Have Questions?

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“Why am I muted?”
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Wlatka Peric-Knowlton, MSN, C-ANP, CDE, FAANP, Diabetes Nurse Practitioner & Consultant

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Matt Lacater
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"How to Optimize Central Nervous System Therapeutics:
Med Chem Strategies, Tactics, and Workflows"

Craig Lindsley
Co-Director and Director of Medicinal Chemistry
Professor of Pharmacology, Chemistry & Biochemistry
Vanderbilt Center for Neuroscience Drug Discovery

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What is less of a concern in CNS drug discovery?

• Depth of pharmacology in a CNS target
• Achieving high CNS exposure
• They are of equal concern
• Neither are of concern
CNS Drug Discovery

Constant Exodus from Neuroscience Drug Discovery
Major Unmet Medical Need

De-risk with tool compound ASAP

Outline ~ Challenges

Not Just Brain Penetration!

- **Target Identification** – Extrapolation to Clinic
  - Mechanism of Action
- **Assays**: Receptor Reserve, Native Systems, EP
  - Medicinal Chemistry Strategy
- **Brain Penetration**: *In Silico vs. Cells vs. In Vivo*
  - Behavioral Model to Drive SAR
    - Genetic Models
- **Chronic Dosing** (early *in vivo* tool compound)
  - Phenotypic Screen for CNS AEs
    - Biomarker Strategy
- **Clinic – Patient Stratification and Selection**
Lessons Learned from the Fate of AstraZeneca's Drug Pipeline: A Five-Dimensional Framework

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

Pharmacoeconomics

**Economics (Costs)**
- Cost minimization
- Cost effectiveness
- Cost benefit
- Cost utility

**Outcomes**
- Clinical benefits
- Survival
- Quality of life (QALY)
- Patient satisfaction/preference
Target Identification – Extrapolation to Clinic

- Basis for target selection?
  - Human Genetics?
  - Animal Studies/Genetics?
    - Me too?
    - Chemical Matter?

- How to select and stratify patients?
  - Biomarkers?
  - Drug naïve? First episode?
  - Stand alone or with standard of care?
  - Disease modifying or symptomatic?
    - Pharmacoeconomics

Challenges, Failures, Commitment (time/resources)

Mechanism of Action

For novel targets, need tool compounds to assess MoA

MoA: agonist, partial agonist, inverse agonist, competitive antagonist, non-competitive antagonist (NAM), PAM, ago-PAM, signal bias, heterodimers

Multiple in vitro and in vivo assays (different receptor reserve) to assess MoA

Evaluate tools with differing MoAs in native tissues (EP) and animal models
  - assess efficacy versus AEs-
  - chronic vs. acute dosing paradigms-

Discovery team now know candidate profile and assays to drive LO to PCC

Upfront chemistry investment, then wait for key data to re-engage
Mechanism of Action

Example, Glycine Transporter Type 1, GlyT1

- Glycine is a simple amino acid inhibitory (Glycine_A site) and excitatory (Glycine_B site) neurotransmitter.
- Two transporters have been identified that modulate glycine reuptake:
  - Glycine transporter Type 1 (GlyT1) - isoforms GlyT1a-f
  - Glycine transporter Type 2 (GlyT2) - isoforms GlyT2a-c

- 1st generation, non-competitive
- Elevate PFC glycine 400-500% basal for 24 h
- Neurotoxic, glycine-sensitive strychnine receptors
- Severe AEs and death upon chronic dosing
  Target depicted as non-druggable
  Research in area halted

- 2nd generation, competitive inhibitors
- Elevate PFC glycine 400-500% basal for 2-5 h
- Not neurotoxic
- Chronic dosing tolerated
- Efficacy in multiple schizophrenia models
  Multiple companies had PCCs
  Several in clinical trials

Mechanism of Action

Agonist only

PAM – no bias

PAM-induced bias

Different Behavioral Pharmacology

Different Safety/AE Profiles

ACS Med Chem Lett. 2015, 6, 716.
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

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

Inducible cell lines – mirror native

Counter-screening lines, same expression level.

Species differences
Understanding AEs with M₁ Ago-PAMs

Receptor Reserve and Native System Pharmacology Assessment

What is an M₁ PAM Candidate Profile?

