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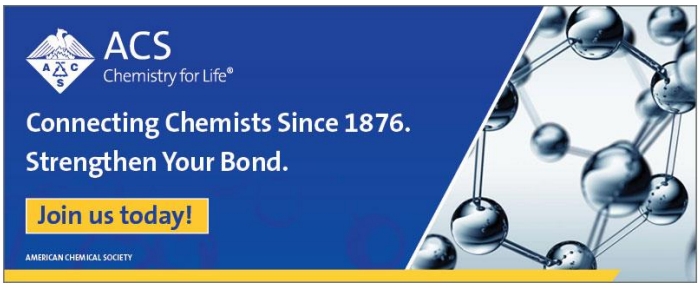

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aaps PharmSci 360 / NOV 4–7, 2018 • WASHINGTON, DC
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YouTube video:
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Chemical Entity and Biomolecule Scientific Program Tracks:

- **Preclinical** (including Discovery)
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Aug. 19-23, 2018 | Boston | **MA**

ACS Technical Division
Medicinal Chemistry (MEDI)

Featuring **4 days of programming** covering advances in *rare diseases, chronic pain, GCPRs, target identification, antibiotic resistance*, and **more**!

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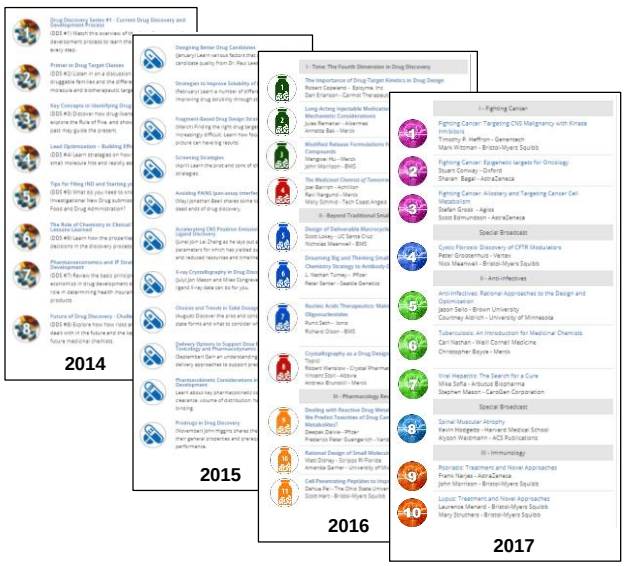

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http://bit.ly/acsDrugDiscoveryArchive

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How has ACS Webinars® benefited you?

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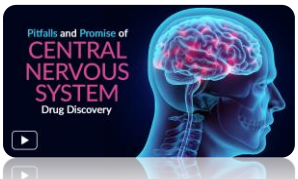
"Dr. Gribkoff gave an excellent presentation which was clinically relevant. As a Nurse Practitioner and daughter of parents who both died of different types of dementia the talk helped me understand why it has been so difficult for pharma to discover disease modifying treatments. Today's speaker identified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

Fan of the Week

Wlatka Peric-Knowlton, MSN, C-ANP, CDE, FAANP, Diabetes Nurse Practitioner & Consultant



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An individual development planning tool for you!

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Thursday, August 2, 2018

Cloudiness in Beer: Considerations and Chemistry
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Experts


Charles Bamforth
UC Davis


Brian Guthrie
Cargill

Thursday, August 9, 2018

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Experts


Tiffany Hoerter
Agilent Technologies


Karen McMillan Tkaczyk
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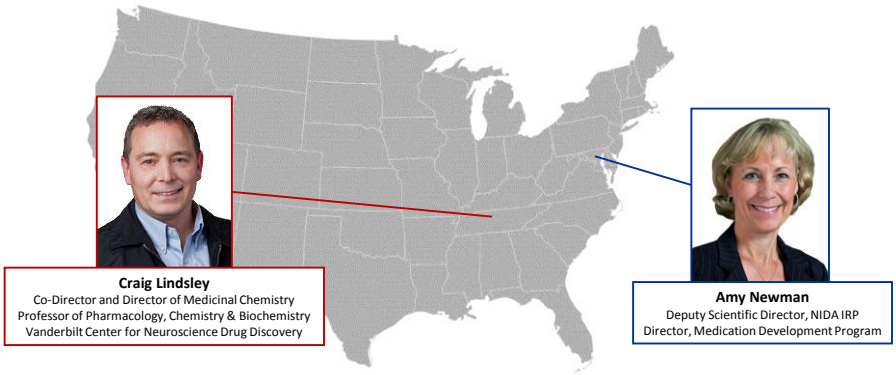
*"**How to Optimize Central Nervous System Therapeutics:** Med Chem Strategies, Tactics, and Workflows"*



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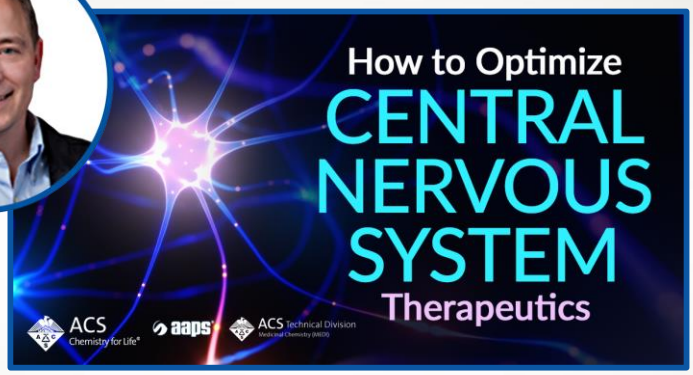

Professor Craig Lindsley, FRSC
Vanderbilt Center for Neuroscience in Drug Discovery

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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

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

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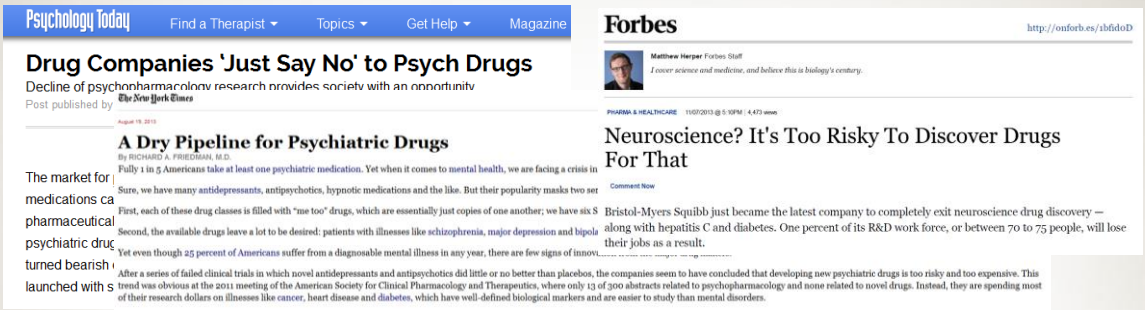
CNS Drug Discovery



Psychology Today | Find a Therapist | Topics | Get Help | Magazine

Drug Companies 'Just Say No' to Psych Drugs

Decline of psychopharmacology research provides society with an opportunity

Post published by The New York Times

A Dry Pipeline for Psychiatric Drugs

By RICHARD A. FRIEDMAN, M.D.

