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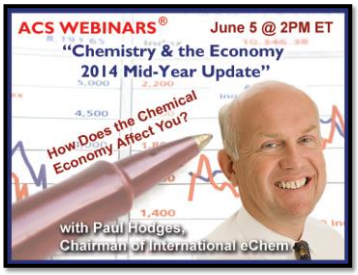

Thursday, June 5, 2014

"Chemistry & the Economy: 2014 Mid-Year Update"

Paul Hodges, Chairman of International eChem

Mark Jones, Executive External Strategy and Communications Fellow at Dow

Thursday, June 13, 2014

"Digitally Pulling Proteins: Molecular Dynamics Simulations"

Dr. Rigoberto Hernandez , Professor in the School of Chemistry and Biochemistry at Georgia Tech

Dr. Stephen Quirk, Global Director of Life Sciences for the Kimberly-Clark Corporation

Next in the Drug Discovery Series!

Thursday, June 26, 2014

"Tips for Filing IND and Starting your Clinical Trials"

Session 5

Dr. Lynn Gold of Camargo Pharmaceutical Services

Dr. John Morrison of Bristol-Myers Squibb

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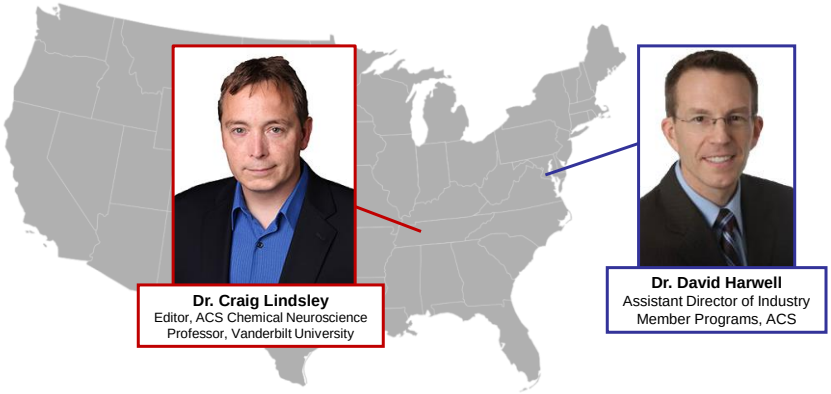
2014 Drug Discovery Series

Session 4: Lead Optimization – Building Efficacy & Safety



Dr. Craig Lindsley
Editor, ACS Chemical Neuroscience
Professor, Vanderbilt University

Dr. David Harwell
Assistant Director of Industry
Member Programs, ACS

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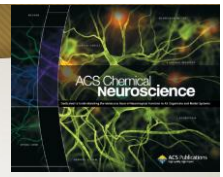

Lead Optimization – Building Efficacy & Safety

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

Lindsley Laboratory

NCDDDG: Discovery of Novel Treatments for Schizophrenia

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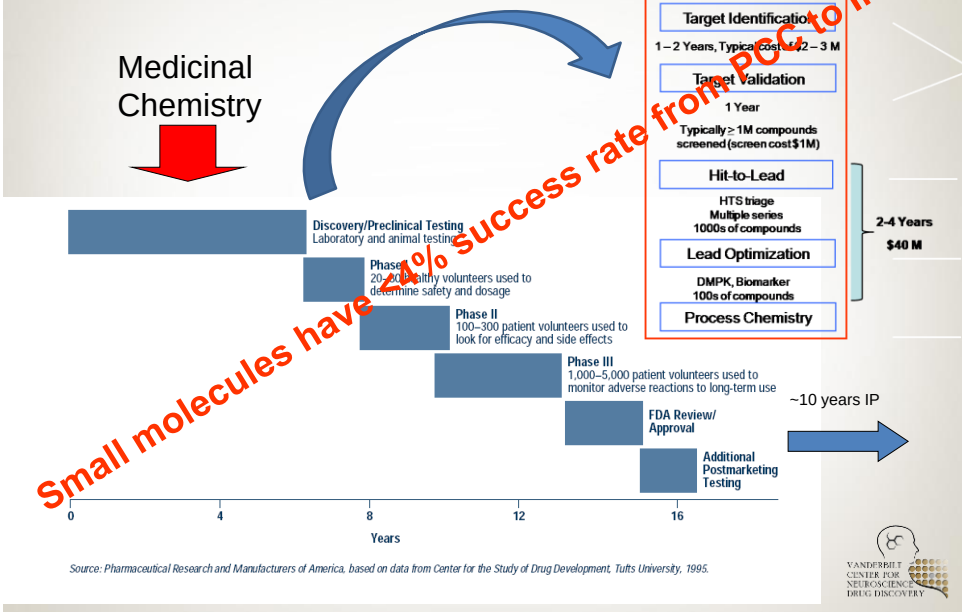
Vanderbilt Specialized Chemistry Center

