

BIOCHEMISTRY SEMINAR

Wade Van Horn, Ph. D

Laskowski Lecture

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"Decoding Polymodal Allostery in Human TRPV1"



Abstract: Therapeutic targeting of the heat-sensing ion channel human TRPV1 has long been hindered by polymodal activation by capsaicinoids, noxious heat, and extracellular protons, where modulating one gating stimulus frequently triggers on-target adverse side effects. Here, we present an integrative biophysical framework to decode mode-selective allosteric coupling in human TRPV1. Utilizing solution NMR spectroscopy and cheminformatics, we establish that protein conformational dynamic signatures directly bridge ligand chemical space with functional gating efficacy. Complementary single-particle cryo-EM reveals structural divergence among clinically relevant antagonist chemotypes engaged within the canonical orthosteric pocket, while functional concatemers demonstrate that distinct activation modalities proceed through structurally asymmetric gating networks. Together, these findings reveal that orthosteric engagement is both dynamically and structurally heterogeneous, establishing dynamic allosteric networks as the critical bridge connecting chemical diversity to modality-selective pharmacology.

Bio: Wade D. Van Horn, Ph.D., is a Professor in the School of Molecular Sciences at Arizona State University, with appointments in the Biodesign Center for Personalized Diagnostics, the Center for Mechanisms of Evolution, and the Magnetic Resonance Research Center. He completed his doctoral studies in the Department of Chemistry at the University of Utah and conducted postdoctoral research as an American Heart Association Fellow in the Department of Biochemistry at Vanderbilt University School of Medicine. The Van Horn Laboratory investigates ion channels and membrane proteins critical to sensation, cellular excitability, and disease. Centered on the principle that biological function emerges from dynamic conformational ensembles, his research seeks to connect protein motion and allosteric mechanisms directly to human physiology. The group deploys an integrated multi-scale toolkit that combines solution nuclear magnetic resonance (NMR) spectroscopy, high-resolution cryogenic electron microscopy, automated and whole-cell electrophysiology, and chemoinformatics to determine how ligands, regulatory proteins, and lipid membranes reshape membrane protein function. A major thrust of this work focuses on resolving polymodal gating and channelopathies in targets such as TRPV1 and TRPM8 to guide the rational design of mode-selective pain therapeutics.