Fully 1 in 5 Americans take at least one psychiatric medication. Yet when it comes to mental health, we are facing a crisis in

Sure, we have many antidepressants, antipsychotics, hypnotic medications and the like. But their popularity masks two ser

First, each of these drug classes is filled with "me too" drugs, which are essentially just copies of one another; we have six S

Second, the available drugs leave a lot to be desired: patients with illnesses like schizophrenia, major depression and bipola

Yet even though 25 percent of Americans suffer from a diagnosable mental illness in any year, there are few signs of innov

After a series of failed clinical trials in which novel antidepressants and antipsychotics did little or no better than placebos, the companies seem to have concluded that developing new psychiatric drugs is too risky and too expensive. This trend was obvious at the 2011 meeting of the American Society for Clinical Pharmacology and Therapeutics, where only 13 of 300 abstracts related to psychopharmacology and none related to novel drugs. Instead, they are spending most of their research dollars on illnesses like cancer, heart disease and diabetes, which have well-defined biological markers and are easier to study than mental disorders.

The market for
medications ca
pharmaceutical
psychiatric drug
turned bearish
launched with s

Forbes http://onforb.es/1bfidoD

Matthew Herper Forbes Staff

I cover science and medicine, and believe this is biology's century.

PHARMA & HEALTHCARE 11/07/2013 @ 5:10PM | 4,473 views

Neuroscience? It's Too Risky To Discover Drugs For That

Comment Now

Bristol-Myers Squibb just became the latest company to completely exit neuroscience drug discovery — along with hepatitis C and diabetes. One percent of its R&D work force, or between 70 to 75 people, will lose their jobs as a result.

Constant Exodus from Neuroscience Drug Discovery

Major Unmet Medical Need

De-risk with tool compound ASAP

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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**

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Lessons Learned from the Fate of AstraZeneca's Drug Pipeline:

A Five-Dimensional Framework

Nature Reviews Drug Discovery Volume: 13, Pages:419–431 Year published:(2014) DOI:doi:10.1038/nrd4309

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

Nature Reviews | Drug Discovery

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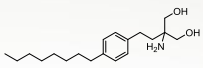
Pharmacoeconomics

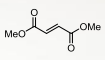
Pharmacoeconomics

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

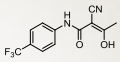
Outcomes
- Clinical benefits
- Survival
- Quality of life (QALY)
- Patient satisfaction/ preference



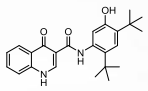
Gilenya™ (fingolimod) **$60,000/patient/year**



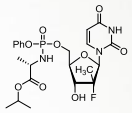
Tecfidera™ (dimethyl fumarate) **$54,900/patient/year**



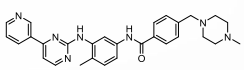
Aubagio™ (teriflunomide) **$51,000/patient/year**



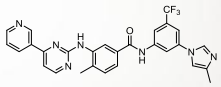
Kalydeco™ (ivacaftor) **>$300,000/patient/year**



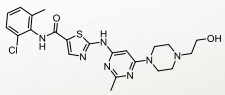
Sovaldi™ (sofosbuir) **$84,000/patient/year**



Gleevec™ (imatinib) **~$92,000/patient/year**



Tasinga™ (nilotinib) **~$115,500/patient/year**



Sprycel™ (dasatinib) **~$123,500/patient/year**

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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)*

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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

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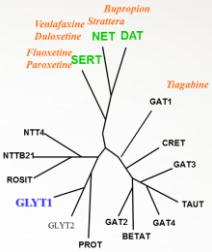
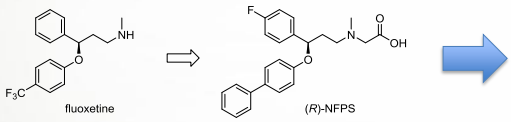
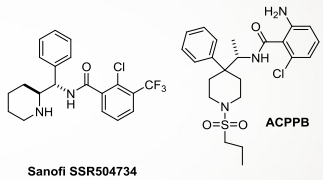
Mechanism of Action

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







Sanofi SSR504734

- 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

disclosures

Curr. Top. Med. Chem. **2006**, *6*, 1883-1896.

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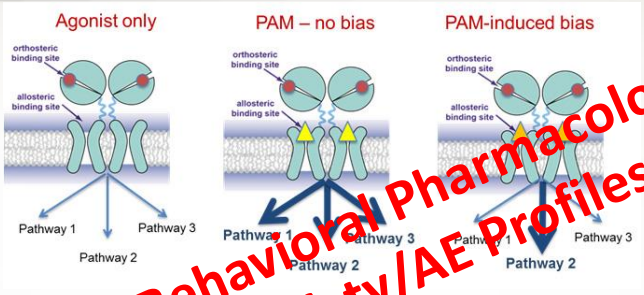
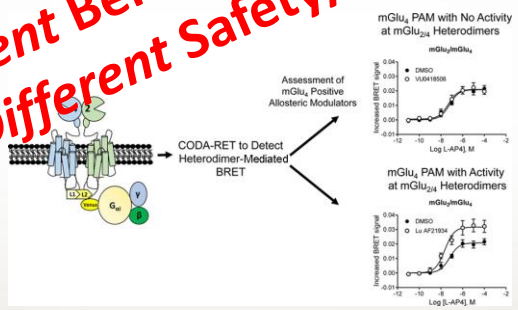
Mechanism of Action



Different Behavioral Pharmacology
Different Safety/AE Profiles



NIswender, et al., *ACS Chem. Neurosci.* **2016**, *7*, 1201-1211.
ACS Med Chem Lett. **2015**, *6*, 716.

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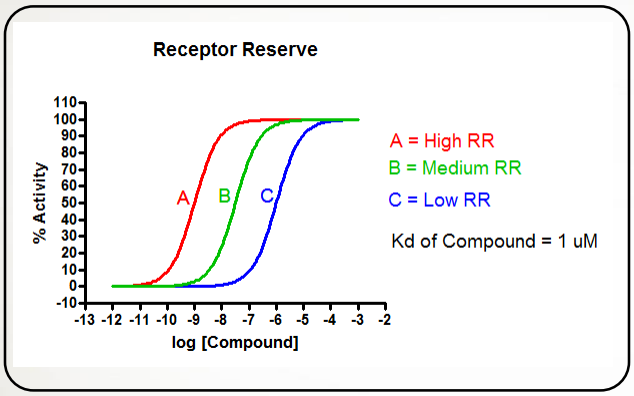
Assays: Receptor Reserve, Native Systems, EP



- 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

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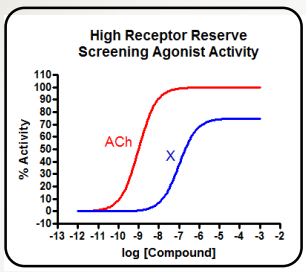
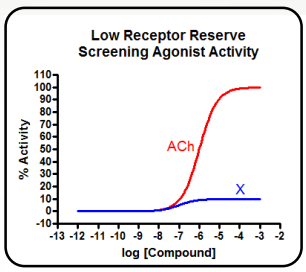
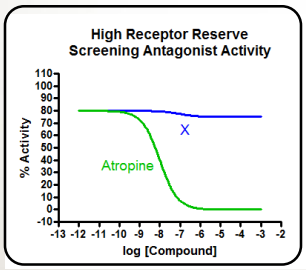
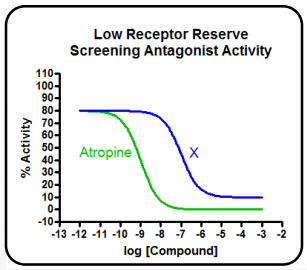
Assays: Receptor Reserve, Native Systems, EP

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
- Inducible cell lines – mirror native
- Counter-screening lines, same expression level.
- Species differences

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Understanding AEs with M_1 Ago-PAMs

Receptor Reserve and Native System Pharmacology Assessment

What is an M_1 PAM Candidate Profile?