Drug Discovery Phases and Timelines



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

Chemical Attributes

- Demonstrable exploitable SAR
- Support for interaction with molecular target
- Selectivity/Profile established

Biochemical Attributes

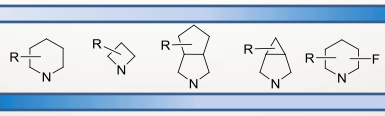
- Assessment of 'drugability' (*in vivo* profile)
- Secondary Assay Funnel Validated

Pharmacology Attributes

Intellectual Property Position

Poor IP — **Solid IP**

Chemotype Frequency



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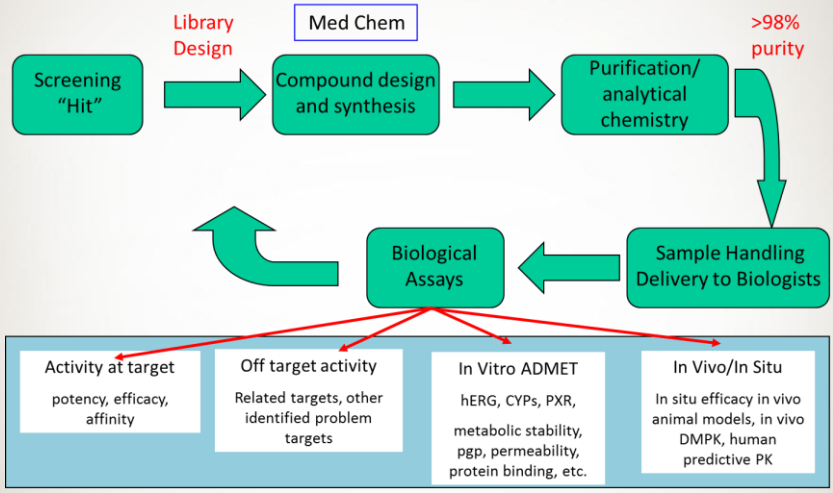
Lead Optimization– an iterative process of compound synthesis, testing, and design



Requires Medicinal Chemists to KNOW Pharmacology

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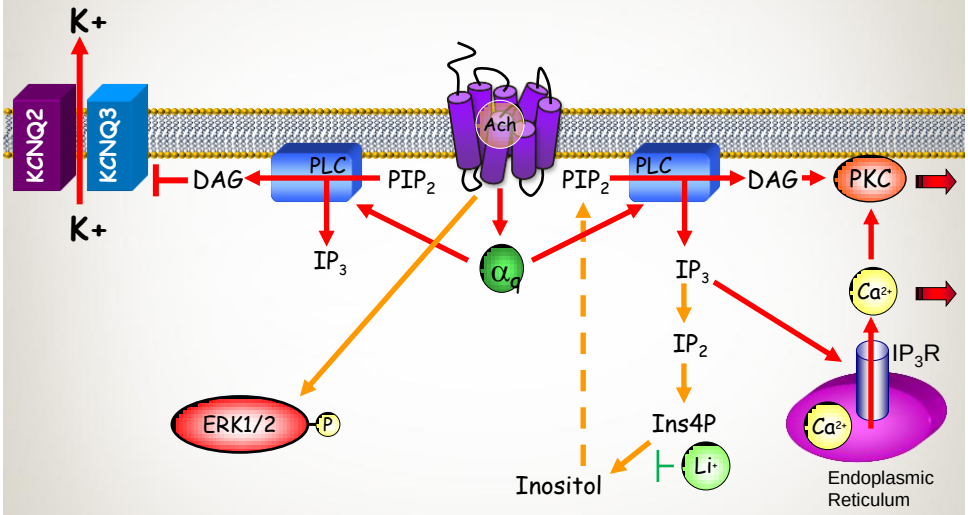
An Overview of M_1 mAChR Signaling – Signal Bias



