THE UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE TUCSON
Pharmacology

Presents

"In search of addiction therapeutics: Design of allosteric modulators that modify GPCR G protein subtype selectivity"

BY

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Abstract: G protein-coupled receptors (GPCRs) signal through one or more transducers, including 16 Gα proteins and 2 β-arrestins. The GPCR neurotensin receptor 1 (NTSR1) is a promising target for the treatment of substance use disorders, but clinical development of balanced NTSR1 agonists, which activate many of these transducers, is precluded by on-target side effects. A decade-long drug discovery effort has led to the identification of β-arrestin-biased allosteric modulators of the NTSR1 that more selectively reduce addiction-associated behaviors. Here, I will share the mechanism by which these compounds achieve their functional selectivity and, capitalizing on this mechanism, describe the design of new allosteric modulators with new activities. Minor changes to a single molecular scaffold targeting the receptor-transducer interface produced small molecules with distinct G protein subtype activation profiles and in vivo activities. Compounds discriminate between and within G protein families, suggesting the ability to engineer ligands with precise transducer selectivity and laying a foundation for targeted, pathway-selective drug discovery.

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11:00 am – Noon
AHSC - Room 8403
https://arizona.zoom.us/j/82268538546