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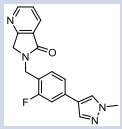
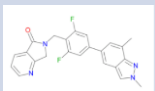
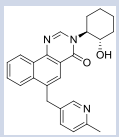
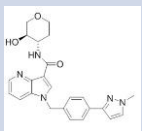
M_1 PAMs

	VU0453595	VU0550164	MK-7622	PF-06764427
Compound Structure				
***In vitro* PAM EC_{50}**	2.0-5.0uM/ 68-98 MAX	324nM 63% MAX	15nM 98% MAX	46nM 79% MAX
***In Vitro* Agonist Activity**	N/A, >10uM	N/A	4.6µM 90% MAX	0.6µM 77% MAX

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Neuropsychopharmacology, in press.

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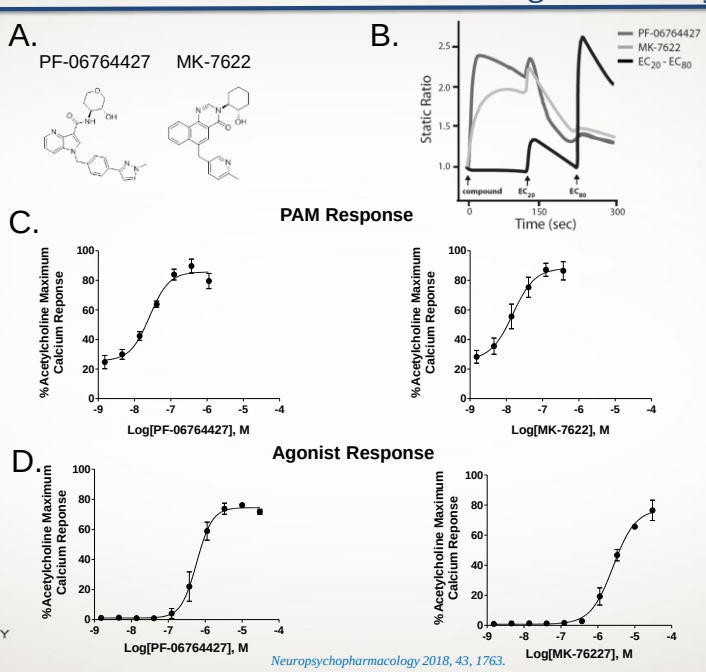
PF-06764427 & MK-7622 have robust agonist activity



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Neuropsychopharmacology 2018, 43, 1763.

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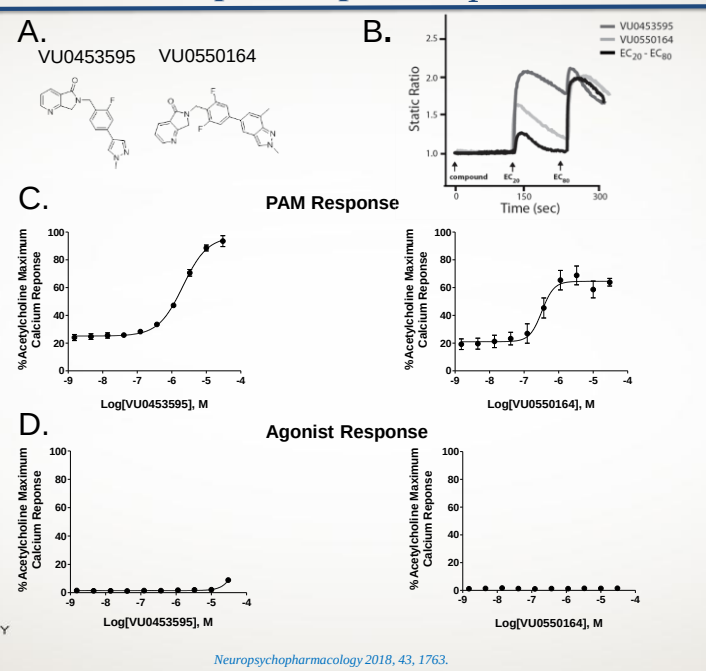
Examples of 'pure' M_1 PAMs



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Neuropsychopharmacology 2018, 43, 1763.

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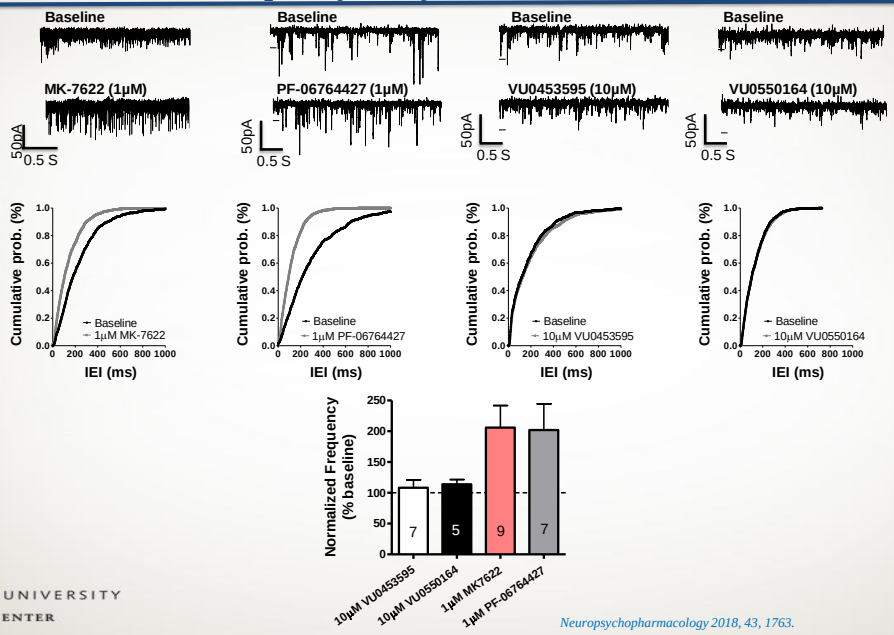
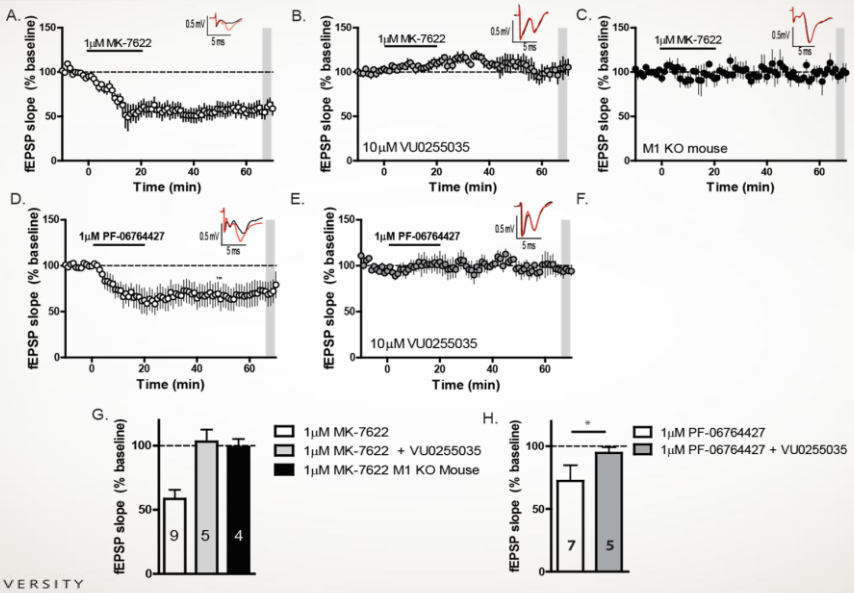
Ago-PAMs but not pure-PAMs increase sEPSC frequency in layer V mPFC neurons



