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Meeting the Challenge: Discovery of new therapeutic agents for treatment of brain disorders

P. Jeffrey Conn

Department of Pharmacology

Vanderbilt Center for Neuroscience Drug Discovery

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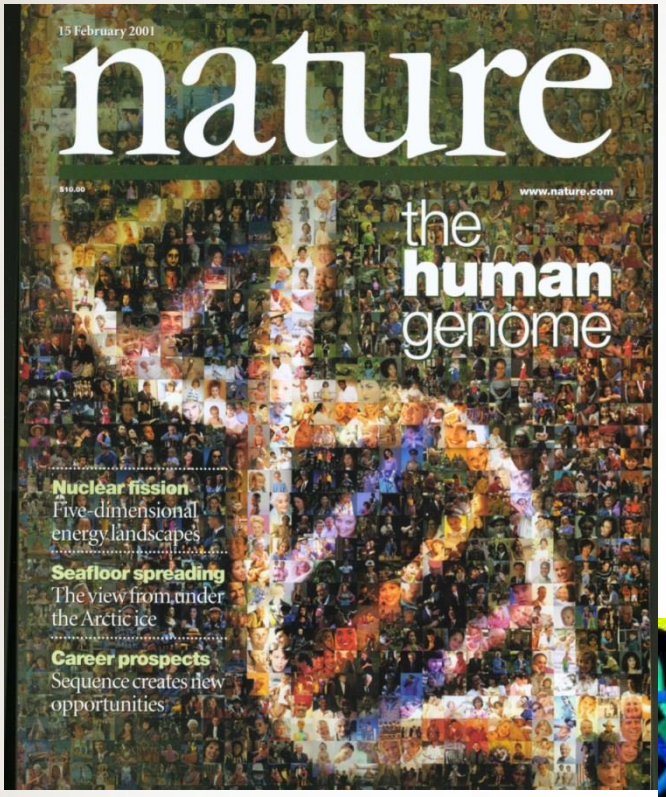

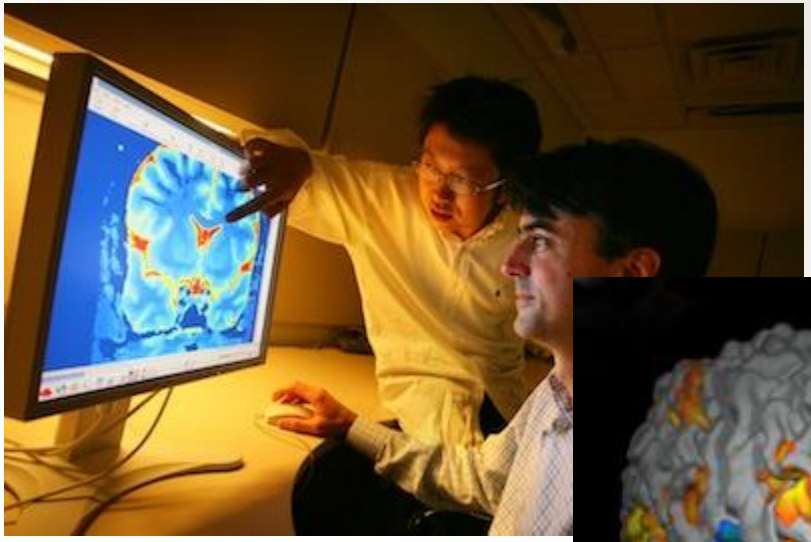

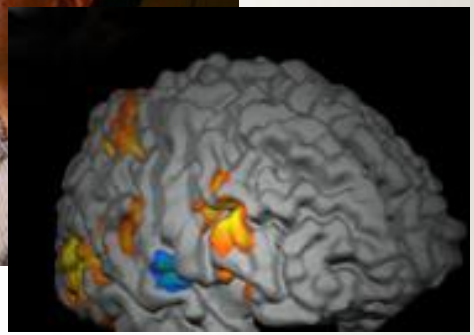

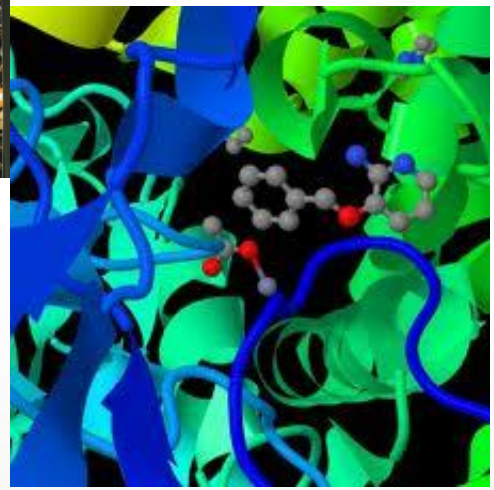

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DRUG DISCOVERY

Classical Drug Discovery Approach

Isolate active components of medicinal plants
or serendipitous discovery of clinical efficacy

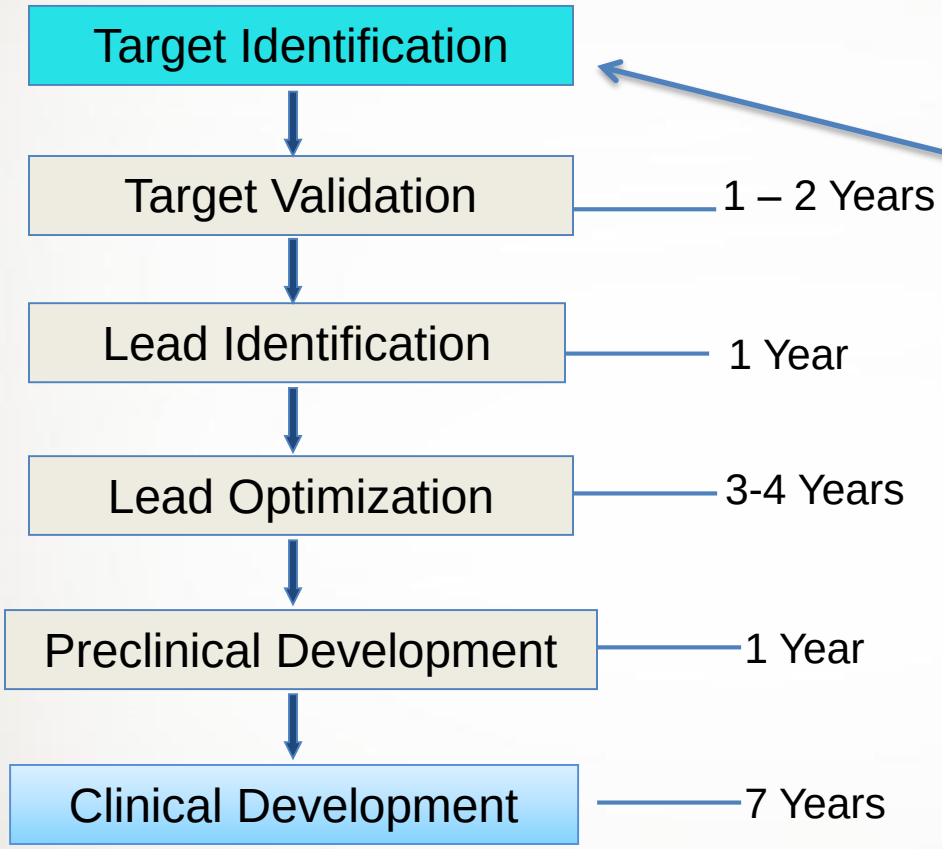
Make modest improvements → *Develop and Market new Medicine*