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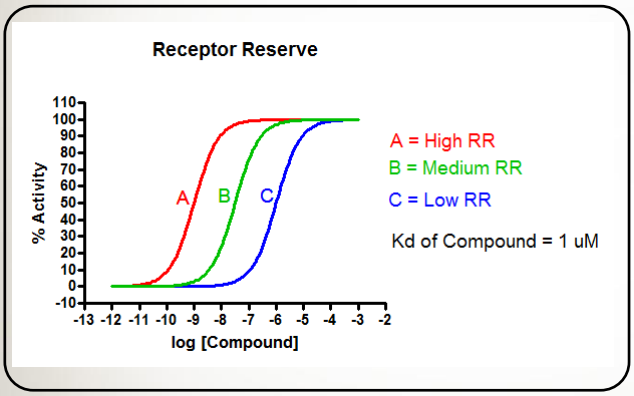
Receptor Reserve: Excess Receptors Beyond Those Necessary for a Maximal Response



- 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

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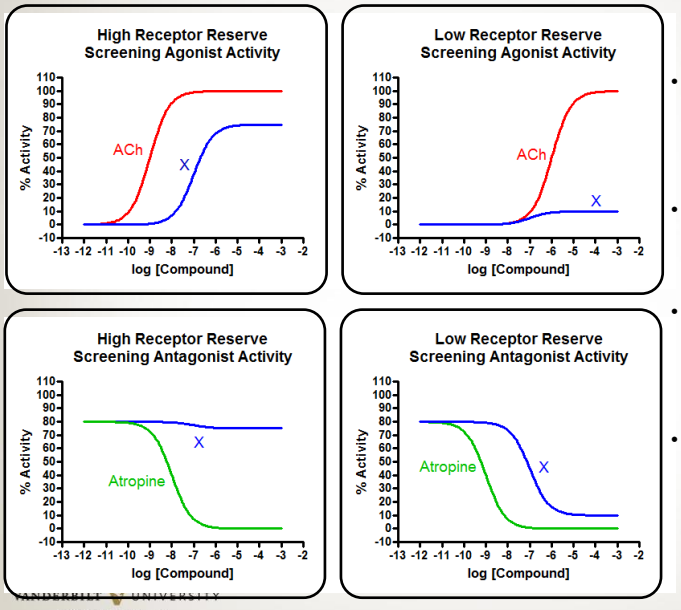
Receptor Reserve – Weak Partial Agonist Considerations



- 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

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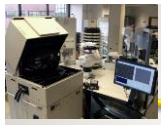
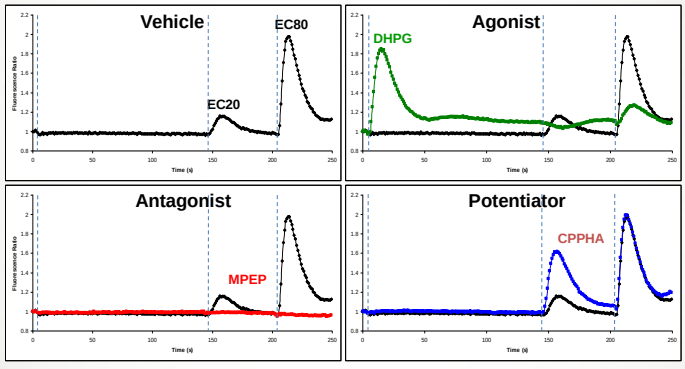


Primary Screening Success

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)