Neuropsychopharmacology 2018, 43, 1763.

30

Ago-PAMs induce robust depression of mPFC fEPSPs in the absence of CCh



Neuropsychopharmacology 2018, 43, 1763.

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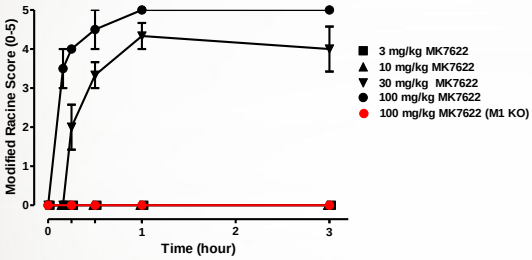
M_1 ago-PAM MK7622 induces robust seizures

A.



B. Modified Racine Score

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

Similar results observed with PF06764427, but not with 'pure' M_1 PAMs

Seizures have been misinterpreted as efficacy in mouse AHL

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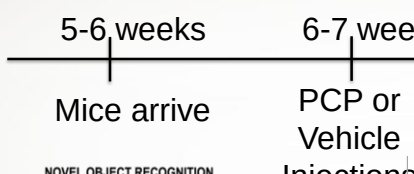
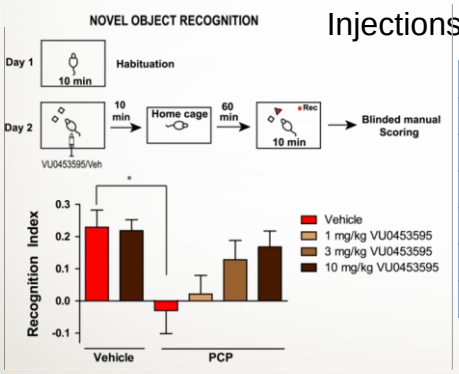
'Pure' M_1 PAMs enhance Novel Object Recognition





Proposed Study Design

PCP or Vehicle	M1 PAM or Vehicle
Vehicle	Vehicle
PCP	Vehicle
PCP	10mg/kg VU0453595
PCP	1mg/kg MK7622
PCP	3mg/kg MK7622
PCP	10mg/kg MK7622

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Neuropsychopharmacology **2016**, *41*, 598-610

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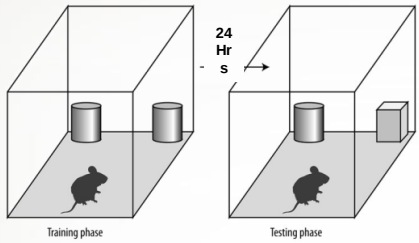
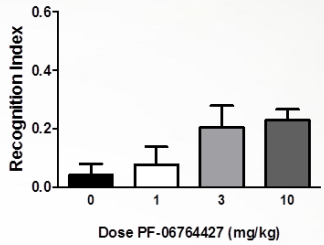
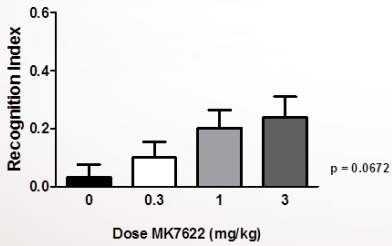
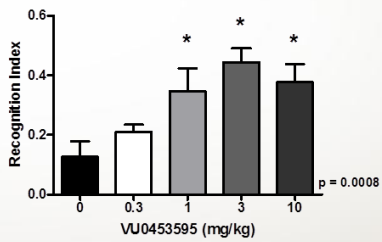
M_1 ago-PAM MK7622 and PF-06764427 fail to induce significant effects on object recognition in WT Rats

Novel Object Recognition









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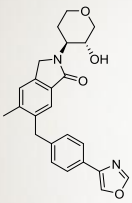
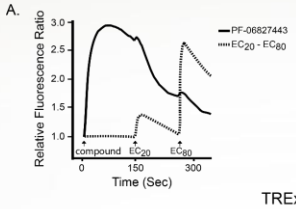
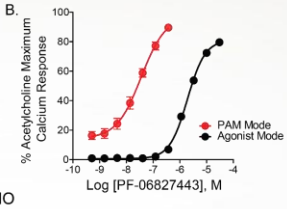
PF-06827443 displays intrinsic agonist activity in rM$_1$-CHO cells with high receptor expression

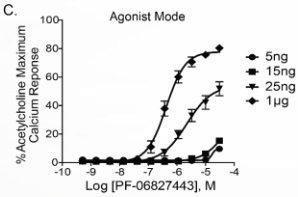


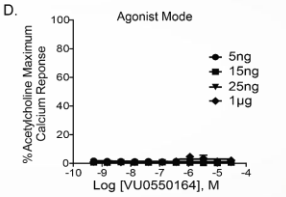
PF-0687443

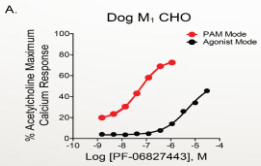


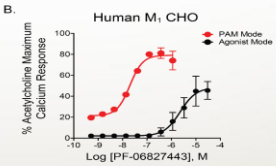


TREx CHO









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ACS Chem. Neurosci., in press

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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which preclinical species (based on PBL data) **is most predictive of human CNS penetration?**

- Rat
- Mouse
- Dog
- NHP

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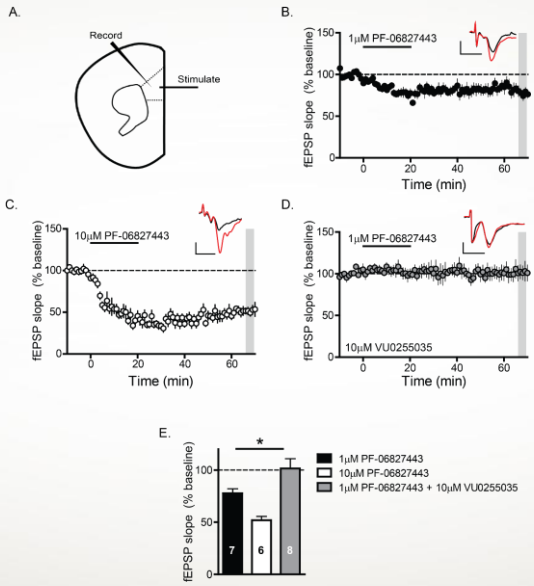
PF-06827443 robustly depress fEPSP slopes recorded in layer V of the prelimbic mPFC evoked by electrical stimulation in layer II/III