Determine Mech. of action

*Success rate was very high and in some cases virtually guaranteed because **efficacy** of agents was known from outset*

This approach is no longer capable of yielding breakthrough medicines to treat the most troubling human diseases.

The modern drug discovery and development process is long, expensive, and high risk

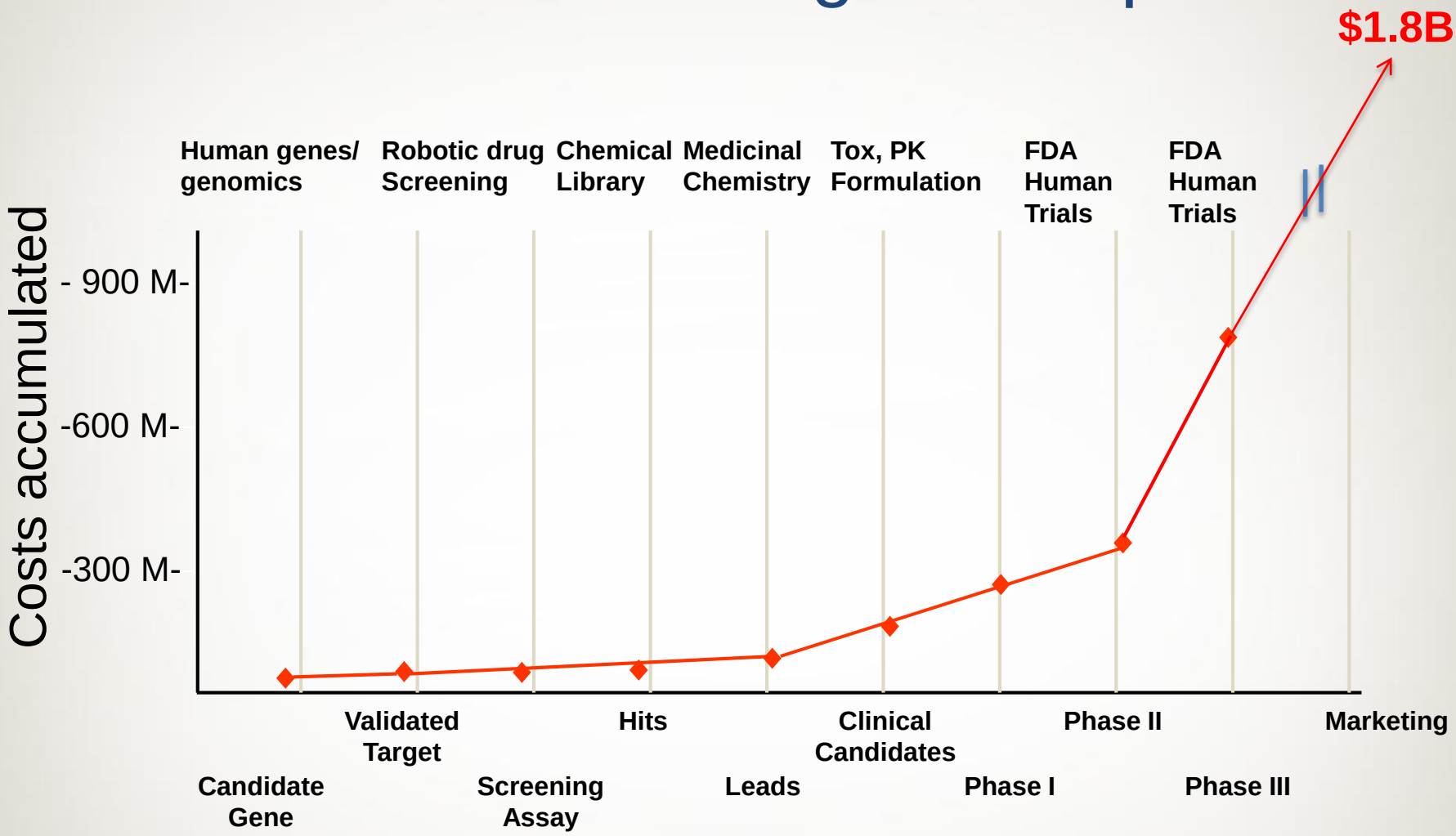


Academic institutions and their investigators traditionally play a key role in identifying novel potential targets but do not participate in later stages of the drug discovery process.

TOTAL DISCOVERY AND DEVELOPMENT TIME 12 – 14 YEARS AND COSTS > $1.8B

Drug companies cannot afford the risk of investing on a novel approach without strong validation that the new approach is viable.

Costs for Modern Drug Development



The large majority of programs fail. Only 3 out of every 10 drugs that successfully reach the market pay for their own development!

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Vanderbilt Center for Neuroscience Drug Discovery

Jeffrey Conn

VCNDD Director

Craig Lindsley

Medicinal Chemistry

Colleen Niswender

Mol. Pharm

Scott Daniels

Drug Metabolism/PK

Carrie Jones

In Vivo/ Translational

Mission: to promote translation of advances in basic science to novel therapeutics by de risking efforts focused on novel approaches for treatment of serious brain disorders.

- Led by world leaders in drug discovery and staffed by veteran drug discovery scientists recruited from major pharmaceutical companies. *(Members of VCNDD leadership team have advanced > 40 drug candidates into clinical development while in industry positions)*

- Includes all major infrastructure for drug discovery traditionally found only in industry settings.