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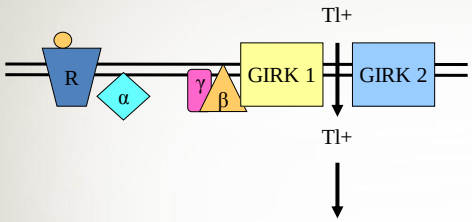
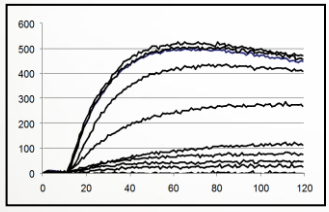
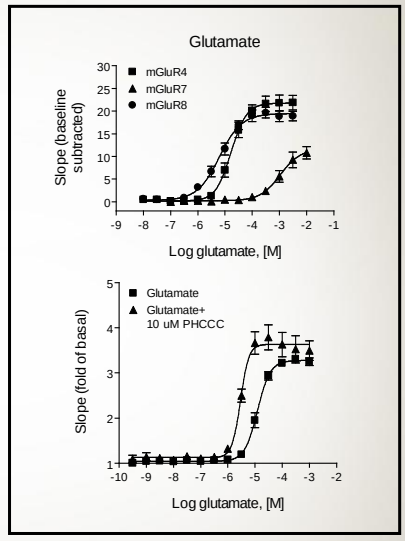
Assay Development



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

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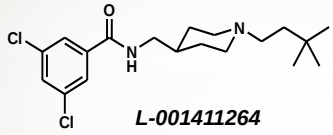
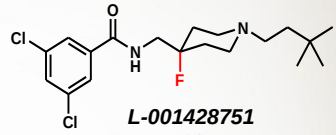
Fluorine Introduction

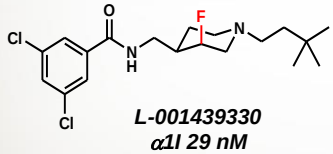
- Inclusion of a F atom to attenuate the basicity of the ring N atom
(J. Med. Chem. **1999** *42* 2087)



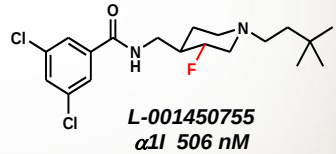
L-001411264
α1I 61 nM
pK_a = 8.7
Panlabs 12 hits



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

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

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

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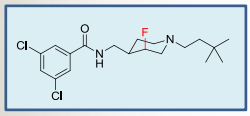
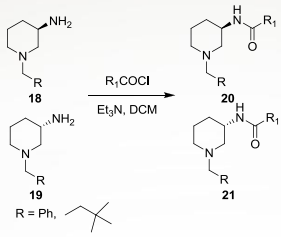
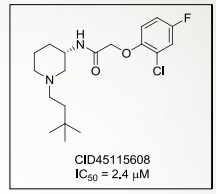
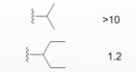
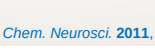
Scaffold Hopping For IP

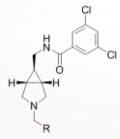




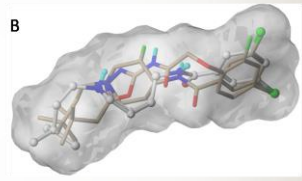


A

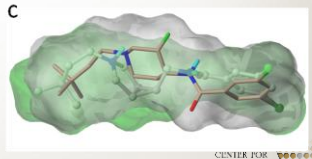
CID	R	IC_{50} (μM)
45115618	Ph	>10
45115620		0.15
46943250		1.9
46943251		>10
46943252		>10
46943253		1.2
46943254		3.0
46943255		>10



B



C



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ACS Chem. Neurosci. **2011**, *2*, 730

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 (CL_{int})
- P450, MAO: DDI & induction
- Metabolite identification (pharmacology/safety)
- Drug safety (Drug Interactions)

AB SCIEX

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

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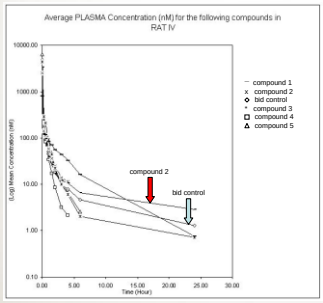
Thermo SCIENTIFIC

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 Microsomes (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.

