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Chair
Neurosciences
University of Toledo College of Medicine
Talk Title tba

Dr. Robert McCullumsmith completed his BS degree with highest distinction and Honors in biochemistry from Indiana University in 1990. He completed his MD and PhD degrees from the University of Michigan in 1997, and he completed a research track residency in Psychiatry in 2002. He is a recipient of numerous awards, including the prestigious ACNP travel award, the ACP Laughlin Fellowship, the ECNP Rafaelsen Scholar, as well as the Kempf Fund award from the APA. He has been continuously funded for the past 16 years by NIMH, with work focusing on the pathophysiology of complex brain disorders, including schizophrenia. His recent work includes using bioinformatics approaches to test hypotheses using large publicly available databases, with the goal of repurposing or first-purposing FDA approved drugs or library-sourced compounds, respectively. Dr. McCullumsmith is currently the Chair of the Neurosciences department at the University of Toledo College of Medicine and the Research Director of the ProMedica Neurosciences Center, Toledo, OH, USA.

Abstract: *Where are the final frontiers in biomedical research?* In this age of sequenced genomes, CRISPR, and organoids, how can there be any truly unexplored spaces? Surprisingly, there are dozens (more than 140!) of understudied protein kinases in the human genome. Many of these have ZERO or very few annotations for downstream substrates, lack knockdown and/or overexpression signatures, and have no identified small molecule inhibitors. Many of these understudied, or “dark” kinases, are present in the NIH Illuminating the Druggable Genome (IDG) program, along with many other non-kinase proteins.
What is the best way to study protein kinases? Interestingly, only ~40% of protein abundance can be explained by mRNA expression levels, while the rest is explained by other factors including post-translational modifications (PTMs). Extending this example, protein abundance does not necessary reflect protein activity. A recent study analyzed 150 tumor samples and found that phosphorylation at specific phospho-sites and overall kinase abundance were generally uncorrelated. Taken together, these concepts highlight how assumptions about biological regulation may confound protein research. What is needed is a *functional* understanding of the cellular mechanisms that drive the disorder.
Peptide activity array profiling of brain substrates. We have deployed complementary approaches to study protein kinase activity changes in disorders of cognition,

anchored by a kinome array platform that permits simultaneous assessment of protein kinase activity at 100s of reporter peptides. Combined with RNAseq, LCMS, and standard biochemical assays, we have detected changes in protein kinase signaling networks in schizophrenia (SCZ), Alzheimer's dementia (AD), and major depressive disorder (MDD). Substrates include iPSCs differentiated into astrocytes and frontal cortical neurons, as well as postmortem brain and animal models.

Major findings are providing new leads for drug development. Alterations in specific protein kinases identified as signaling nodes in SCZ (SGK kinase) and AD (AMPK kinase) are being confirmed using standard biochemical approaches. We are also using in silico bioinformatics approaches to identify library compounds and repurposed drugs that may be advanced for development of novel treatment strategies for these often devastating disorders.