- Approximately 100 full time FTEs in the VCNDD

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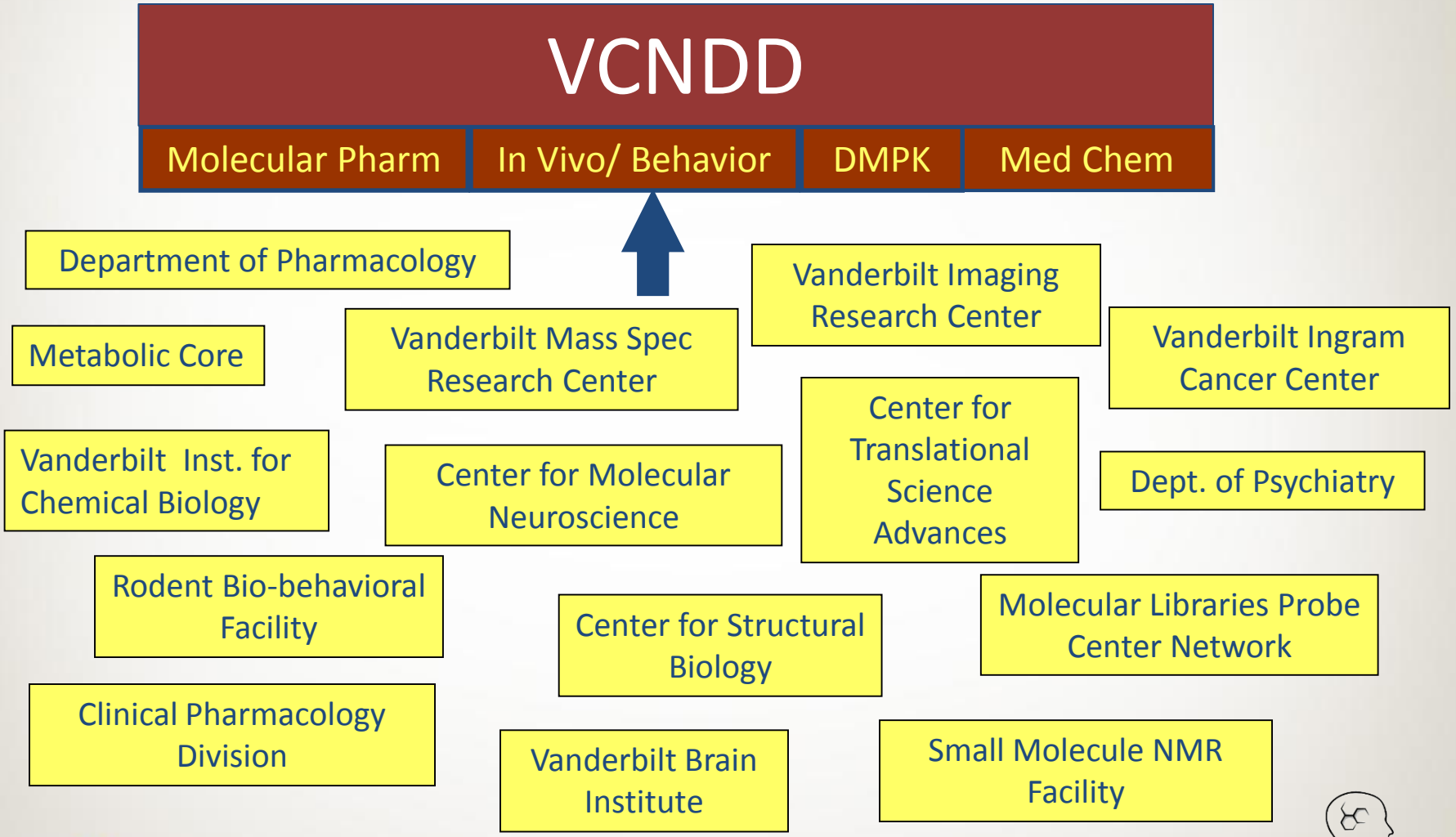
VCNDD resources are leveraged with large research infrastructure at Vanderbilt



Increasing Success: A Return to "Bedside to Bench" Research

70% of failures for drugs developed for CNS indications are due to lack of efficacy seen in Phase II or III studies.

- Building on new understanding from clinical studies that do not directly involve specific drugs (mGluR4 PAMs for PD)
- Building on insights from clinical experience and serendipitous discoveries with drugs in the clinic (M1/M4 PAMs for schizophrenia and AD)
- Discovery of mechanism of action of validated therapeutic agents (Ketamine/mGluR5 NAMs for major depression).

Parkinson's Disease

Characterized by:

- Tremor
- Bradykinesia
- Rigidity
- Disturbance of posture

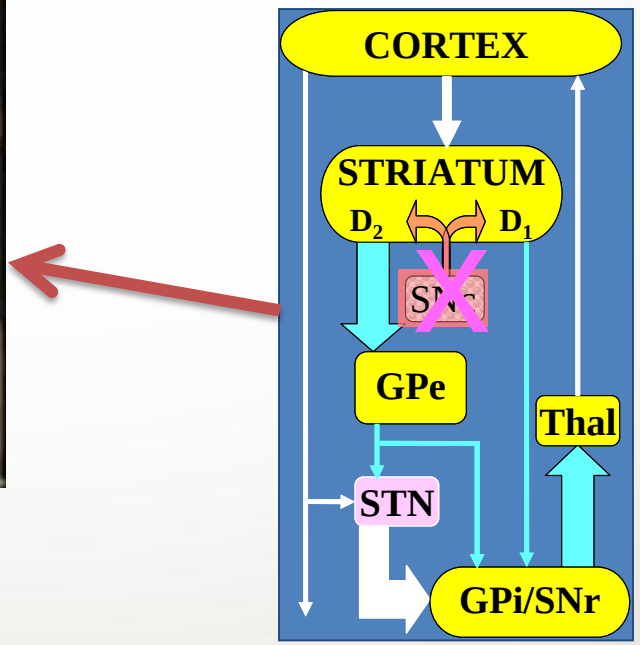
Current treatments are effective early but have severe adverse effects and lose efficacy as the disease progresses

Dyskinesias - grimacing, head bobbing, oscillatory rocking movements of arms, legs, or trunk.

Behavioral disturbances - hallucinations, paranoia, mania, insomnia, anxiety, nightmares,

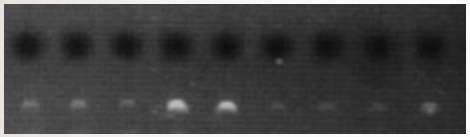
Fluctuations in response – Lack of reliable efficacy combined with severe motor side effects

Thanks to Drs. Mahlon Delong and Jerry Vitek, Emory Univ.