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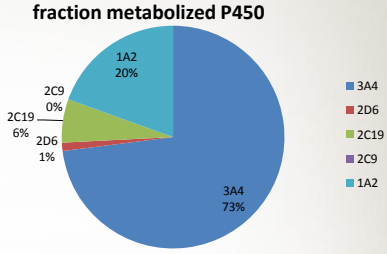
P450 fraction metabolized (f_m)

	Substrate Depletion Clearance[a]		
	CL_{int} (mL/min/kg)	CL_H (mL/min/kg)	Fraction metabolized
rh3A4	69.5	16.1	73.0
rh2D6	0.3	0.3	1.2
rh2C19	1.5	1.4	6.3
rh2C9	not detected	0.0	0.0
rh1A2	5.4	4.3	19.5

[a]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!

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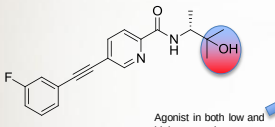
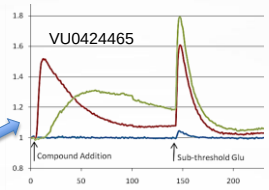
$mGlu_5$ PAM vs. Agonist - Neurotoxicity

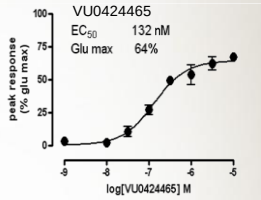
Allosteric agonism at $mGlu_5$

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



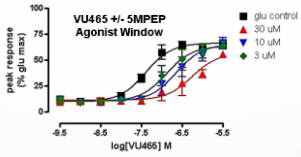
Agonist in both low and high expressing systems

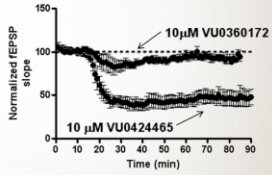




VU0424465
EC_{50} = 7 nM (69%)
Cell: Ago-PAM
Astrocytes: Agonist

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.

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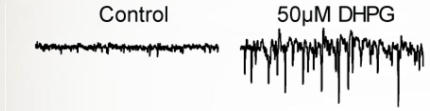
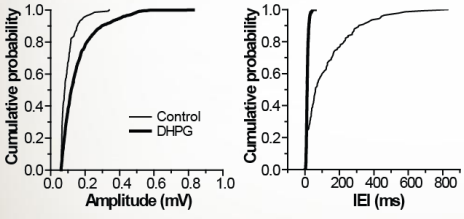
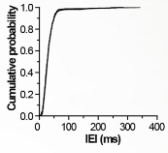
$mGlu_5$ orthosteric and allosteric agonists induce epileptiform activity in hippocampal area CA3





VU0430644 (Pure PAM)



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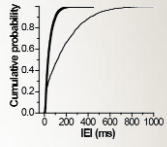

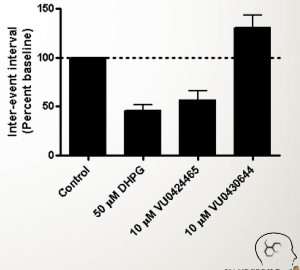

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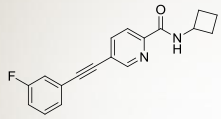
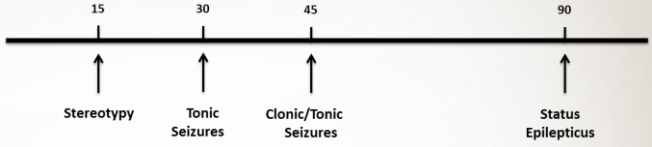
VU0403602 induces seizure activity after IP administration

