THE UNIVERSITY OF ARIZONA
College of Medicine

DEPARTMENT OF PHARMACOLOGY

Seminar Series

Presents

"Protease Activated Receptor 2 Modulators"

By

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The University of Arizona

Endogenous proteases, in addition to their first accepted role as degradative enzymes, contribute to many pathological processes through the direct activation of protease activated receptors. This four member family of G-protein coupled receptors (GPCRs) includes the thrombin receptor (protease activated receptor-1; PAR_1) and three other members (PAR_2, PAR_3, PAR_4). PAR_2 is known to play an important role in pathologies that are associated with a release of proteases; these include asthma, chronic pain, cancer, vascular diseases, and inflammatory conditions in general. Much of our knowledge of PAR_2 function is due to the availability of PAR_2 knockout models and peptide/peptidomimetic agonists. However, possible efficacy of PAR_2 antagonists in preclinical models has been limited due to lack of available tools or clinical candidate compounds. The primary objectives of our research are to develop PAR_2 modulators (biased antagonists and agonists) and use our established discovery pipeline and pharmacological tools to design new PAR2 modulators with improved drug-like properties to probe PAR_2 function in the context of animal models (pain and asthma). We have developed a panel of unique PAR_2 modulator: (i) the most potent, specific and efficacious PAR_2 agonists to date; (ii) a potent and specific peptidomimetic antagonist C291 (blocking multiple signaling pathways(Gq-dependent iCa^{2+} release and MAPK); and (iii) biased antagonist of iCa^{2+} release (without stimulation or inhibition of MAPK).
In current study, we work on transition of these compounds into "drug lead" compounds and to fully evaluate PAR_2 ligand potency/efficacy in context of different signaling pathways.

Wednesday, February 10, 2016

11:00 am – 12:00 pm

AHSC, Room 8403