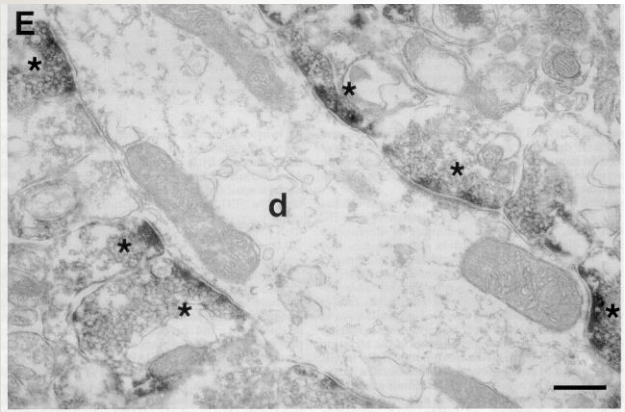


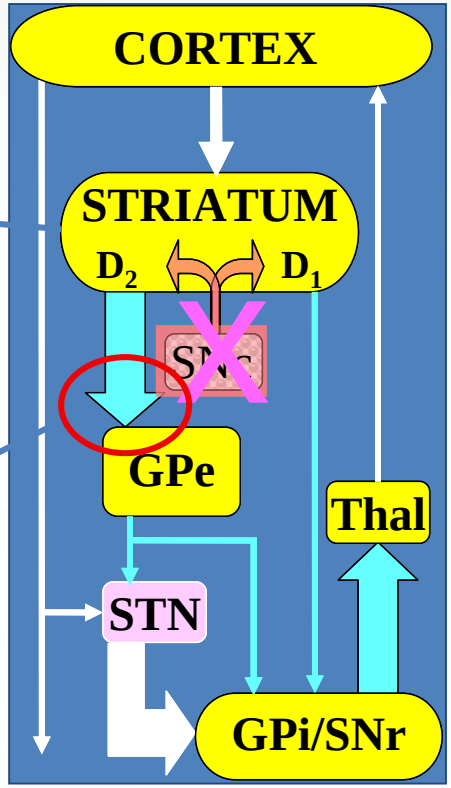
Antiparkinsonian activity of mGluR4 agonists

Gene profiling reveals mGluR4 mRNA in striatum

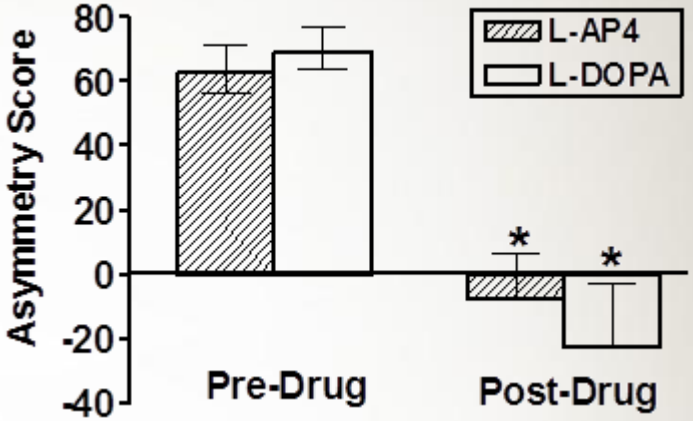


mGluR4 protein in presynaptic terminials at overactive striato-Gpe synapse

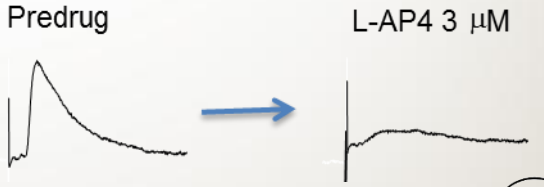




Activation of mGLuR4 has robust efficacy in multiple animal models



Activation of mGluR4 reduces transmission at overactive striato-Gpe synapse.



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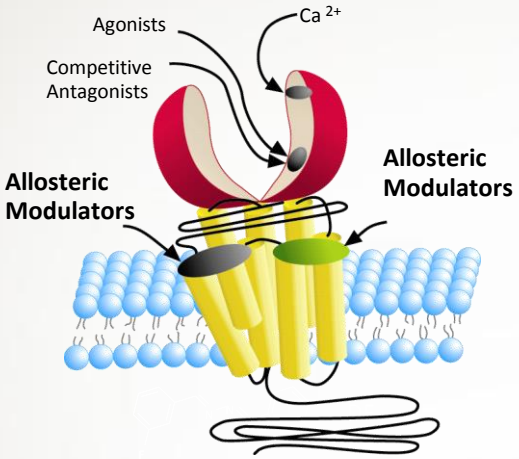
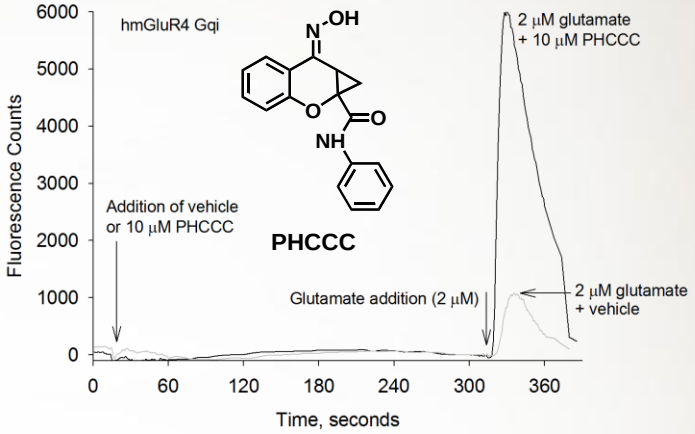
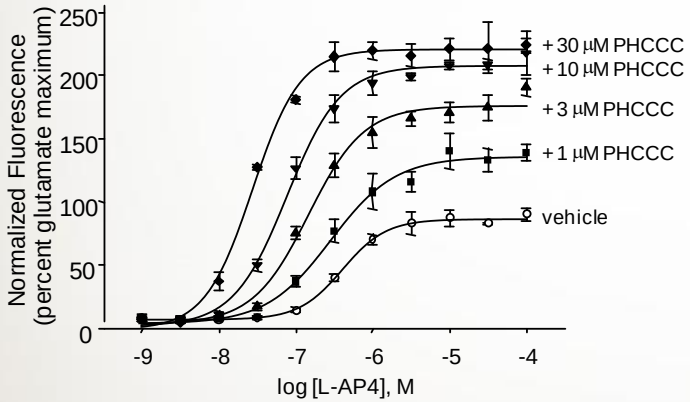
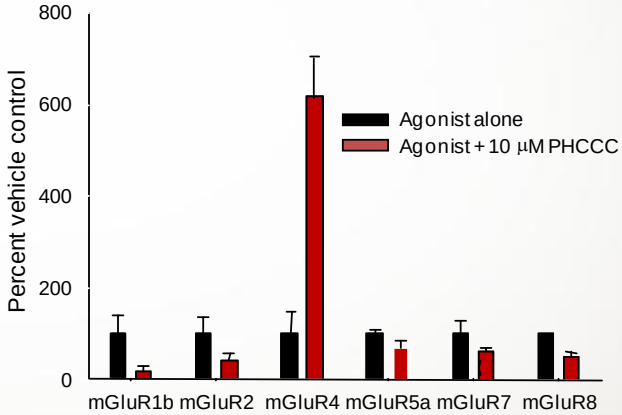
Discovery of PHCCC as a novel positive allosteric modulator of mGluR4







