Seminario de Química Orgánica

Martes 14 de noviembre de 2023, 13 h

AULA SEMINARIO DQO – 3º piso – PAB. II – CIUDAD UNIVERSITARIA

AULA VIRTUAL DQO: https://zoom.us/my/qo.aula01 - Clave: exactas20

YouTube: https://www.youtube.com/channel/UCyIYRdx196IH55Do6PVMzXA

"Discovery of modulators of purinergic signaling for chronic disease treatment".

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The purinergic signaling system ("purinome") includes membrane-bound receptors for extracellular purines and pyrimidines, and enzymes/transporters that regulate endogenous agonist concentration. Those receptors, all GPCRs, include: adenosine (A_1, A_{2A}, A_{2B}, and A_3) and nucleotide P2Y ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$, as well as P2X ion channels. Receptor activation, especially accompanying physiological stress or injury, creates a temporal signaling sequence to counteract this stress and either mobilize (P2Rs, P2XRs) or suppress (adenosine receptors) immune responses. Furthermore, in the tumor microenvironment blocking adenosine signaling, e.g. inhibiting CD73, and boosting P2 signaling are beneficial. Experimental structures represent each of the three receptor families, to enable structure-guided approaches to ligand design. We have introduced many selective purinergic receptor ligands as pharmacological probes and clinical candidate molecules for treating autoimmune inflammatory diseases, ischemia, cancer, pain, etc. Our prototypical A_3AR agonists (IB-MECA, piclodenoson and Cl-IB-MECA, namodenoson) are safe and efficacious in advanced clinical trials for psoriasis and liver diseases. Recently discovered A_3AR agonists, utilizing conformational control of selectivity, are being developed for pain and stroke treatment. Nonaddictive A_3AR agonists in rodents attenuate chronic neuropathic pain and reduce side effects of opioid pain treatment, including tolerance and withdrawal. Anti-inflammatory $P2Y_{14}$R antagonists were discovered using a structure-guided approach to identify piperidine ring conformations, enforced by carbon bridges, e.g. 2-azanorbornane derivative MRS4738. We also introduced double prodrugs, to turn zwitterionic antagonists into neutral molecules with qualitatively better anti-inflammatory activity in a protease-mediated asthma model. Either $P2Y_6$R or $P2Y_{14}$R selective knockout in mouse adipocytes induces in vivo metabolic protection in obesity model, suggesting that antagonists of either subtype are potentially useful for treating diabetes and obesity. Thus, modulation of the purinergic signaling network has broad potential for treating chronic diseases, and both structural and empirical approaches to ligand discovery are productive, leading to multiple clinical trials.