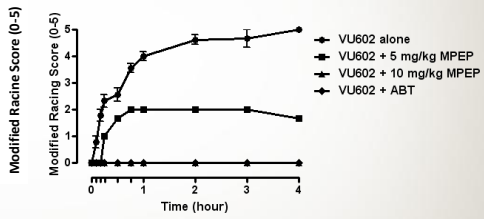


VU0403602
EC_{50} = 22 nM H10H PAM



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

Racine Score of Behavioral Manifestations of VU0403602-induced seizure activity



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

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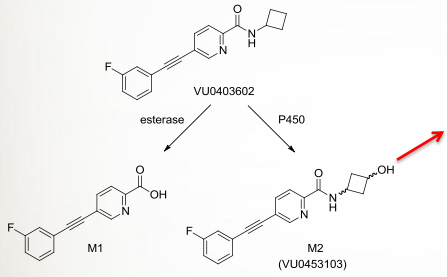
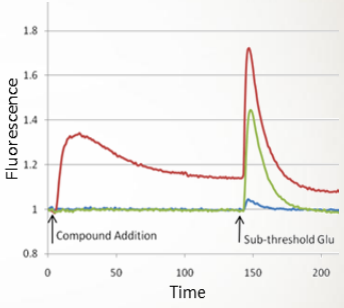
Major metabolite of VU0403602 (VU0453103) has robust agonist activity

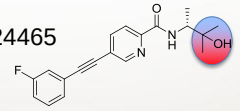
In vivo hepatic metabolism of VU0403602.



VU0453103 has allosteric agonist activity



VU0424465



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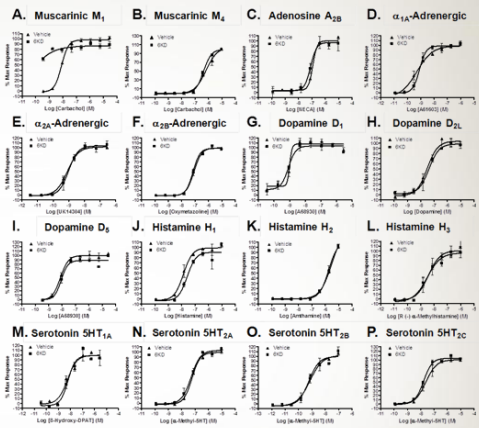
Ancillary Pharmacology

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.
Compound: VU319-M1, PT #: 1169908						
200510	Adenosine A_1	331860	hum	2	10 µM	26
200610	Adenosine A_{2A}	331861	hum	2	10 µM	7
200720	Adenosine A_3	331823	hum	2	10 µM	7
203100	Adrenergic α_{1A}	331862	rat	2	10 µM	-3
203200	Adrenergic α_{1B}	331863	rat	2	10 µM	7
203400	Adrenergic α_{1D}	331864	hum	2	10 µM	16
203630	Adrenergic α_{2A}	331865	hum	2	10 µM	67
204010	Adrenergic β_1	331854	hum	2	10 µM	0
204110	Adrenergic β_2	331855	hum	2	10 µM	-9
285010	Androgen (Testosterone) AR	331880	rat	2	10 µM	7
212510	Bradykinin B_1	331866	hum	2	10 µM	0
212620	Bradykinin B_2	331867	hum	2	10 µM	8
214510	Calcium Channel L-Type, Benzothiazepine	331890	rat	2	10 µM	12
214600	Calcium Channel L-Type, Dihydropyridine	331868	rat	2	10 µM	12
216000	Calcium Channel N-Type	331822	rat	2	10 µM	1
217030	Cannabinoid CB_1	331869	hum	2	10 µM	12
219500	Dopamine D_1	331897	hum	2	10 µM	7
219700	Dopamine D_{2S}	331833	hum	2	10 µM	14
219800	Dopamine D_3	331834	hum	2	10 µM	0
219900	Dopamine $D_{4.2}$	331835	hum	2	10 µM	1
224010	Endothelin ET_A	331817	hum	2	10 µM	-5
224110	Endothelin ET_B	331818	hum	2	10 µM	4
225510	Epidermal Growth Factor (EGF)	331821	hum	2	10 µM	4
226010	Estrogen $ER\alpha$	331889	hum	2	10 µM	15
226600	GABA$_A$, Flunitrazepam, Central	331840	rat	2	10 µM	3
226500	GABA$_A$, Muscimol, Central	331841	rat	2	10 µM	-5
228610	$GABA_{B1A}$	331887	hum	2	10 µM	1
232030	Glucocorticoid	331830	hum	2	10 µM	8
232700	Glutamate, Kainate	331885	rat	2	10 µM	6
232810	Glutamate, NMDA, Agonism	331886	rat	2	10 µM	19
232910	Glutamate, NMDA, Glycine	331884	rat	2	10 µM	3
233000	Glutamate, NMDA, Phencyclidine	331883	rat	2	10 µM	5
239610	Histamine H_1	331941	hum	2	10 µM	10
239710	Histamine H_2	331842	hum	2	10 µM	1



Essential for ion channels, prior to CV dog

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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?