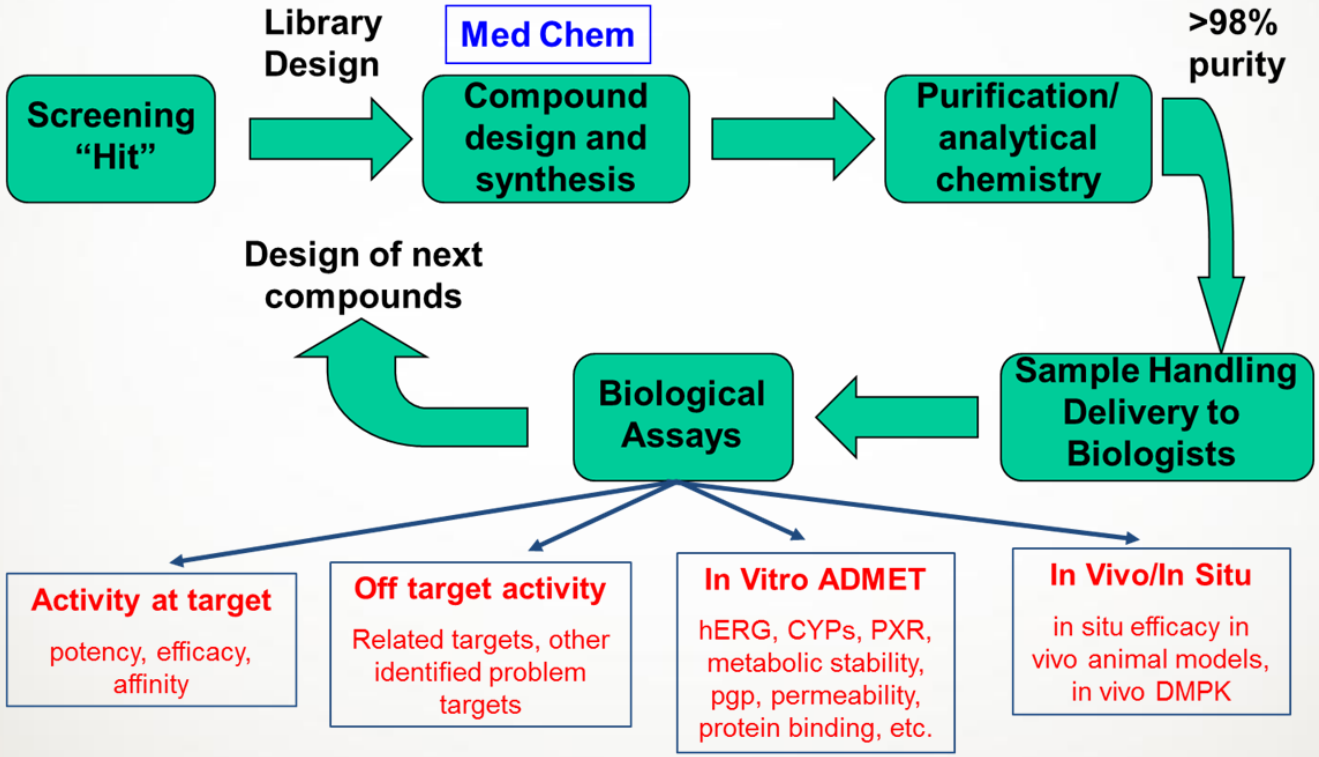


- Potentiates mGluR4 regulation of transmission at the striato-GP synapse.
- Has antiparkinsonian effect in rodent models when injected icv.

Marino et al., (2003) *Proc. Natl. Acad. Sci. U.S.A.* 100: 13668.

Funding by Michael J. Fox Foundation allowed discovery of new mGluR4 PAM drug candidates

160,000 compounds → (10 µM singlicate) → 1355 primary PAM hits → (10 point concentration response) → 434 confirmed PAMs



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THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

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NATIONAL INSTITUTES OF HEALTH

Bristol-Myers Squibb

September 2012. *Vanderbilt and BMS announced partnership to advance drug candidates to clinical testing for Parkinson's disease!*

FierceBiotech Research

Bristol-Myers, Vanderbilt U. forge Parkinson's drug development deal

September 25, 2012 | By Mark Hollmer

CNBC

Vanderbilt University and Bristol-Myers Squibb Sign Collaboration Agreement to Develop Novel Treatments for Parkinson's Disease Friday, 21 Sep 2012 | 8:30 AM ET

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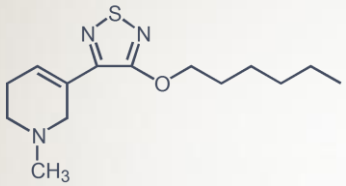
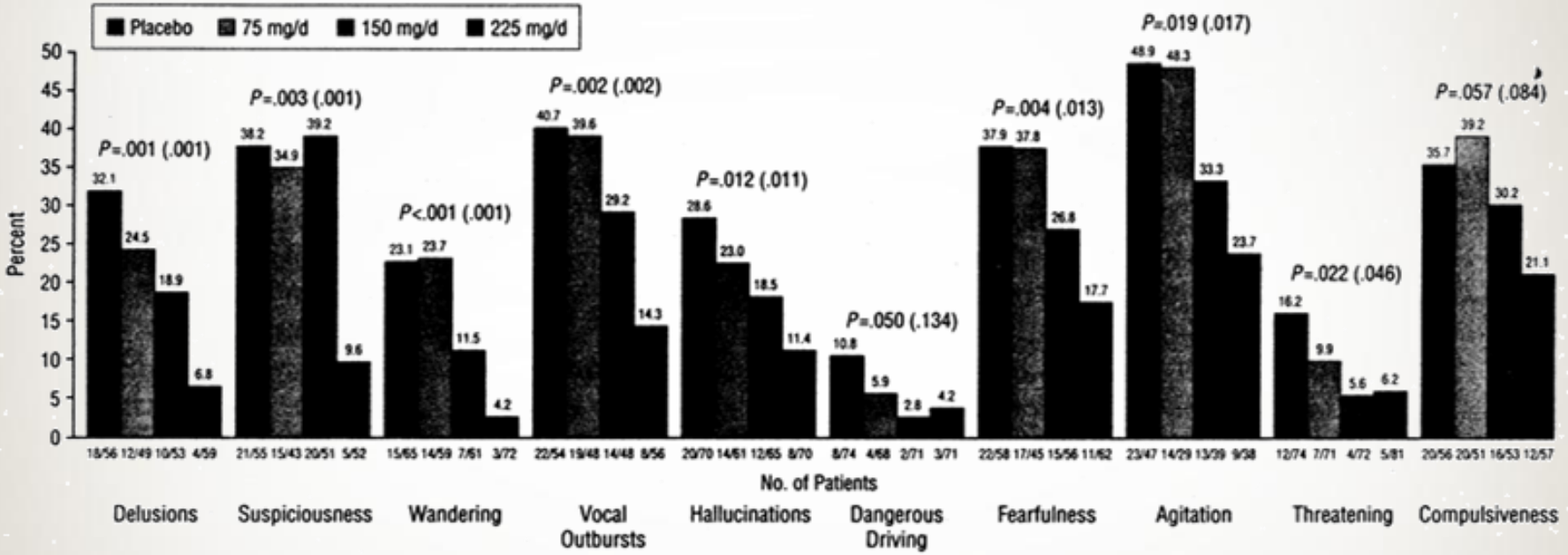
Xanomeline Induces Robust Improvement in Behavioral Disturbances in AD Patients