<table>
<thead>
<tr>
<th>Compound Structure</th>
<th>VU0453595</th>
<th>VU0550164</th>
<th>MK-7622</th>
<th>PF-06764427</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro PAM EC₅₀</td>
<td>2.0-5.0uM/68-98 MAX</td>
<td>324nM 63% MAX</td>
<td>15nM 98% MAX</td>
<td>46nM 79% MAX</td>
</tr>
<tr>
<td>In Vitro Agonist Activity</td>
<td>N/A, &gt;10uM</td>
<td>N/A</td>
<td>4.6µM 90% MAX</td>
<td>0.6µM 77% MAX</td>
</tr>
</tbody>
</table>

*Neuropsychopharmacology, in press.*
PF-06764427 & MK-7622 have robust agonist activity

A. PF-06764427  MK-7622

C. PAM Response

D. Agonist Response

Examples of ‘pure’ M₁ PAMs

A. VU0453595  VU0550164

C. PAM Response

D. Agonist Response
Ago-PAMs but not pure-PAMs increase sEPSC frequency in layer V mPFC neurons

Ago-PAMs induce robust depression of mPFC fEPSPs in the absence of CCh
**M₁ ago-PAM MK7622 induces robust seizures**

**A.**

![Graph showing Modified Racine Score over time](image)

**B. Modified Racine Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Behavioral stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change in behavior</td>
</tr>
<tr>
<td>1</td>
<td>Sudden behavioral arrest, motionless staring (with orofacial automatisms)</td>
</tr>
<tr>
<td>2</td>
<td>Head nodding</td>
</tr>
<tr>
<td>3</td>
<td>Forelimb clonus with lordotic posture</td>
</tr>
<tr>
<td>4</td>
<td>Forelimb clonus, with rearing and falling</td>
</tr>
<tr>
<td>5</td>
<td>Generalized tonic-clonic activity with loss of postural tone, often resulting in death, wild jumping</td>
</tr>
</tbody>
</table>

Similar results observed with PF06764427, but not with ‘pure’ M₁ PAMs

Seizures have been misinterpreted as efficacy in mouse AHL

---

**‘Pure’ M₁ PAMs enhance Novel Object Recognition**

<table>
<thead>
<tr>
<th>5-6 weeks</th>
<th>6-7 weeks</th>
<th>7-8 weeks</th>
<th>8-9 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice arrive</td>
<td>PCP or Vehicle Injections</td>
<td>Washout</td>
<td>NOR</td>
</tr>
</tbody>
</table>

**Proposed Study Design**

<table>
<thead>
<tr>
<th>PCP or Vehicle</th>
<th>M₁ PAM or Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>Vehicle</td>
</tr>
<tr>
<td>PCP</td>
<td>Vehicle</td>
</tr>
<tr>
<td>PCP</td>
<td>10mg/kg VU0453595</td>
</tr>
<tr>
<td>PCP</td>
<td>1mg/kg MK7622</td>
</tr>
<tr>
<td>PCP</td>
<td>3mg/kg MK7622</td>
</tr>
<tr>
<td>PCP</td>
<td>10mg/kg MK7622</td>
</tr>
</tbody>
</table>

---
M₁ ago-PAM MK7622 and PF-06764427 fail to induce significant effects on object recognition in WT Rats

Novel Object Recognition

PF-06827443 displays intrinsic agonist activity in rM₁-CHO cells with high receptor expression
Which preclinical species (based on PBL data) is most predictive of human CNS penetration?

- Rat
- Mouse
- Dog
- NHP

PF-06827443 robustly depress fEPSP slopes recorded in layer V of the prelimbic mPFC evoked by electrical stimulation in layer II/III.
PF-06827443 increases sEPSC frequency in layer V mPFC neurons

PF-06827443 induces behavioral convulsions in mice. C57Bl6/j mice

When a PAM is not a “PAM”: brief comments on M₁ PAMs

- PAM EC\(_{50}\) determined with a subthreshold concentration of ACh (EC\(_{20}\)). Thus, underestimates in vivo potency, where ACh tone > EC\(_{20}\). Risk of over-stimulation.
- Ago-PAM EC\(_{50}\) depends on receptor reserve in cell lines (and brain regions in vivo).
- PAM binding site is topographically distinct from ACh binding site.
- Like mGlu₅ PAMs, need to assess pharmacology in both low and high-expressing cell lines, as well as native systems (for M₁, LTD). Ago-PAM activity in cell lines and native systems is a non-starter. Fold-shift, residence time, internalization, metabolites and signal bias (ERK, β-Arr, PLD) must be understood.
- PAM pharmacology can vary even within a highly conserved series – stabilizing unique active conformations. Generalizations are dangerous.
- Phenotypic seizure model in mice ideal triage (M₁ agonists induce seizures)
- In our hands, both MK-7622, PF-06764427 and PF-06827443 interact with the ACh site, display agonism in cell lines and native systems (induce robust LTD), induce seizures, display unfavorable signal bias and are not ‘M₁ PAMs’. Thus, their cholinergic side effects and AEs are anticipated.
- A translatable M₁ PAM must have no agonism in native systems, favorable signal bias and an in vitro EC\(_{50}\) in the 100-400 nM potency range to avoid over stimulation of M₁.
**Assays:** Receptor Reserve, Native Systems, EP

