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WARREN CENTER  
FOR NEUROSCIENCE DRUG DISCOVERY  
at Vanderbilt University

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## The WCNDD and Parkinson's Disease

### M<sub>4</sub> antagonists for the treatment of dystonia and tremor in PD

Dystonia and Parkinson's disease are two neurological disorders of unmet medical need that result in impairments in movement that can be debilitating for patients. It is known that blockade of a family of receptors, called muscarinic receptors, in the brain has shown promise in the treatment of aspects of both of these movement disorders in people. Unfortunately, usage of these antagonists has been limited due to severe side effects resulting from their broad inhibition of each of the five muscarinic receptor subtypes. Within the muscarinic receptor family, the M<sub>4</sub> receptor is involved in regulating the activity of dopamine and is highly expressed in regions of the brain required for proper movement integration. We are excited to report that we have developed a highly selective M<sub>4</sub> receptor antagonist, as well as multiple "backup" compounds, with the potential to treat aspects of both PD and dystonia. Our lead compound is now progressing through the stages of development needed for approval for testing by the FDA and is poised to become our third candidate to progress into clinical trials!

### G2019S-LRRK2 selective inhibitors for PD

Continuing with our mission to address unmet clinical needs for serious neurological disorders, we are delighted to announce our program for the development of selective inhibitors of the enzyme G2019S-LRRK2. Current therapies for both sporadic and familial PD primarily treat the motor symptoms of the disorder without affecting disease progression. In contrast, a G2019S mutation in the enzyme LRRK2 has been linked to neurodegeneration and is the most common mutation found in familial PD. This mutation causes the LRRK2 protein to become overactive, and inhibitors of this mutant enzyme are thought to be a potential avenue for the treatment of this form of PD without some of the caveats of inhibiting the nonmutant enzyme. We have developed highly selective G2019S-LRRK2 inhibitors with a strong patent position as well as a biomarker strategy that will ensure robust evaluation of safety and efficacy in clinical studies. We are seeking active partners for this program, including licensing of the patent family and securing a 12-24 month sponsored research program to develop backup compounds, to ensure the best chance of clinical success. Please send inquiries to Craig W. Lindsley and Thomas Utley ([craig.lindsley@vanderbilt.edu](mailto:craig.lindsley@vanderbilt.edu) and [thomas.j.utley@vanderbilt.edu](mailto:thomas.j.utley@vanderbilt.edu)); we would love to work with you!



**GRANT ALERT:** Jeff Conn, Founding Director of the WCNDD, and Colleen Niswender, Senior Director of Molecular Pharmacology for the Center, are excited to announce the renewal of the grant, "Regulation of Signaling by mGluR5". This grant provides funding for the team to continue their work on signaling mechanisms of metabotropic glutamate receptors with therapeutic relevance for the treatment of schizophrenia, autism, and cognitive disorders. If you are looking for a graduate project or a postdoctoral fellowship that combines molecular pharmacology of novel compounds, electrophysiology, and rodent behavior, we have a project for you!

## Advocacy and Outreach

I'M SPEAKING AT



**Rx and Illicit  
Drug Summit**

Where new data, concepts, and ideas  
are discussed to create solutions

for the addiction  
epidemic.

JOIN ME! APRIL 10-13, 2023 | ATLANTA [RX-SUMMIT.COM](http://RX-SUMMIT.COM)

Our Director of Outreach and Advocacy Programs, Kristen Gilliland, has been busy educating students about the developing adolescent brain, the dangers of using high potency THC cannabis, street drugs, and the neurobiology of addiction. She presented the importance of practicing self-compassion, mindfulness, and self-care as the foundation for building healthy minds to the 10-12 graders (and their parents) at Battle Ground Academy last month. In addition, she presented similar topics to parents at the Metro Nashville First Time Drug Offenders Course, attendees of the Wilson County Substance Prevention Coalition and Dickson County's Celebrate Recovery. Kristen was also a guest on Sheila Tulley's Podcast "Our Modern Emotional Lives. Through Vanderbilt University Medical Center, Kristen served as an author to a program that recently launched titled, "Preparing Educators to Help Save Lives: What you should know about Opioid Use and Adolescents". This month, Kristen will showcase parts of the documentary, *Speaking Through Me*, to conference participants at the Rx

and Illicit Drug Summit in Atlanta, GA. At the Rx Conference, Kristen was personally invited to meet and discuss her outreach efforts with Rahul Gupta, Director of the White House Office of National Drug Control Policy. Lastly, filming begins this month for teaching videos that will complement the WCNDD Outreach website and documentary.

### We are excited to announce several new publications from March and April 2023!

"Selective M5 muscarinic acetylcholine receptor negative allosteric modulator VU6008667 blocks acquisition of opioid self-administration", *Neuropharmacology*, by Laura Teal, Michael Bubser, Edith Duncan, Robert Gould, Craig Lindsley, and Carrie Jones

"The importance of PK-PD", *Journal of Medicinal Chemistry*, by James Barrow and Craig Lindsley

"Synthesis and SAR of a novel Kir6.2/SUR1 channel opener scaffold identified by HTS", *Bioorganic Medicinal Chemistry Letters*", by Cayden Dodd, Keagen Chronister, Upendra Rathnayake, Lauren Parr, Sichen Chang, Dehui Mi, Emily Days, Joshua Bauer, Hyekyung Cho, Olivier Boutaud, Jerod Denton, Craig Lindsley, and Changho Han

"Identification of potent, selective, and peripherally restricted serotonin receptor 2B antagonists from a high throughput screen", *Assay Drug Development Technologies*, by Aaron Bender, Michael Valentine, Joshua Bauer, Emily Days, Craig Lindsley and W David Merryman

"GRM7 gene mutations and consequences for neurodevelopment" *Pharmacology, Biochemistry, and Behavior*, by Geanne Freitas and Colleen Niswender