John A. Allen, PhD
Assistant Professor
Pharmacology and Toxicology

Discovery of GPR52 Agonists with Antipsychotic and Procognitive Activity as Potential Therapeutic Agents for Schizophrenia

John Allen is Assistant Professor in the Dept. of Pharmacology and Toxicology at the University of Texas Medical Branch. He earned a PhD in Physiology & Biophysics from the University of Illinois College of Medicine studying cell and molecular mechanisms regulating G protein-coupled receptors (GPCRs) followed by post-doctoral training at the University of North Carolina School of Medicine researching mechanisms of antipsychotic drug action and the neuropharmacology of serotonin and dopamine receptors. Prior to joining UTMB, John spent several years at Pfizer Neuroscience where his research advanced therapeutic targets and drug candidates to treat neurological and psychiatric diseases. His recent work has studied functional selectivity at the dopamine receptors and determined molecular mechanisms enabling ligand bias. John is a member of the Society for Neuroscience and ASPET and is the recipient of research awards including a Young Investigator Award from the American College of Neuropsychopharmacology, NARSAD Young Investigator Award and PhRMA Foundation Research Starter Award.

Abstract: To date there are no treatment options for the cognitive impairments associated with schizophrenia and although existing antipsychotics effectively treat psychosis, better treatment options are needed. GPR52 is an orphan G protein-coupled receptor selectively expressed in the ventral striatum and prefrontal cortex. Based partly on GPR52 expression pattern and functional coupling, agonists of this receptor can modulate cortico-striatal circuits and may treat both cognitive and positive symptoms in schizophrenia. In this talk, I will describe our ongoing efforts to create novel GPR52 agonists and evaluate them in preclinical models. Notably, we have determined that GPR52 is an excitatory receptor that sets the tone of basal cAMP levels and that GPR52 expression and activation profoundly modulates dopamine D2 receptor signaling and pharmacology. Integrating medicinal chemistry and neuropharmacology studies, we have also determined agonist features crucial for GPR52 activation. This has led to our discovery of PW0787, an orally bioavailable, brain penetrant, selective GPR52 agonist that shows antipsychotic activity. Perspectives from studies of additional GPR52 agonists that demonstrate

enhancement of cognitive function in various preclinical rodent models will also be discussed. Our research suggests GPR52 is a druggable brain target and that GPR52 agonists may have therapeutic utility as novel treatments for both psychosis and cognitive symptoms in psychiatric disorders.