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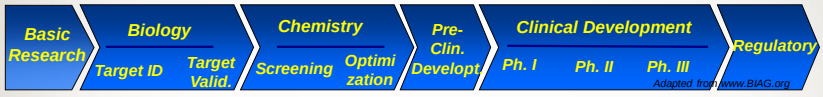
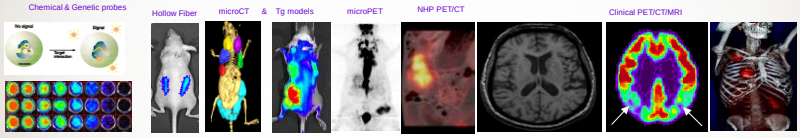
Imaging Biomarker Initiative

Cost ($M) 165 205 39 120 94 46 86 101 26 $881





- **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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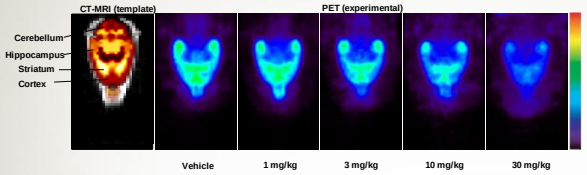
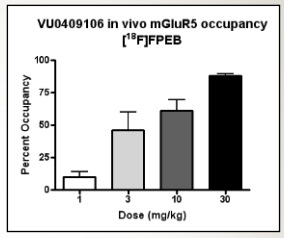
Biomarkers

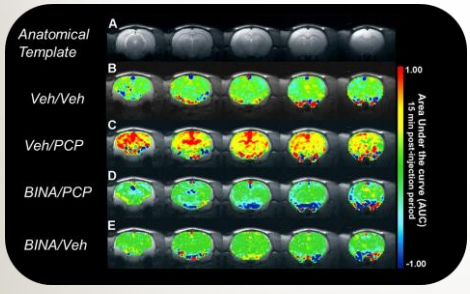
PET



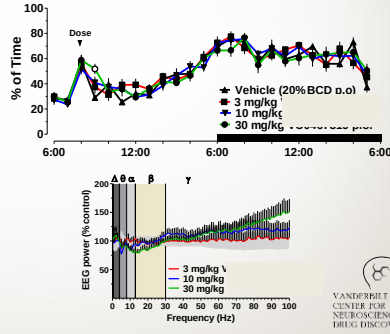


VU0409106 50% Occupancy gives full efficacy in primary PD model

fMRI



Sleep-Wake EEG



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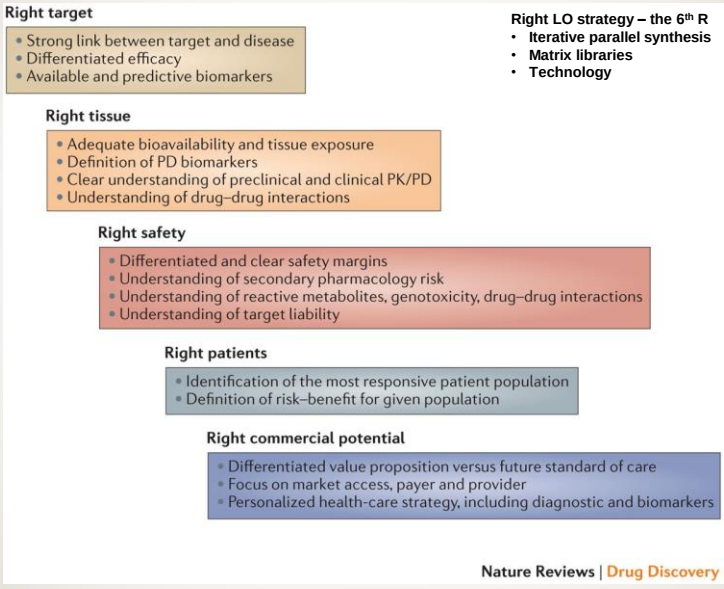
AstraZeneca: The 5R Framework for Successful Lead Optimization



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NRDD, doi:10.1038/nrd4309

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Questions??