ACS Chem. Neurosci, in press

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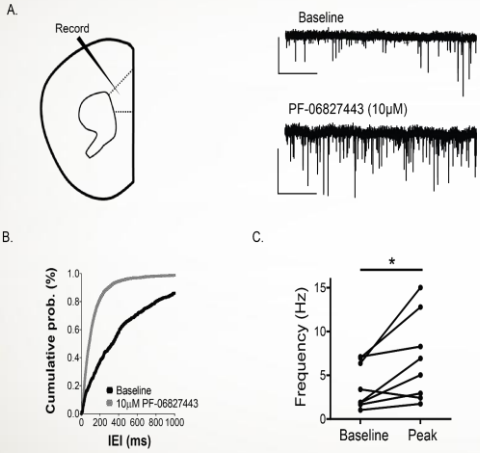
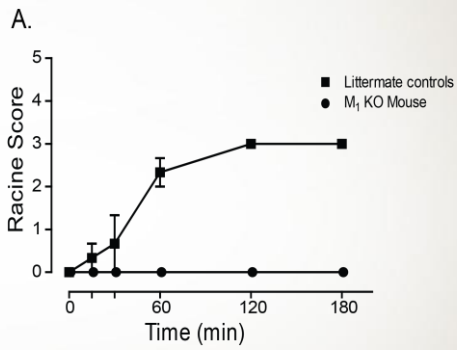
PF-06827443 increases sEPSC frequency in layer V mPFC neurons

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





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ACS Chem. Neurosci., in press

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When a PAM is not a "PAM": brief comments on M_1 PAMs

- PAM EC_{50} determined with a subthreshold concentration of ACh (EC_{20}). Thus, under-estimates *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 $mGlu_5$ PAMs, need to assess pharmacology in both low and high-expressing cell lines, as well as native systems (for M_1, 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 (M_1 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 ' M_1 PAMs'. Thus, their cholinergic side effects and AEs are anticipated.
- A translatable M_1 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 M_1.

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disclosures

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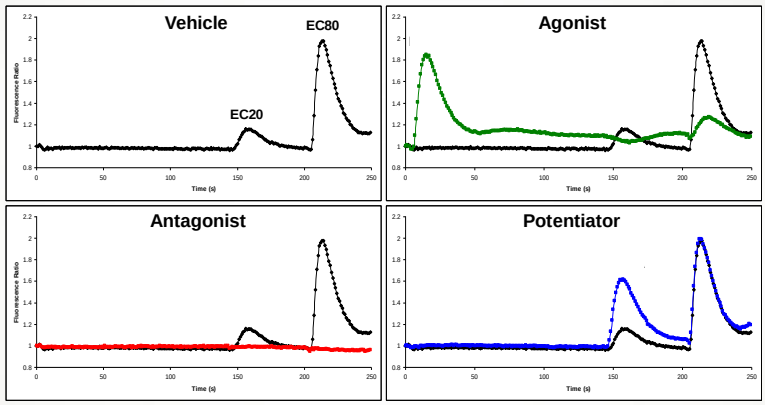
Assays: Receptor Reserve, Native Systems, EP

Triplicate Screening Technology



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

Melancon, et al., *J. Med. Chem.* **2012**, *55*, 1445-1464.

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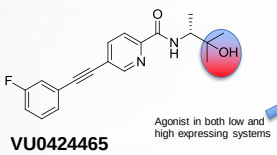
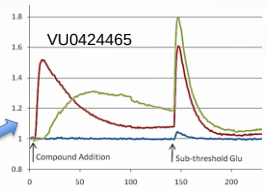
$mGlu_5$ PAM vs. Agonist - Neurotoxicity

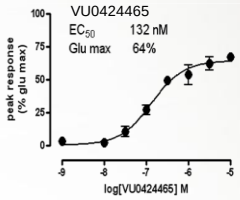
Allosteric agonism at $mGlu_5$

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



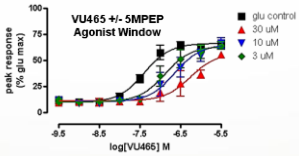
Agonist in both low and high expressing systems

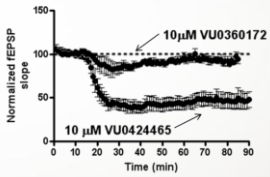




VU0424465
EC_{50} = 7 nM (69%)
Cell: Ago-PAM
Astrocytes: Agonist

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





VU0424465 appears to be consistent with over-activation of $mGlu_5$ alone via Ago-PAM profile.

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

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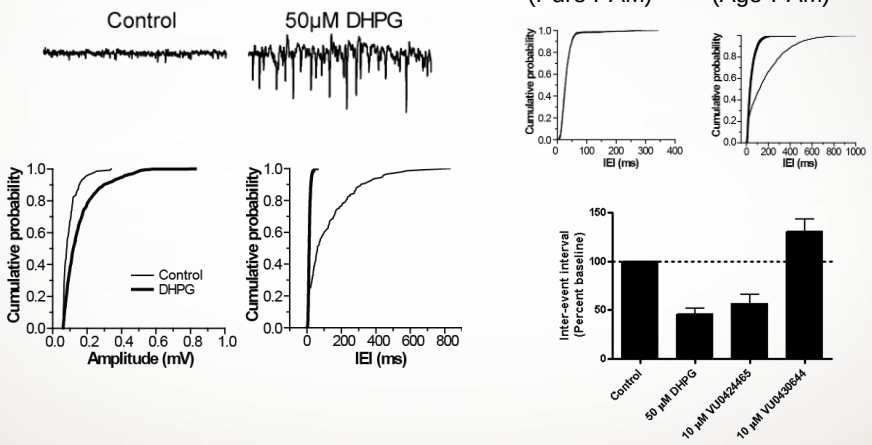
$mGlu_5$ orthosteric and allosteric agonists induce epileptiform activity in hippocampal area CA3



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

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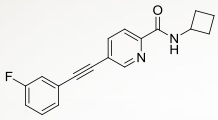
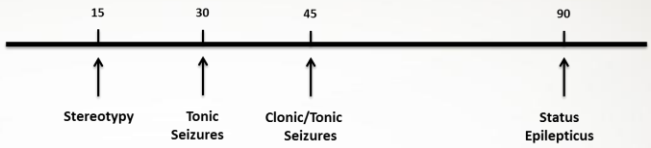
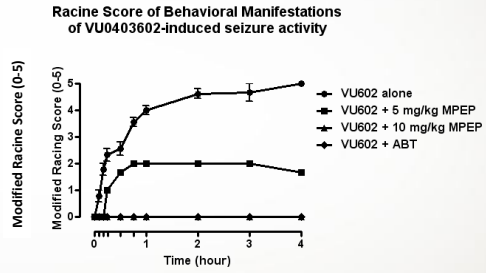
VU0403602 induces seizure activity after IP administration