**Triplicate Screening Technology**

- Identify agonist and antagonist (full and partial), PAMs, allosteric agonists
- Must routinely perform counter-screens

---

**mGlu<sub>5</sub> PAM vs. Agonist - Neurotoxicity**

**Allosteric agonism at mGlu<sub>5</sub>**

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

VU0424465
EC<sub>50</sub> = 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 mGlu<sub>5</sub> alone via Ago-PAM profile.

---

Bridges, et al., *Drug Metab. & Dispos.* 2013, 41, 1703-1714
mGlu₅ orthosteric and allosteric agonists induce epileptiform activity in hippocampal area CA3

VU0430644 (Pure PAM)  VU0424465 (Ago-PAM)

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

VU0403602 induces seizure activity after IP administration

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

EC₅₀ = 22 nM H10H PAM

VU0430644

Modified Racine Score (0-9)

- VU02 + MPEP
- VU02 + ABT

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

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

---

**VU0430644 provides a picolinamide biaryl acetylene with pure PAM activity and no epileptiform activity**

PAM CRC  

Agonist CRC  

LTD  

Epileptiform activity
Understanding Ago-Liability and Understanding Signal Bias gave Window to Allow PCC Approval

Positive Allosteric Modulation of mGlu5

VU0092273
No stimulus bias

VU0409551-induced Stimulus bias

Orthosteric binding site
Allosteric binding site

Gq
NMDAR

Antipsychotic-like efficacy

ADVERSE EFFECTS
Cognition enhancing efficacy

Medicinal Chemistry Strategy

- No one size fits all
- Driven by organization/legacy

- 'Chance favors prepared mind'
- Libraries as diverse hypothesis testing vehicles
- Iterative/matrix
- Ensure hypotheses fully vetted
- No "holes" in the SAR
- Quickly see patterns
- Better IP position
- Fuller DMPK understanding
- Limited human resources
- Key for the first in vivo tool!
For CNS, ‘fluorine walk’ is ideal optimization approach:
  • size, lipophilicity, HBA, van der Waals, block metabolic hot spots

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

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

JMC, 2008, 51, 3692; JMC, 2008, 51, 6471
Scaffold-hopping/patent busting

- Many engaged in similar exercise – may lose IP if not first to file
  - Suboptimal pharmacology may ‘tag’ along
  - Limited diversity (chemotype-mediated AEs, limited tools)

*New HTS for novel chemical matter and broader array of pharmacology – more diverse tools to understand your target and ask questions*

**Brain Penetration: In Silico vs. Cells vs. In Vivo**

*In vivo* trumps all. Need experimental measures to validate *in silico* and cell data

Plasma:Brain Level Cassettes in mice, rats and NHPs (4 novel plus control)
- $K_p$, total plasma:brain partitioning coefficient (ie., $K_p > 0.3$)
- $K_{p,uu}$, unbound plasma:brain partitioning coefficient (ie., $K_{p,uu} > 0.3$)
- Discrete $K_p/K_{p,uu}$ via PO, IP or SC dosing (time/$C_{max}$, $T_{max}$)
- For some lipophilic molecules (where BHB $f_u$ low), CSF levels better predictor of *in vivo* efficacy (or plasma:csf ratio)
  - Must be determined for every target and every chemical series/tool

- *In Vivo* pharmacology may be driven by either free or total brain
  - Must be determined for every target and every chemical series/tool
  - $K_p/K_{p,uu}$ may be the same, or very different, for mice and rats – check before efficacy studies
ER ratio <3 for non-Pgp substrates
$P_{\text{app}} > 20 \times 10^{-6}$ cm/s

