

BIOCHEMISTRY SEMINAR

Mining the GPCR Conformational Space for Drug Discovery of Novel Pharmacological Mechanisms: A Focus on Serotonin and Opioid GPCRs

John McCorvy

Associate Professor, Medical College of Wisconsin



Abstract: G protein-coupled receptors (GPCRs) remain lucrative and extremely promising drug targets, but recent structural and computational based approaches in GPCR drug discovery still rely on existing simple definitions of mechanism of action (agonist or antagonist). Our aim is to generate “biased” or “pathway-selective” agents by mining orthosteric or allosteric binding sites upon activation and deliver new tool compounds to exploit novel GPCR conformations. Using a combination of structure-based, computational, and medicinal chemical approaches, I will show progress on several GPCR receptor systems where we have success generating new chemical matter that differs mechanistically from the FDA-approved drugs for these targets, either via serendipity or rational-design, resulting in key tool compounds and possible next-generation therapeutics. Next, I will outline progress on the fields of psychedelic drug research and the opioid crisis and how our tool compounds shape our understanding of the underlying physiology of neuroplasticity and respiratory depression, respectively. Finally, I will end on some of our new GPCR drug discovery platform technologies and workflows that aim to bridge the gap between preclinical and clinical, increasing confidence in interpreting animal behavior and initiating human clinical studies. Overall, this seminar will focus on discovering new biology within protein conformational space that will inevitably lead to new mechanisms of action for next-generation medicines.



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3:30 pm



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About John McCorvy:

Dr. John McCorvy is an Associate Professor in the Department of Cell Biology at Medical College of Wisconsin-Milwaukee. Dr. McCorvy received his PhD from Purdue University in 2012 under Dr. David Nichols and worked as a post-doctoral research in Bryan Roth's lab University of North Carolina until 2018. Dr. McCorvy's primary expertise is in G protein-coupled receptor (GPCR) mechanisms, with an emphasis on serotonin and psychedelic drug action at the molecular level. His lab is well-funded with a NIGMS R35 grant on GPCR mechanisms, and two R01 grants from NIDA and NIMH focusing on psychedelic mechanisms at the serotonin receptors as they pertain toward methamphetamine misuse and rapid antidepressant action. Dr. McCorvy's lab also works with collaborators from across the world interested in GPCR mechanisms and several biotech companies in the private sector. His research spans several disciplines including drug discovery, molecular and structural biology, and neuroscience, and training next-generation scientists in neuropharmacology.