VU0403602
EC_{50} = 22 nM H10H PAM



Dose (mg/kg) i.p.	Behavioral Effects
3	None
10	Stereotypy
30	Status Epilepticus



➢ 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

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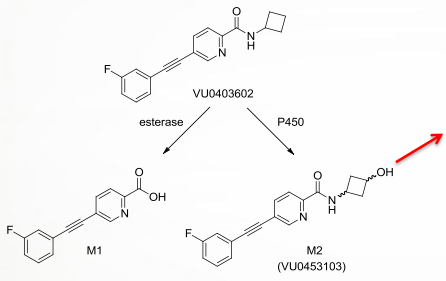
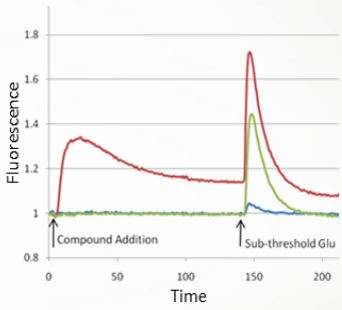
Major metabolite of VU0403602 (VU0453103) has robust agonist activity

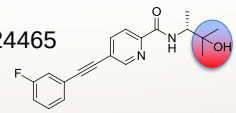
In vivo hepatic metabolism of VU0403602.



VU0453103 has allosteric agonist activity



VU0424465



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

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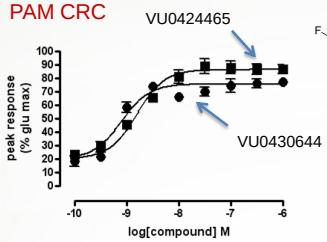
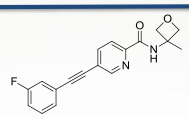
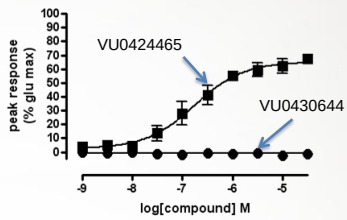
VU0430644 provides a picolinamide biaryl acetylene with pure PAM activity and no epileptiform activity

PAM CRC

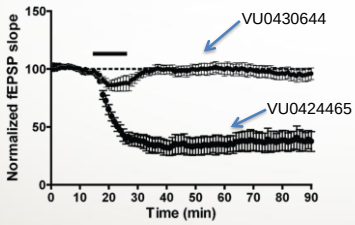




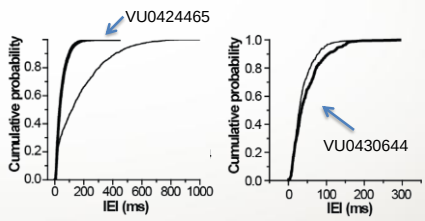
Agonist CRC



LTD



Epileptiform activity



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

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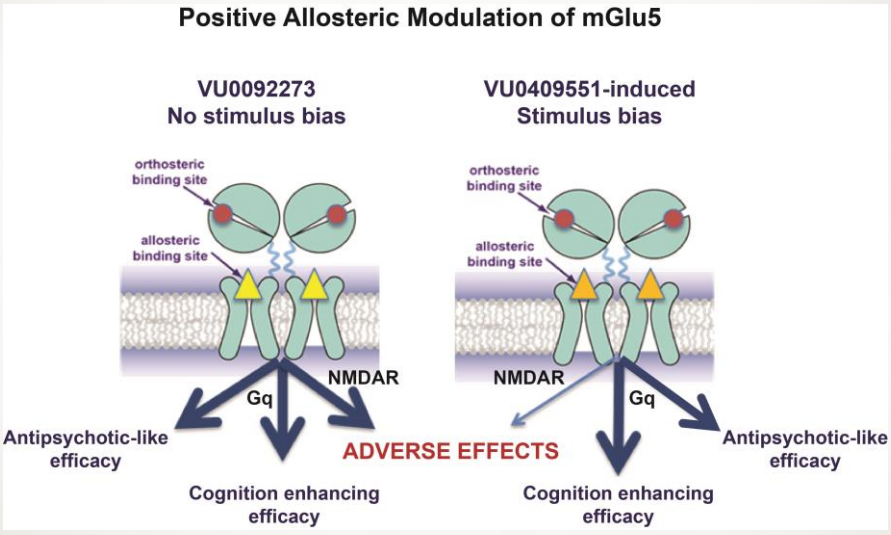
Understanding Ago-Liability and Understanding Signal Bias gave Window to Allow PCC Approval



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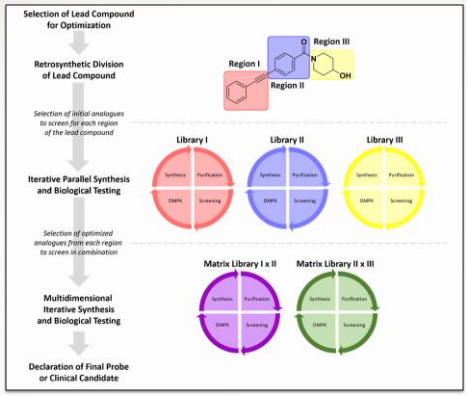
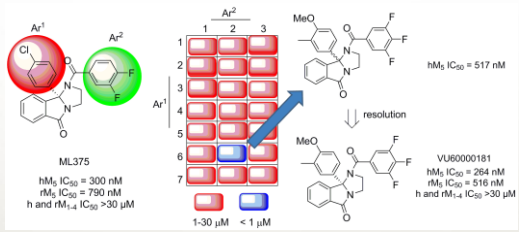
Medicinal Chemistry Strategy



- 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!



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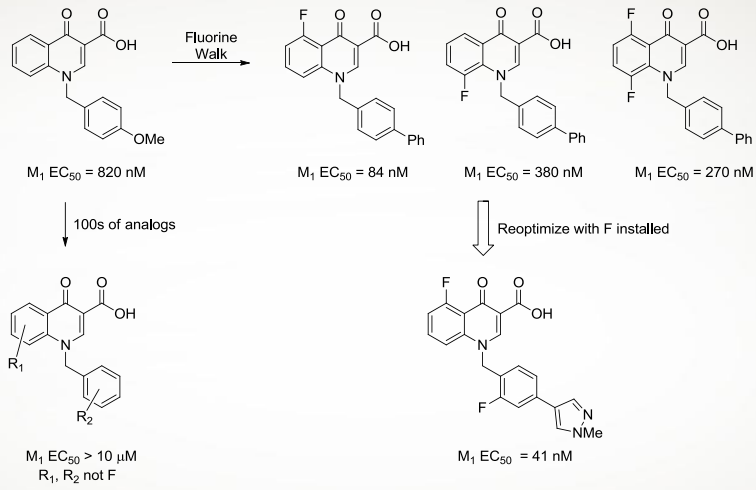
Medicinal Chemistry Strategy



For CNS, 'fluorine walk' is ideal optimization approach:

- **size, lipophilicity, HBA, van der Waals, block metabolic hot spots**

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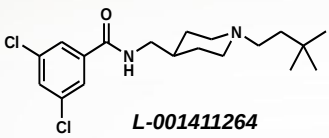
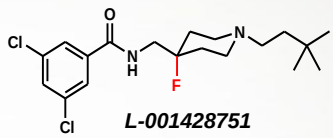
Medicinal Chemistry Strategy