Xanomeline (LY246708)

M1/M4 preferring agonist

Bodick et al., Arch Neurology (1997) 54(4):465-73.



➢ AChE inhibitors have antipsychotic efficacy in AD patients (double blind, placebo-controlled trials) (Cummings et al., 2001; Raskind et al., 1997; McKeith et al., 2000).

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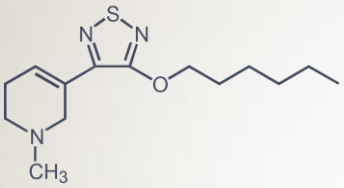
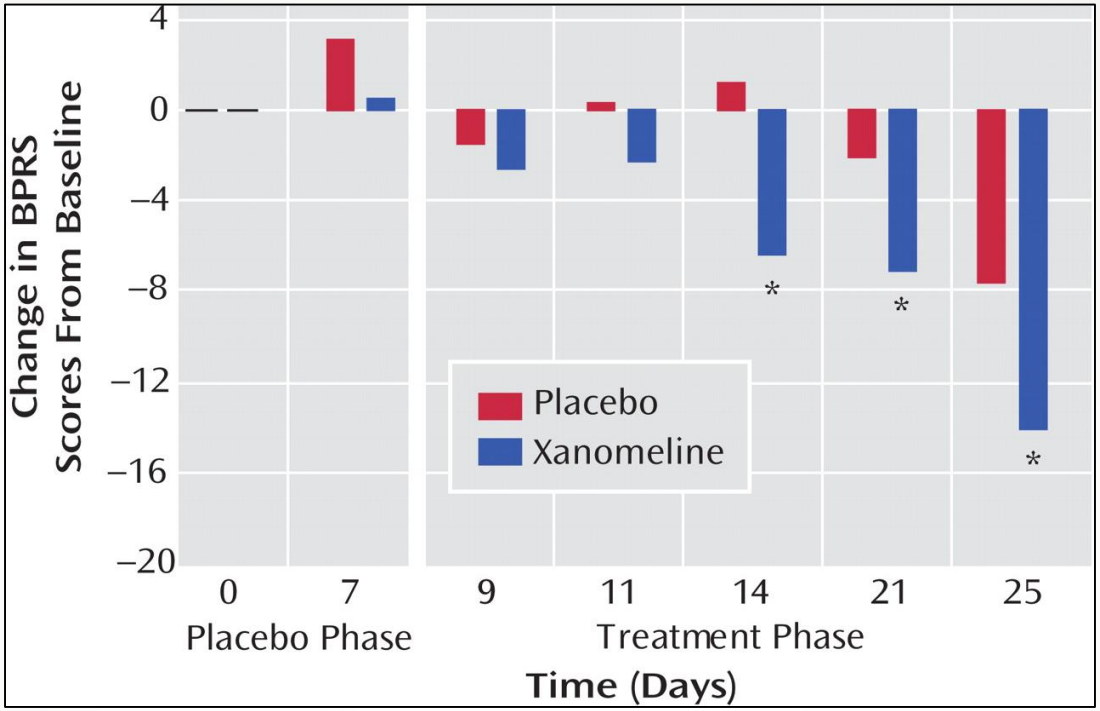
Clinical Evidence for Efficacy of Xanomeline in Schizophrenia

Shekhar et al. Am J Psychiatry (2008) 165:1033-1039.



Xanomeline (LY246708)

