

Primary Screening Success

Kinetic assays, multiplexed additions, and careful data analysis result in outstanding success with numerous screens (~15)

- A single HTS identifies agonists, PAMs, NAMs, agonists and antagonists
- For routine primary screen, identifies ‘molecular switches’
- Enables us to identify ago-PAMs (safe/desirable versus severe AEs, based on target)
Assay Development

Excitation at 488 nm
Emission at 540±30 nm

Niswender et al., Mol Pharm 2008

Do not drive on a single assay read-out – native when possible

Fluorine Introduction

- Inclusion of a F atom to attenuate the basicity of the ring N atom
  (J. Med. Chem. 1999 42 2087)

L-001411264
α1I 61 nM
pKₙ = 8.7
Panlabs 12 hits

L-001428751
α1I 66 nM
pKₙ = 7.9
Panlabs 4 hits

L-001439330
α1I 29 nM
pKₙ = 7.9
Panlabs 4 hits

L-001450755
α1I 506 nM
pKₙ = 6.7

- Efficacious in sleep, HIC, essential tremor, Wag-Rij, AHL, Pain

JMC, 2008, 51, 3692; JMC, 2008, 51, 6471
Scaffold Hopping For IP

\[ \text{Chemical Structures} \]

\[ \begin{align*}
\text{CID} & \quad R & \quad \text{IC}_{50} (\mu\text{M}) \\
45159619 & \quad \text{Ph} & > 10 \\
45119620 & \quad & 0.15 \\
45643250 & \quad & 1.9 \\
45643251 & \quad & > 10 \\
45643252 & \quad & > 10 \\
45643253 & \quad & 1.2 \\
45643254 & \quad & 3.0 \\
45643255 & \quad & > 10 \\
\end{align*} \]

In vitro Drug Metabolism & Pharmacokinetics

**Molecular Metabolism**
- Permeability - CNS & intestinal
- Active uptake/efflux (disposition)
- Drug-drug interactions (DDI)
- Human hepatocytes (human PK)

Caco-2, MDCK cells, vesicles (tissue culture facility, outsource)

**Biotransformation**
- Clearance mechanisms (\(\text{Cl}_{\text{int}}\))
- P450, MAO: DDI & induction
- Metabolite identification (pharmacology/safety)
- Drug safety (Drug Interactions)

**HT Bioanalysis → Bedrock Function**
- automated sample prep'n
- state-of-art mass spec techniques
- automated data analysis/storage

ACS Chem. Neurosci. 2011, 2, 730
In vitro Drug Metabolism & Pharmacokinetics

**Tier 1**

- **CYP Inhibition**
  - 3A4, 2D6, 2C9, 1A2
- **Protein Binding**
  - Rat, human (mouse)
- **Microsome Stability**
  - (m,r,h)
- **Intrinsic Cl**
  - (m,r,h)

Ideally...

- >20 μM
- <96%
- 80% @ 30 min
- half of hepatic BF

**Cassettes**

- Cassette PBL
- Standard PBL
- IV/PO mouse/rat
- Metabolite ID
- CYP mapping, etc.

**P450 fraction metabolized (f_m)**

<table>
<thead>
<tr>
<th>Substrate Depletion Clearance*</th>
<th>CL_{int} (mL/min/kg)</th>
<th>CL_H (mL/min/kg)</th>
<th>Fraction metabolized</th>
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<tbody>
<tr>
<td>rh3A4</td>
<td>69.5</td>
<td>16.1</td>
<td>73.0</td>
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<tr>
<td>rh2D6</td>
<td>0.3</td>
<td>0.3</td>
<td>1.2</td>
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<tr>
<td>rh2C19</td>
<td>1.5</td>
<td>1.4</td>
<td>6.3</td>
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<tr>
<td>rh2C9</td>
<td>not detected</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>m1A2</td>
<td>5.4</td>
<td>4.3</td>
<td>19.5</td>
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</table>

<table>
<thead>
<tr>
<th>fraction metabolized P450</th>
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<tbody>
<tr>
<td>3A4</td>
</tr>
<tr>
<td>2C9</td>
</tr>
<tr>
<td>2C19</td>
</tr>
<tr>
<td>206</td>
</tr>
<tr>
<td>1A2</td>
</tr>
</tbody>
</table>

Recombinant P450 CL_{int} values were scaled and then corrected using ISEF correction factors for known isoform specific substrates and incorporated published values of hepatic expression.