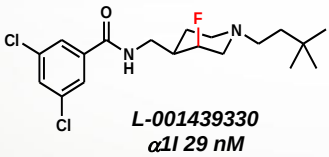
- Inclusion of a F atom to attenuate the basicity of the ring N atom
(J. Med. Chem. **1999** *42* 2087)



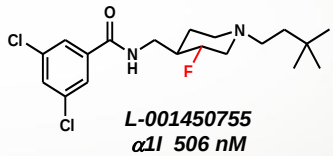
L-001411264
α1I 61 nM
pK_a = 8.7
Panlabs 12 hits



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



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



L-001450755
α1I 506 nM
pK_a = 6.7

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

JMC, 2008, 51, 3692; JMC, 2008, 51, 6471

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Medicinal Chemistry Strategy

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

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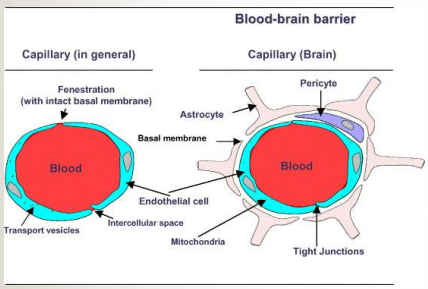
Brain Penetration: *In Silico* vs. *Cells* vs. *In Vivo*



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

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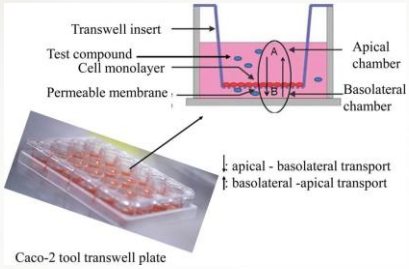
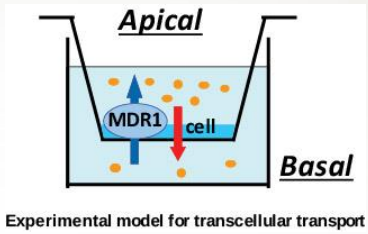
Brain Penetration: *In Silico* vs. *Cells* vs. *In Vivo*





Experimental model for transcellular transport

ER ratio <3 for non-Pgp substrates
P_{app} >20 x 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

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Int J Pharm. 2005 Jan 20;288(2):349-59

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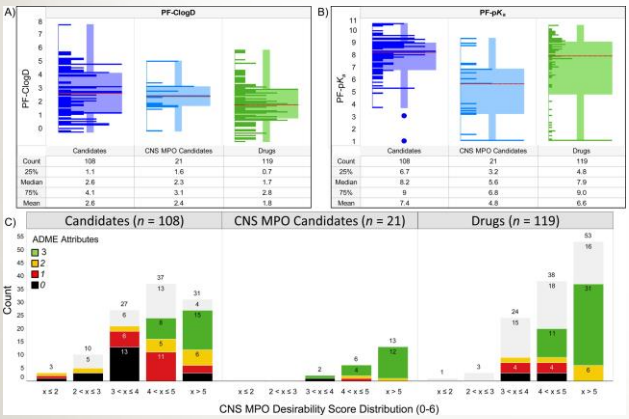
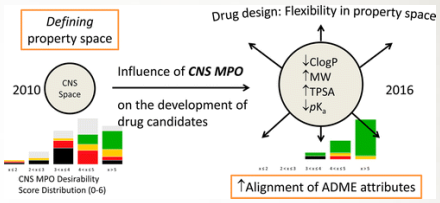
Brain Penetration: *In Silico* vs. *Cells* vs. *In Vivo*

Lipinski's Rules Rule of 3 CNS MPO Score





CNS MPO Calculator		
Property	**Value**	**T0**
ClogP	3.7	0.65
ClogD	2.7	0.65
TPSA	90	1.00
MW	375	0.89
HBD	1	0.83
pKa	9	0.50
	CNS MPO	**4.5**

Embedded tool in HTML

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ACS Chem. Neurosci. 2016, 7, 767-775

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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

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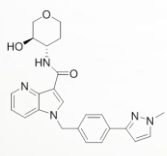
Chronic Dosing (early *in vivo* tool compound)

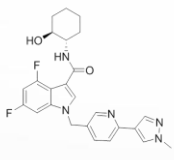
- Compound efficacy and AEs may differ based on acute versus chronic administration and/or drug challenge

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

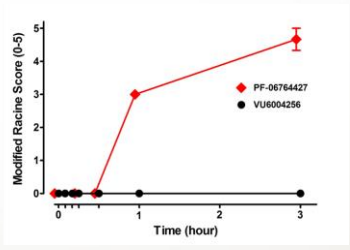
Phenotypic Screen for CNS AEs



PF-06764427
active in mouse AHL
inactive in rat AHL
efficacious in rat NOR
Adverse Events



VU6004256
inactive in mouse AHL
inactive in rat AHL
efficacious in rat NOR
NO Adverse Events



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Use most sensitive preclinical species

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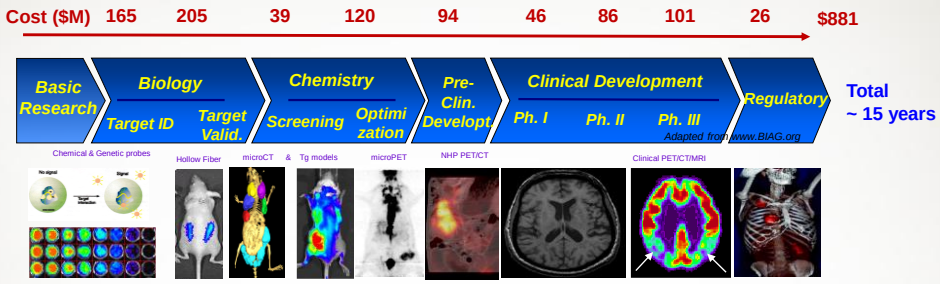
Imaging Biomarker Initiative

*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**

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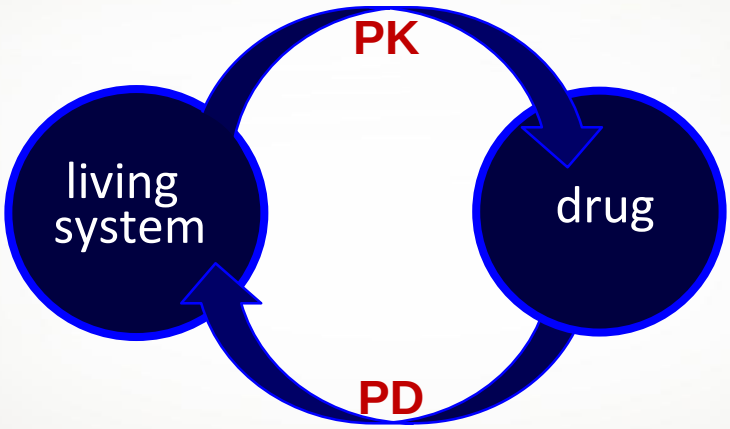
Two types of information with PET

