Vanderbilt Center for Neuroscience Drug Discovery: Translating Basic Science into Patient Care

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Vanderbilt Center for Neuroscience Drug Discovery
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
VCNDD resources are leveraged with large research infrastructure at Vanderbilt.
Imaging Studies in VCNDD Efforts

**PET**

VU0409106 50% Occupancy gives full efficacy in primary PD model

**fMRI**

Has predicted activity important in brain circuits important for Schizophrenia
Vanderbilt Institute for Clinical and Translational Research

Mission

• Systematically remove impediments to translation
• Create novel, research-enabling infrastructure
• Train the next generation of investigators
• Evaluate program effectiveness.

Integrated effort to advance mGluR5 NAMs into POC studies for major depression using animal models, animal and human PET and fMRI, and clinical POC studies
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

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

Characterized by:
- Tremor
- Bradykinesia
- Rigidity
- Disturbance of posture

Deep Brain Stimulation For the Treatment Of Parkinson's Disease

Vanderbilt University Medical Center
Antiparkinsonian activity of mGluR4 agonists

Gene profiling reveals mGluR4 mRNA in striatum

mGluR4 protein in presynaptic terminals 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.

L-AP4
L-DOPA
Pre-Drug Post-Drug

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

In partnership with MJFF we have optimized drug candidates that are positive allosteric modulators and are ready to advance to clinical testing in PD patients!
Current mGluR4 PAM clinical candidates have excellent profile for advancing to clinical development

- EC50 values 20 – 100 nM; in vivo potencies 0.5 – 2 mg/kg
- Highly selective for mGlu4 relative to other mGluR subtypes
- Clean ancillary pharmacology; no activity at cardiac channels, Excellent CYP profile
- Clean in AMES (gene tox) tests
- High oral bioavailability; Highly brain penetrant
- Robust efficacy in relevant animal models of Parkinson’s disease

$ED_{50} = 1.4 \text{ mg/kg (0.6-3.9)}$
Staging of Pipeline

Target ID/Validation
- mGluR3
- M5 PAMs
- mGluR7
- mGluR8
- GLP-1 agonists
- MCH antagonists
- AKT1
- T-type Ca channels
- Phospholipase D
- KCNQ
- Choline Transporter

In Vivo POC
- mGluR2 PAMs (schizophrenia)
- M1 allosteric agonists/PAMs (Sz/Alzheimers)
- M1 antagonists (FXS/Dystonia)
- M4 PAMs (Sz/Alzheimers)

Lead Optimization
- mGluR5 NAMs (FXS; depression)
- mGluR5 PAMs (Schizophrenia)
- mGluR4 PAMS (Parkinson’s)

Clinical Development Candidate
- GlyT1 Inhibitors (Schizophrenia)

Traditional Academic funding NIH, Foundations, etc.
VPDD Budget and Growth

Unique Training Grant for Neuroscience Drug Discovery
VCNDD productivity and recognition

- 119 patents filed, 2007-present. Represents over 11% of all Vanderbilt University Disclosures!

- >160 manuscripts published 2007-present.

- Growth from zero to >$85 million external funding since 2004 (> $18M in 2011).

- 4 partnerships for fully engaged drug discovery efforts: 1) Parkinson’s (MJFF), 2) Schizophrenia (J&J/Janssen), 3) Fragile X/Autism (Seaside Therapeutics), 4) Schizophrenia (NIH)

- >40 Companies have contacted VPDD over past 3 yr asking for opportunities to partner or license IP.