Allosteric Modulators of mGluRs for Treatment of CNS Disorders

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Surgical Lesions Correct Imbalance in Motor Circuit in Parkinson’s Patients
Potential antiparkinsonian activity of mGluR4 agonists

Profiling

mGluR4 Anatomy

Behavioral effects of mGluR4 agonist

Robust efficacy in:
- Reserpine – induced akinesia
- Haloperidol-induced catalepsy
- 6-OHDA lesions/forelimb asymmetry

mGluR4 Physiology

Predrug

L-AP4 3 μM

50 pA

10 msec
PHCCC is an allosteric potentiator of mGluR4

- Potentiates mGluR4 regulation of transmission at the striato-GP synapse.
- Has antiparkinsonian effect in rodent models when injected icv.
High throughput screening results in the identification of novel mGluR4 PAMs

160,000 compounds → 10 µM singlicate → 1355 primary PAM hits

10 point concentration response → 434 confirmed PAMs
Lead Optimization – an iterative process of compound synthesis, testing, and design

- **Screening “Hit”**
- **Library Design**
- **Compound design and synthesis**
- **Med Chem**
- **Purification/analytical chemistry**
- **Sample Handling Delivery to Biologists**

**Design of next compounds**

**Biological Assays**

- Activity at target
  - potency, efficacy, affinity
- Off target activity
  - Related targets, other identified problem targets
- In Vitro ADMET
  - hERG, CYPs, PXR, metabolic stability, pgp, permeability, protein binding, etc.
- In Vivo/In Situ
  - In situ efficacy in vivo, animal models, in vivo DMPK, human predictive PK

>98% purity
VU03423 is more potent than PHCCC, has agonist activity, and has antiparkinsonian effects.

- **VU0003423**
  - **Potentiation of Glu response**
  - **Intrinsic agonist activity**

- **Haloperidol-induced catalepsy**
- **Reserpine-induced akinesia**

- mGluR4 potency: 20 - 80 nM
- High selectivity
- Fold shift of Glu response: 45

- Rapidly metabolized by rat and human microsomes
- Rapid Clearance
- High plasma protein binding
- Poor oral bioavailability
VU0361737 provides a systemically active mGluR4 PAM and has antiparkinsonian effects

- mGluR4 potency: 110 nM
- Highly selective relative to other mGluRs
- Fold shift of Glu response: 35 fold
- Brain/Plasma ratio: 3.5
- First Systemically active mGluR4 PAMs

Chemistry effort focused on optimizing 3 major chemical series to achieve properties required for development candidate.
Millipore GPCR Profiler Screen: VU0361737 is highly selective for mGluR4
mGluR4 PAMs for Treatment of Parkinson’s Disease

**Parkinsonism**

- **CORTEX**
- **STRIATUM**
  - $D_2$
  - $D_1$
- **GPe**
- **Thal**
- **STN**
- **GPI/SNr**

**Brainstem**

**Spinal cord**

**HTS/Lead Identification**

**Lead Optimization**

**Parkinsonian Monkey**

**POC Clinical Study**

**Pharma Partner**

**Full clinical development for treatment of PD**

**Completed**

**In Progress**

**Collaboration with Emory**

**Terminate Effort on Target**
mGluR8 PAM Screen

mGluR8 Thalium Flux assay

- Agonist
- mGluR8
- Gi/o G protein activation and G βγ-mediated stimulation of GIRK
- GIRK 1
- GIRK 2
- Th+
- BTC-AM loading dye
- Excitation at 488 nm
- Emission filter at 540 ± 30 nM

Calcium Fluorescence

- 308 primary hits
- 99 confirmed hits after secondary assays
- 7 confirmed hits from cheminformatics screen
Cheminformatics database mining based on other mGluR PAMs yields mGluR7 PAMs.
Positive Allosteric Modulators of GPCRs

- mGluR5 PAMs have efficacy in models of antipsychotic and cognition enhancing activity
- mGluR2 PAMs have efficacy in models of anxiety disorders and antipsychotic activity
- M1 and M4 mAChR PAMs have efficacy in animal models of antipsychotic activity
- M1 mAChR PAMs have efficacy in animal models of cognition-enhancing activity and AD
- Selective M5 mAChR PAMs now optimized and under investigation
Staging of Pipeline

Target ID/Validation

- mGluR3 PAMs (stress/sz)
- M5 PAMs (addiction/ADD)
- mGluR7 NAMs and PAMs
- mGluR8 PAMs (Parkinsons)
- GLP-1 PAMs (diabetes)
- mGluR2/3 antagonists

In Vivo POC

- mGluR2 PAMs (schizophrenia)
- M1 allosteric agonists/PAMs (Sz/Alzheimers)
- M1 antagonists (Dystonia)
- M4 PAMs (Sz/Alzheimers)

Lead Optimization

- mGluR5 antagonists (FXS; anxiety)
- mGluR5 PAMs (Schizophrenia)
- mGluR4 PAMs (Parkinson’s)

Clinical Development Candidate

- GlyT1 Inhibitors (Schizophrenia)

Traditional Funding Mechanisms; NIH, Foundations, etc.

NCDDDG: Discovery of Novel Treatments for Schizophrenia

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## Vanderbilt Program in Drug Discovery

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- Usha Menon
- Matt Mulder
- Katrina Brewer
- Ryan Morrison

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Assay development and screens supported by the NIH Roadmaps MLPCN network.
The mGluR8 agonist S-3,4-DCPG Reverses Chronic, but not Acute, Reserpine-Induced Akinesia

Acute Reserpine: 2 Hours

20 Hours post Reserpine:

- DCPG reverses catalepsy after chronic but not acute haloperidol treatment
- DCPG reverses forelimb asymmetry in unilateral 6-OHDA-lesioned rats