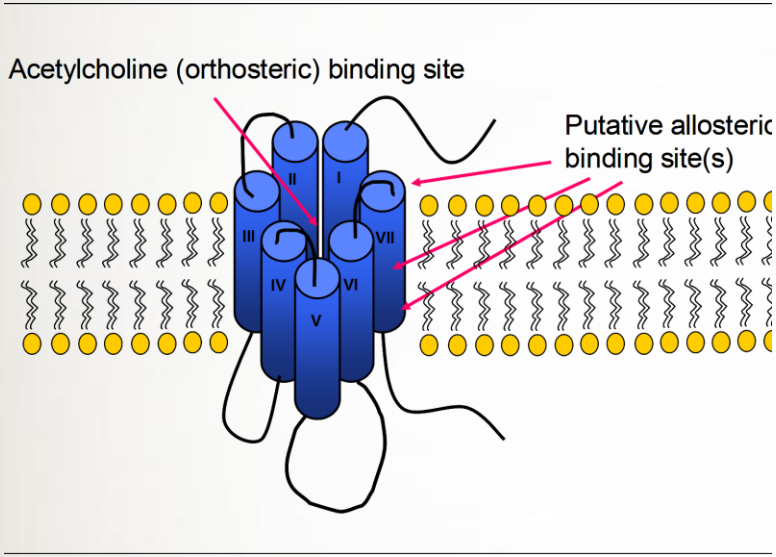
M1/M4 preferring agonist

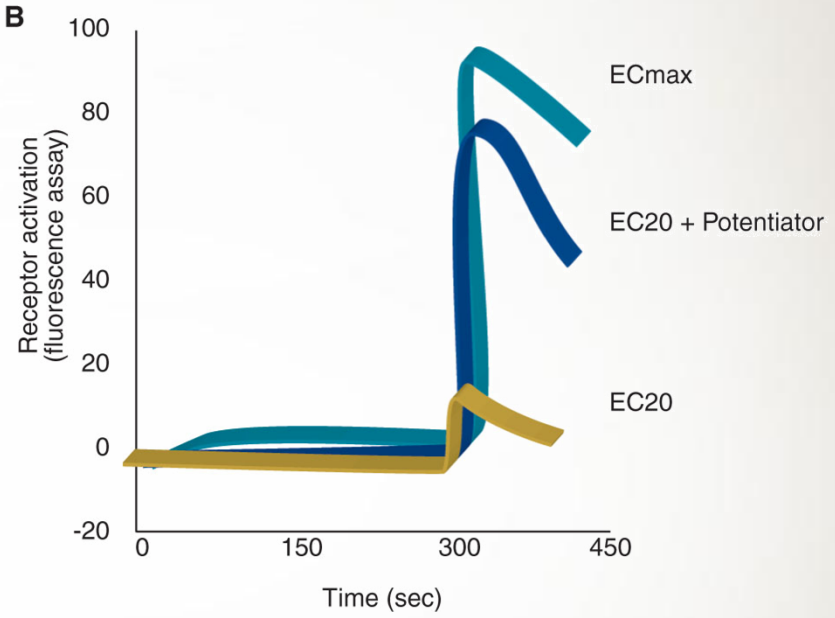


- ✓N = 20; Randomized, Double blind, Placebo controlled 4 week study; 225 mg/day.
- ✓Efficacy on total BPRS (Brief Psychiatric Rating Scale) and PANSS (Positive and Negative Syndrome Scale) scores.
- ✓Efficacy on measures of verbal learning and short-term memory function.
- ✓Efficacy was observed with a faster onset than traditional antipsychotics.

The major issue leading to failure of Xanomeline and other M1 and M4 agonist programs was failure to achieve high subtype selectivity with orthosteric agonists.

Positive Allosteric Modulators of mAChRs?

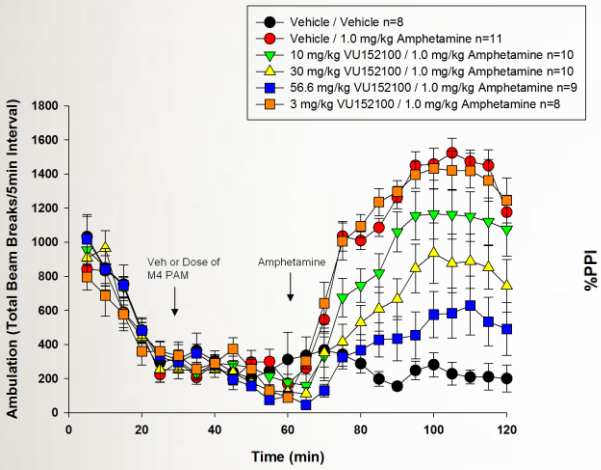




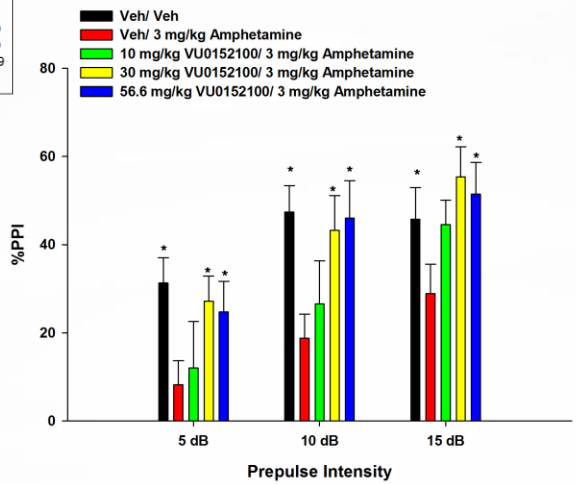
Will it be possible to develop selective M1 and M4 PAMs to help understand the contributions of each receptor subtype to the in vivo effects of mAChR agonists?

VU0152100 produces robust efficacy in preclinical models predictive of antipsychotic-like activity

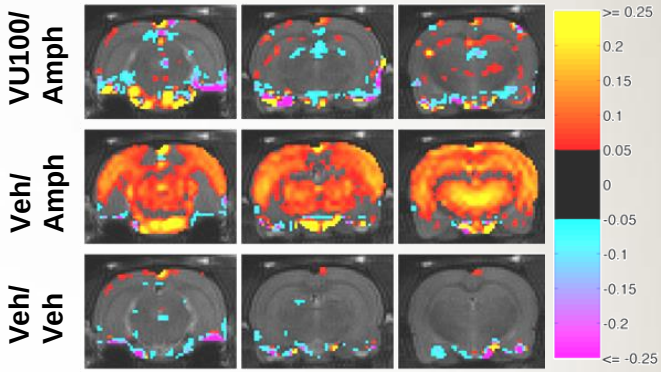
Blockade of Amphetamine-Induced Hyperlocomotion



Inhibition of Amphetamine-Induced Disruption of Prepusle Inhibition



Inhibition of Amphetamine-Induced Brain activation



- Reversal of Amphetamine-induced increases in dopamine release in prefrontal cortex and nucleus accumbens using *in vivo* microdialysis.
- Similar effects were observed on PCP-induced hyperactivity and disruption of PPI
- VU0152100 PCP and amphetamine-induced disruption fo contextual conditioned fear response.

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Novel Approaches for Treatment of Schizophrenia Targeting Glutamate Signaling

Drug candidates from Vanderbilt efforts could provide a breakthrough with efficacy in treatment of all major symptom clusters of schizophrenia!

- *Hallucinations, delusions*
- *Social withdrawal, inability to experience pleasure,*
- *Impaired cognitive function*

THE WALL STREET JOURNAL.