1. Information about a labeled drug.



2. Information about a biological event.

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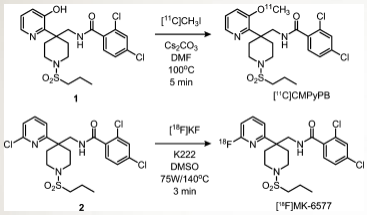
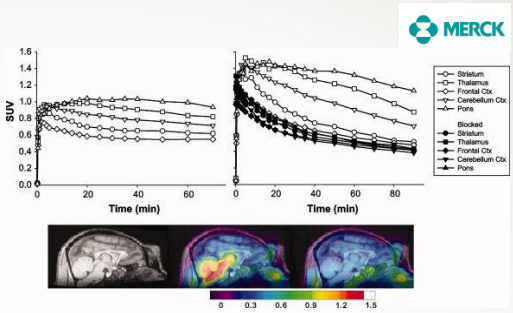
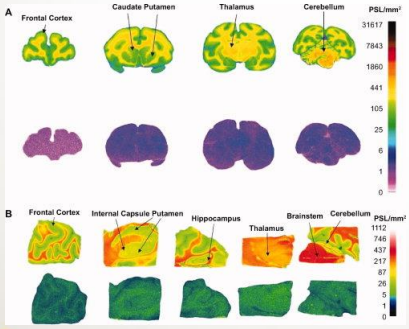
Development of a Clinical PET Tracer [^{18}F]MK-6577







cf of ^{11}C and ^{18}F tracers

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

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

Hamill, et al. *Synapse*. **2011**, *65*, 261-270.

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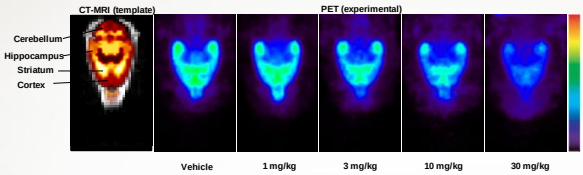
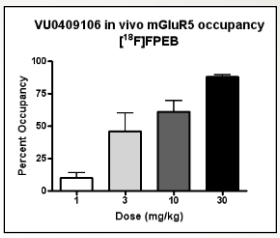
Imaging and Biomarker Strategies

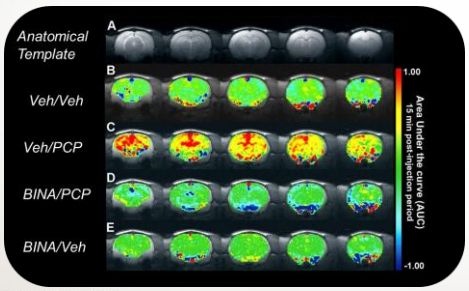
PET



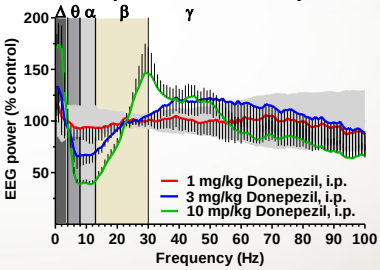


VU0409106 50% Occupancy gives full efficacy in primary PD model

fMRI



EEG Spectral Analysis



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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

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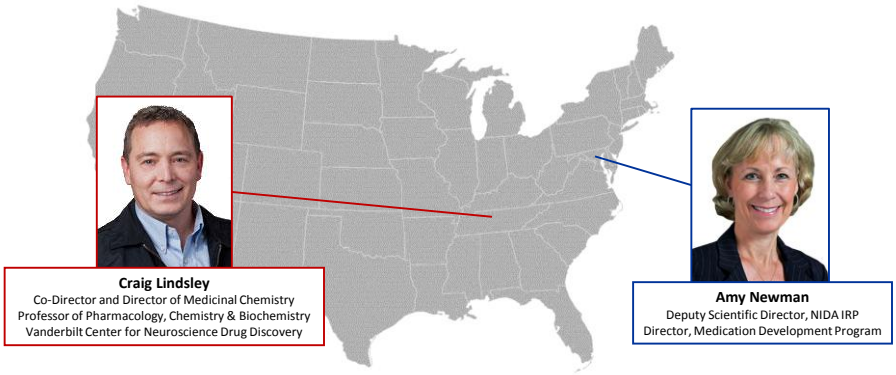

Craig Lindsley
Co-Director and Director of Medicinal Chemistry
Professor of Pharmacology, Chemistry & Biochemistry
Vanderbilt Center for Neuroscience Drug Discovery

Amy Newman
Deputy Scientific Director, NIDA IRP
Director, Medication Development Program

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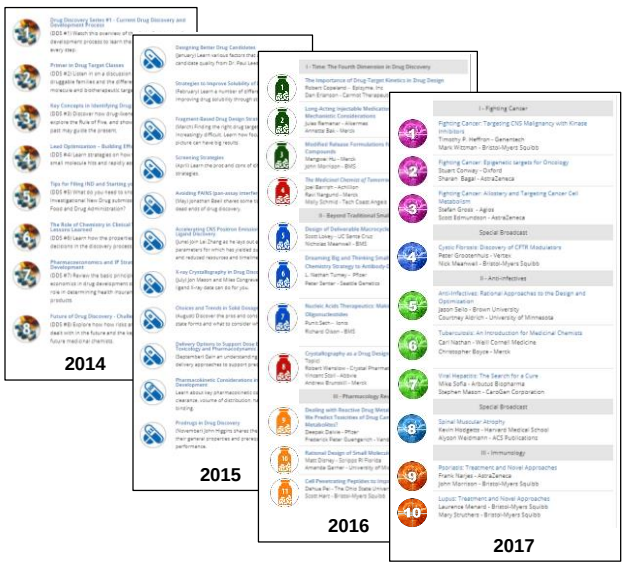

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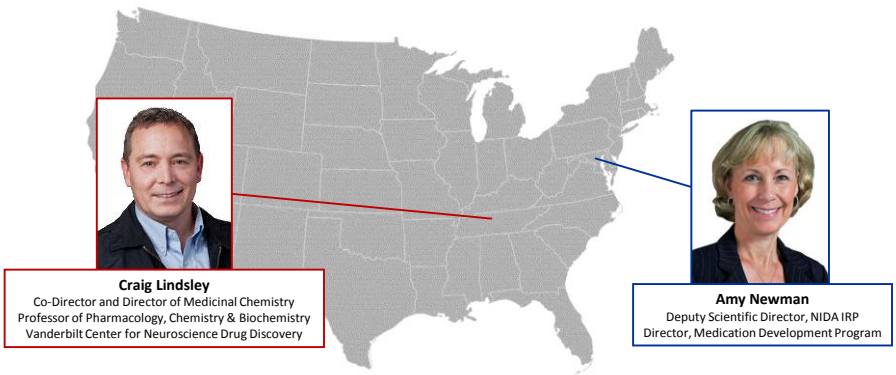

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Final Thoughts

- 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

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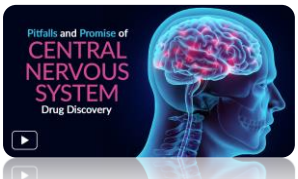
Fan of the Week

Wlatka Peric-Knowlton, MSN, C-ANP, CDE, FAANP, Diabetes Nurse Practitioner & Consultant



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