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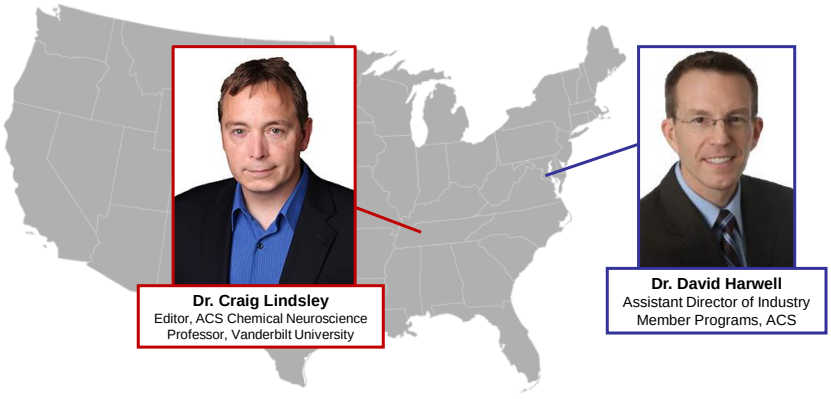

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Editor, ACS Chemical Neuroscience
Professor, Vanderbilt University

Dr. David Harwell
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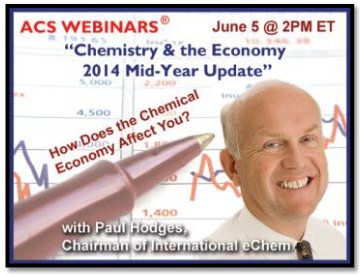

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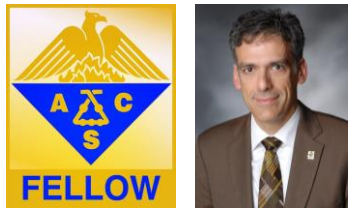

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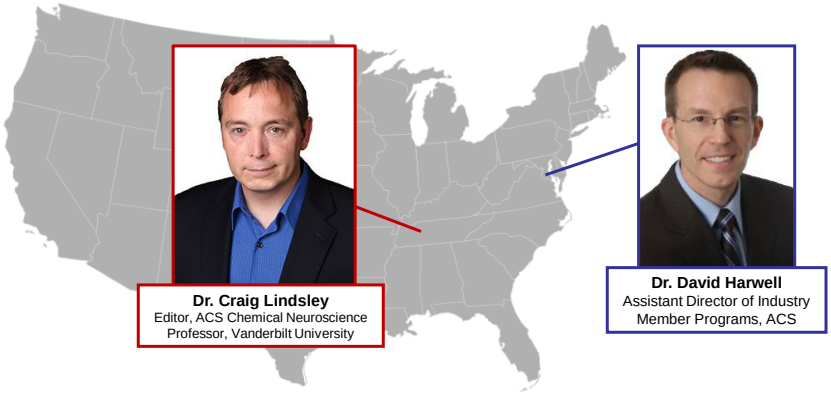

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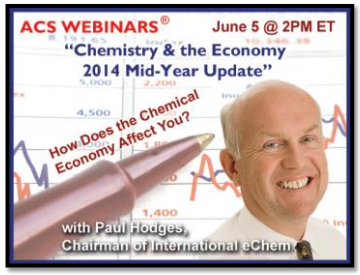

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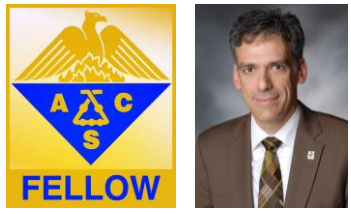

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