ACS Chemistry for Life®

The San Diego Chemist

American Chemical Society **San Diego Section**
Volume 30, Number 4 **April 2018**

SEARCHING FOR SELECTIVITY: THE IDENTIFICATION OF NOVEL MODULATORS THAT TARGET DOPAMINERGIC SIGNALING

David R. Sibley, Ph.D.

Section Chief and Senior Investigator
Molecular Neuropharmacology Section
National Institute of Neurological Disorders & Stroke/NIH, Bethesda, MD

DATE: **Wednesday, April 18, 2018**

TIME: **6:00 PM Social Hour, Light Supper**
7:00 PM Lecture

PLACE: **San Diego State University**
Department of Chemistry and Biochemistry, SSW 1500
5500 Campanile Drive, San Diego, CA 92182

RSVP: **By Sunday, April 15, 2018**
https://davidsibley-sdsu.eventbrite.com

DIRECTIONS: **From Interstate 8**
Take College Ave Exit and head South. The Chemical Sciences Laboratory building is right next to the exit ramp on College Ave. Stay in the left lane and turn left at the first red light. Drive into Parking Structure 1 and park in any Faculty/Staff slot on Level 1 (no parking permit needed). Take the garage elevator to Floor 6 and walk across the pedestrian bridge over College Avenue. Walk across Aztec Circle Drive and take the 13 steps ahead of you. Walk 95 steps towards the clock tower and you will see SSW 1500 Lecture Hall on your right.

ABOUT THE SPEAKER

Dr. Sibley received his B.S. degree in Biology from San Diego State University and worked on his undergraduate research projects in the biochemistry laboratory of Professor Steve Dahms. Dr. Sibley received his Ph.D. in Physiology/Pharmacology from the University of California, San Diego, where he worked with Professor Ian Creese studying the ligand binding properties of dopamine receptors. He subsequently carried out postdoctoral work with Robert Lefkowitz at Duke University where he characterized adrenergic receptor regulatory mechanisms. Dr. Sibley moved to the NINDS in 1987 and was appointed Chief of the Molecular Neuropharmacology Section in 1992. His laboratory is currently investigating the molecular, cellular and biochemical properties of dopamine receptors and their role in neuronal signaling.

ABOUT THE PRESENTATION

Dopamine is a critical neurotransmitter in the brain and periphery and is involved in the control of movement, memory, reward, cognition and neuroendocrine modulation. Correspondingly, dysregulation of dopaminergic signaling is implicated in various diseases such as schizophrenia, Parkinson's disease, depression, Tourette's syndrome and ADHD. The hallmark of all these disorders is that they are treated with drugs that either stimulate or block dopamine receptor subtypes. The actions of dopamine are mediated by a family of five unique G protein-coupled receptors (D1 – D5). Notably, the D2 dopamine receptor is one of the most validated targets in neuropsychiatry serving as the primary target for drugs that treat schizophrenia, Parkinson's disease and several other disorders. Unfortunately, many drugs that target the D2 receptor lack selectivity and cross-react with other GPCRs leading to numerous deleterious side effects. Further, recent evidence suggests that the D2 receptor signals through various intracellular pathways only some of which may be linked to therapeutic effects. As such, it would be highly beneficial to have therapeutics that target the D2 receptor, and it's signaling pathways, in a more selective fashion. We have recently used high throughput screening to interrogate large chemical libraries to identify novel chemical scaffolds with unique pharmacological characteristics for targeting the D2 receptor. The use of medicinal chemistry approaches to optimize these hit compounds has led to the discovery of highly selective antagonists of the D2 receptor that may represent improved antipsychotics for the treatment of schizophrenia. Similarly, we have identified functionally-selective, or signaling biased agonists of the D2 receptor that have provided molecular insights into how this receptor activates multiple signaling pathways. Overall, these studies illustrate how dopamine receptors can be targeted more selectively to potentially result in improved therapeutics for neuropsychiatric disorders.