Human and rodent may differ – need rodent Pgp transporter line

NHP PBL: terminal NHP study to build confidence in MDR1 data

---

**Brain Penetration: In Silico vs. Cells vs. In Vivo**

**Lipinski’s Rules**  **Rule of 3**  **CNS MPO Score**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>T0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClogP</td>
<td>3.7</td>
<td>0.65</td>
</tr>
<tr>
<td>ClogD</td>
<td>2.7</td>
<td>0.65</td>
</tr>
<tr>
<td>TPSA</td>
<td>90</td>
<td>1.00</td>
</tr>
<tr>
<td>MW</td>
<td>375</td>
<td>0.89</td>
</tr>
<tr>
<td>HBD</td>
<td>1</td>
<td>0.83</td>
</tr>
<tr>
<td>pKa</td>
<td>9</td>
<td>0.50</td>
</tr>
<tr>
<td>CNS MPO</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

**CNS MPO Calculator**

- Model for predicting CNS penetration
- Rule of 3: Lipinski’s Rule
- CNS MPO Score

**Brain Penetration: In Silico vs. Cells vs. In Vivo**

**Apical**

Experimental model for transcellular transport

**Basal**

Caco-2 tool transwell plate
Behavioral Model to Drive SAR

- Initially, may have nothing to do with human disease
- Shows target engagement in vivo to drive optimization
- Refine over time to be relevant to disease indication
- Transition from mouse to rat to NHP (or other mammal)
  - Drug challenge models (ensure no DDI)
- Investigate acute versus chronic (or prenatal) drug challenge
  (these may afford different phenotypes)

Genetic Models

- Prefer relative to Drug challenge models
- Is your genetic model more relevant to human disease?
  - Have KO mice to confirm pharmacology*
  - Have knock-in mice models to confirm pharmacology*
- Consider genetic rats for targets where mice are extremely sensitive

Chronic Dosing (early in vivo tool compound)

- Compound efficacy and AEs may differ based on acute versus chronic administration and/or drug challenge

- Drug: amphetamine vs. MK-801 vs. NR1 KD mouse

Phenotypic Screen for CNS AEs

Use most sensitive preclinical species
**Imaging Biomarker Initiative**

*Initiate in parallel to LO***

- **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**

---

**Two types of information with PET**

1. Information about a labeled drug.

   ![Diagram](image1)

   - **PK**
   - **PD**

   **living system**

   **drug**

2. Information about a biological event.

   ![Diagram](image2)
Development of a Clinical PET Tracer $^{18}$F-MK-6577

Autoradiography in A) rhesus and B) human. Top total and Lower panel is block by ACPPB.

t$_{1/2}$ = ~20 min for $^{11}$C and 110 min for $^{18}$F


Imaging and Biomarker Strategies

VU049106 50% Occupancy gives full efficacy in primary PD model

PET

fMRI

EEG Spectral Analysis

VU049106 in vivo mD2RS occupancy $^{18}$F-PE2EA

PET (experimental)

Vehicle

fMRI (template)

Hippocampus

Striatum

Cortex

Cerebellum

30 mg/kg

10 mg/kg

3 mg/kg

1 mg/kg

1 mg/kg Donepezil, i.p.

3 mg/kg Donepezil, i.p.

10 mg/kg Donepezil, i.p.

0 10 20 30 40 50 60 70 80 90 100

200 150 100 50 0

α β γ
Clinic – Patient Stratification and Selection

- The clinic is key to success
  - The right patients make all the difference
  - Well controlled – individual dosing/control
  - Biomarker/genetic/drug naïve segregated
    - Stand alone or combination
  - Early efficacy measures/engagement/drug challenge ~quick kill~
  - KOLs at inception of program – evolve with discovery
“How to Optimize Central Nervous System Therapeutics: Med Chem Strategies, Tactics, and Workflows”

Craig Lindsley
Co-Director and Director of Medicinal Chemistry
Professor of Pharmacology, Chemistry & Biochemistry
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Final Thoughts

• CNS drug Discovery – ‘high risk, high reward’

• Understanding and appreciation for mechanism of action

• The ‘right’ assays in place to drive LO

• Diverse chemical matter to launch an effort

• In vivo POC tool compound(s) ASAP

• Biomarkers

• Patients

Soluble, CNS penetrant and the ‘right’ potency/pharmacology for your target

Patients are Waiting

How has ACS Webinars benefited you?

“Dr. Gribkoff gave an excellent presentation which was clinically relevant. As a Nurse Practitioner and daughter of parents who both died of different types of dementia the talk helped me understand why it has been so difficult for pharma to discover disease modifying treatments. Today’s speaker identified many reasons and barriers that explain the 100% failure rate for Alzheimer’s and other neurodegenerative disease.”

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