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Novel Neurotherapeutics Based on Modulation of Voltage-gated Na+ Channels

Dr. Laezza is a Professor in the Department of Pharmacology & Toxicology at the University of Texas Medical Branch. Her research aims at developing novel pharmacological treatments for psychiatric disorders. With a therapeutic strategy targeting protein:protein interaction interfaces, her team works in collaboration with medicinal chemists, behavioral pharmacologists and clinicians to identify novel allosteric modulators of voltage-gated Na+ channels. With minimal expected off-target effects, a precise mechanism of action and the ability to fine-tune neuronal firing in a highly specific manner, these modulators and the therapeutic strategy behind them hold the promise to transform the neuropsychopharmacology landscape, laying the groundwork for precision medicine in psychiatry. Dr. Laezza is the Chair and co-founder of the Mental Health Research Cluster (MHRC) at the Gulf Coast Consortia (http://www.gulfcoastconsortia.org) which encompasses 185+ principal investigators in the Texas Medical Center with interests in biological, translational and clinical psychiatry. She is also the founder and president of IonTx Inc., a start-up company devoted to the commercialization of neurotherapeutics based on allosteric modulation of voltage-gated Na+ channels.

Abstract:
Background: With the support of a diverse ensemble of auxiliary proteins tightly regulating their function, voltage-gated Na+ (Nav) channels serve as the fundamental molecular determinants of neuronal excitability. Crucially, recent studies have shown that disruption of protein:protein interactions that regulate the function of Nav channels leads to neural circuitry aberrations that are implicated in the etiology of psychiatric disorders. From a pharmacological perspective, these protein:protein interaction interfaces that become perturbed are highly specific and flexible, and could, therefore, serve as ideal surfaces for the development of targeted chemical probes and neurotherapeutic lead compounds. Here, we present recent advancements in a high-throughput screening campaign, which entails experimental modalities ranging from in silico to ex vivo and in vivo, to identify modulators of the protein:protein interactions between Nav1.6 and its auxiliary protein fibroblast growth factor 14 (FGF14). With the

protein:protein interactions between these two proteins being known to modulate intrinsic firing properties of medium spiny neurons in the nucleus accumbens, a promising lead compound with modulatory effects on the reward circuit and on goal-directed behaviors has emerged from this campaign.

Hypothesis/goals: The FGF14:Nav1.6 macromolecular complex is a novel druggable target suitable for the development of neurotherapeutics to treat motivational dysfunctions and positive valence symptoms.

Methods: We employed medicinal chemistry to synthesize and optimize, as well as chemoinformatics, the split-luciferase complementation assay, surface plasmon resonance, whole-cell patch-clamp electrophysiology, single-unit recordings, behavioral pharmacology, pharmacokinetics and toxicology studies to discover and validate allosteric modulators of the Nav1.6 channel as novel neurotherapeutics.

Results: We screened 44,480 compounds from the ChemBridge and Maybridge libraries against the FGF14:Nav1.6 protein:protein interaction interface to identify small molecules capable of inhibiting assembly of the two proteins. Through a cascade of primary, secondary and orthogonal screenings combining the split-luciferase complementation assay, surface plasmon resonance, and whole cell patch-clamp electrophysiology, we identified three hit compounds, one of which was chemically optimized for further evaluation. The optimized lead compound, PW1028, showed nanomolar binding affinity toward both the FGF14 and Nav1.6 proteins. In whole-cell patch-clamp electrophysiology studies, PW1028 was shown to increase Nav1.6 channel availability by shifting the voltage dependence of steady-state inactivation and to potentiate firing of medium spiny neurons in the nucleus accumbens. Concomitantly, systemic administration of PW1028 increased both the firing rate of nucleus accumbens neurons in vivo and the motivation to press a lever for sucrose in satiated animals.

Conclusions: These results identify the FGF14:Nav1.6 complex as a druggable target for the development of novel neuromodulators of the reward circuit with a promising therapeutic value for psychiatric disorders associated with motivational dysfunctions and positive valence symptoms.

Acknowledgements: We acknowledge our funding sources, which are as follows: PhRMA Foundation Fellowship in Pharmacology (PAW); NIH/NIA Grant T32AG051131 (PAW); UTMB MD/PhD Combined Degree Program (PAW); CPRIT grant RP150578 (CCS); NIH/NIGM Grant T32GM008280 (DMN); NIH/NIMH Grant R01MH111107 (FL); NIH/NIMH Grant R01MH095995 (FL); R01MH124351 (FL); John Sealy Memorial Endowment Funds (FL); Technology Commercialization Program, UTMB (FL).