- In vitro CL_{int} with recombinant human P450 suggests 3A4 is the major oxidative metabolic pathway
  (other routes of clearance not covered by this approach)
- Need to assess AO/XO – non-CYPS for many common heterocycles
- f_m values are used to estimate DDI potential
- Understand induction – chronic dosing study to assess drug exposure
- Synthesize and characterize major metabolites!
**mGlu₅ PAM vs. Agonist - Neurotoxicity**

**Allosteric agonism at mGlu₅**
- DHPG induces prolonged epileptiform discharges in native systems
- DHPG (ICV) induces limbic seizures and can be inhibited by antagonists

**VU0424465**
- EC₅₀ = 7 nM (69%)  
- Cell: Ago-PAM  
- Astrocytes: Agonist

- cLogP = 3.6  
- PPB (h, r) 97.8, 97.2% (rac)  
- AHL- beh. disturbances

VU0424465 appears to be consistent with over-activation of mGlu₅ alone via Ago-PAM profile.

**mGlu₅ orthosteric and allosteric agonists induce epileptiform activity in hippocampal area CA3**

-Bridges, et al., Drug Metab. & Dispos. 2013, 41, 1703-1714
VU0403602 induces seizure activity after IP administration

<table>
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<tr>
<th>Dose (mg/kg)</th>
<th>Behavioral Effects</th>
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<tr>
<td>i.p.</td>
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</tr>
<tr>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>Stereotypy</td>
</tr>
<tr>
<td>30</td>
<td>Status Epilepticus</td>
</tr>
</tbody>
</table>

AE profile is blocked by MPEP and ABT (P450 Inhibitor)

VU0403602 EC$_{50}$ = 22 nM H10H PAM

Wood, et al., Biochemistry 2011, 50, 2403-2410; Bridges, et al., Drug Metab. & Dispos. 2013, 41, 1703-1714

Major metabolite of VU0403602 (VU0453103) has robust agonist activity

In vivo hepatic metabolism of VU0403602.

VU0453103 has allosteric agonist activity

VU0424465

Wood, et al., Biochemistry 2011, 50, 2403-2410; Bridges, et al., Drug Metab. & Dispos. 2013, 41, 1703-1714
Ancillary Pharmacology

Essential for ion channels, prior to CV dog

<table>
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<td>35010</td>
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<td>Atrazine A4</td>
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<td>35080</td>
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<td>num</td>
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<td>1µM</td>
<td>10</td>
</tr>
</tbody>
</table>

PD Models

- Does preclinical rodent model(s) mimic the human disease? Is translational?
- Is there capacity to drive a lead optimization program?
- Is there a genetic model?
- Should you employ animal models?
- Test mechanism in disease population with assurance you have target engagement?
## Imaging Biomarker Initiative

### Preclinical Research and Development
- In vivo target evaluation – Drug efficacy testing, faster identification of optimal molecule
- In vivo animal model development – Enabling more predictive models
- Evaluate potential drug safety liability

### Early Clinical Development (From Phase I to Phase II POC)
- Target engagement
- Dose selection and early demonstration of efficacy and/or toxicity
- Stratification of patient cohorts – Shorter and successful clinical trials
- Quick Kill ... Cheap Failure ! Faster re-deployment of resources and $

### Late Clinical Development

---

## Biomarkers

### PET

VU0409106 50% Occupancy gives full efficacy in primary PD model

### fMRI

### Sleep-Wake EEG
AstraZeneca: The 5R Framework for Successful Lead Optimization

Right target
- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right tissue
- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety
- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity, drug–drug interactions
- Understanding of target liability

Right patients
- Identification of the most responsive patient population
- Definition of risk–benefit for given population

Right commercial potential
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostic and biomarkers

Questions??
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