HEALTH INDUSTRY

J&J, Vanderbilt Team Up on Schizophrenia Drugs

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FierceBiotech

THE BIOTECH INDUSTRY'S DAILY MONITOR

Vanderbilt scores another neuroscience drug pact as AstraZeneca signs on

January 14, 2013 | By John Carroll

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Autistic Spectrum Disorder

Negatively impacts
- communication,
- social interaction
- behavior

- $60 billion annual cost
- 60% of costs are in adult services.
- Cost of lifelong care can be reduced by 2/3 with early intervention

Forbes

BUSINESS: Pharma & Healthcare

Contributor
Emily Willingham

Autism Prevalence Is Now At 1 In 50 Children

Tuberous sclerosis

Asperger Syndrome

Idiopathic Autism

Fragile X Sydrome

Rett Sydrome

Childhood disintegrative disorder

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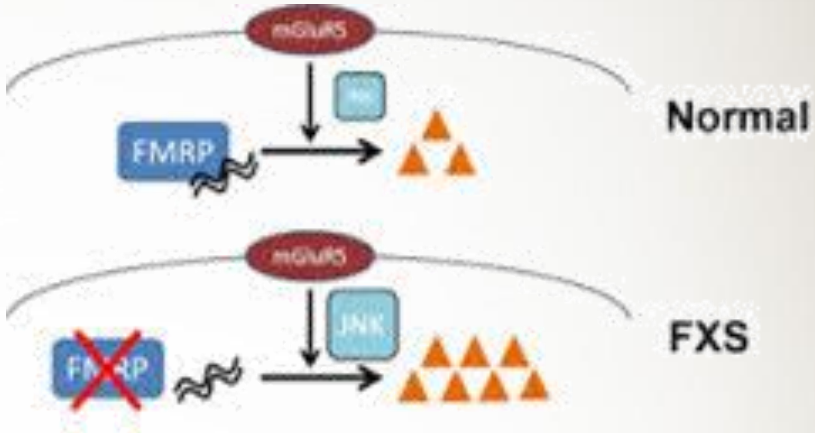
Fragile X Syndrome: The most common genetic cause of Autism



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VCNDD has developed novel mGlu5 receptor antagonists that are to be tested for treatment of Fragile X.

Studies at VCNDD and others suggest potential utility in treatment of *Rett* syndrome and other autism-spectrum disorders.

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AUTISM SPEAKS It's time to listen.

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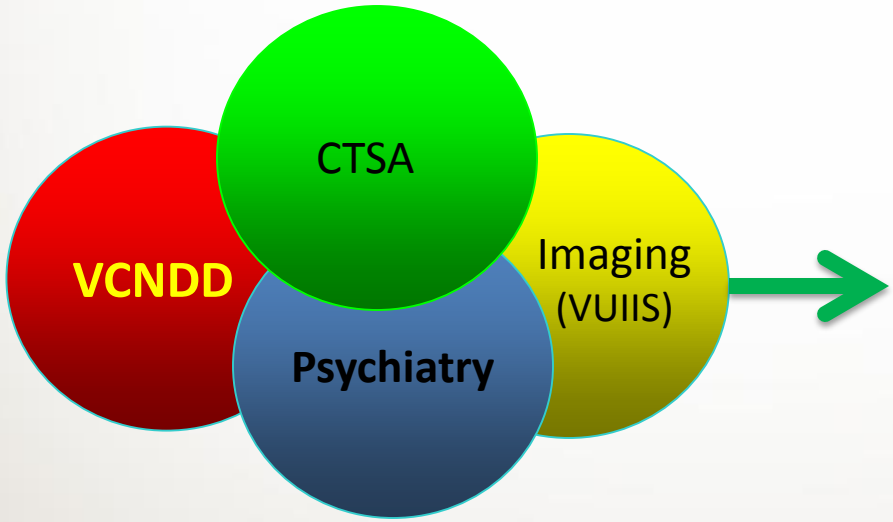
Collaborative effort to test mGlu5 antagonists for testing in patients suffering from major depression

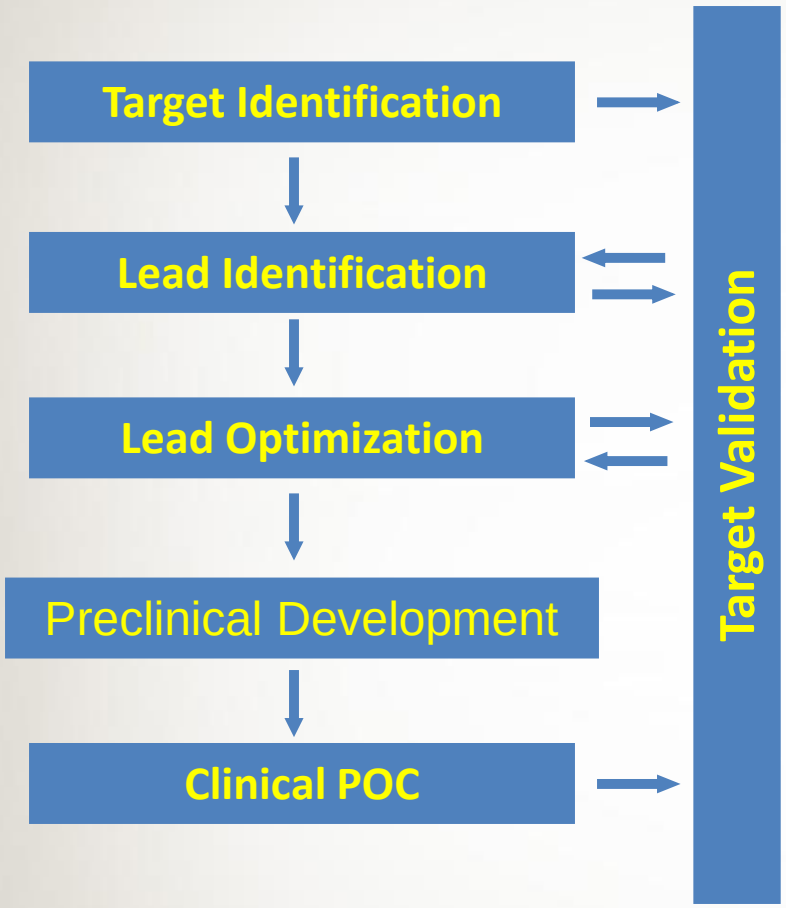
- Ketamine has rapid and sustained antidepressant effects in refractory patients

- *mGlu5 receptor antagonists have effects in the same brain circuits as ketamine but effects are more subtle and may not induce similar adverse effects.*



Integrated effort to advance mGluR5 antagonists into clinical studies for major depression using animal models, animal and human imaging, GLP tox, and clinical proof of concept studies

Drug Discovery and Development – New Academic Role



Explore early stage targets and concepts that are not ready for full drug discovery efforts. Establish needed assays and reagents

Develop Initial leads and proof of concept compounds. Use these to test hypotheses regarding biological effect of small molecule acting at that target.

As leads are optimized, further refine and rigorously test hypotheses. Aggressively work to provide highly optimized research tools to explore utility in multiple indications.

Proof of concept hypothesis testing in the clinic.

Develop biomarkers and assess target engagement.

Expand understanding to provide POC for multiple indications; inform clinical trial design in industry settings.

GOAL: *De risk Innovative novel approaches to treatment of CNS disorders to facilitate full discovery and development in industry!*