DIPARTIMENTO DI FARMACIA E BIOTECNOLOGIE

AVVISO DI SEMINARIO

Il giorno mercoledì **24 Luglio 2019**
alle ore **16:00**
presso Aula 1, via Belmeloro 6, Bologna

Dr Kenneth A. Jacobson, Ph.D.

Chief, Molecular Recognition Section, Laboratory of Bioorganic Chemistry
National Institute of Diabetes & Digestive & Kidney Diseases
National Institutes of Health, Bethesda, MD USA
(ospite Prof.ssa Bolognesi)

terrà un seminario dal titolo:

EXPANDING THE REPERTOIRE OF NUCLEOSIDES FROM GPCRS TO DIVERSE TARGETS

Colleghi e studenti sono cordialmente invitati

Commissione Ricerca e Attività Correlate - FaBiT

ABSTRACT

We study nucleosides and nucleotides at their classical targets in purinergic signaling pathways, e.g. adenosine receptors, P2Y/P2X nucleotide receptors and ribokinases.[1] A conformationally constrained, bicyclic ring system (bicyclo[3.1.0]hexane, also called methanocarba) substituted in place of ribose can increase their potency and selectivity at these targets. We have also repurposed this robust scaffold to satisfy the pharmacophoric requirements of various other GPCRs and diverse enzyme and transporter targets. By this approach we discovered novel antagonists of $5HT_2$ serotonin and kappa-opioid receptors[1,2] and allosteric modulators of the dopamine transporter (DAT).[3] This class of rigid nucleosides is indeed a privileged scaffold (but not broadly promiscuous) for the design of novel receptor ligands and potentially as therapeutic agents for a wide variety of conditions.

References:

1. Jacobson, *et al.* Polypharmacology of conformationally locked methanocarba nucleosides. Drug Disc. Today, 2017, 22:1782-1791.
2. Tosh, *et al.* Repurposing of a nucleoside scaffold from adenosine receptor agonists to opioid receptor antagonists. ACS Omega, 2018, 3:12658-12678.
3. Tosh, *et al.* Scaffold repurposing of nucleosides (adenosine receptor agonists): enhanced activity at the human dopamine and norepinephrine sodium symporters. J. Med. Chem., 2017, 60:3109-3123.

BIOGRAPHICAL SKETCH

Kenneth A. Jacobson, Ph.D. is Chief of the Molecular Recognition Section, Laboratory of Bioorganic Chemistry at the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health in Bethesda, Maryland, USA. Dr. Jacobson is a medicinal chemist with interests in the structure and pharmacology of G protein-coupled receptors, in particular receptors for adenosine and for purine and pyrimidine nucleotides.

He has introduced many of the widely used ligand tools for studying adenosine receptors and P2Y receptors for extracellular nucleotides. More than 35 compounds introduced by Jacobson and coworkers are available commercially as research tools. Three of his GPCR modulators are being developed by pharma industry for treatment of autoimmune inflammatory diseases, cancer and other conditions. The A3 adenosine receptor agonist IB-MECA is in Phase III CF101 trials for rheumatoid arthritis and psoriasis. Highly selective A3 tor agonists invented in the Jacobson lab are also promising for the treatment of chronic neuropathic pain.

Dr. Jacobson is active in the structural elucidation of G protein-coupled receptors and uses these structures for ligand discovery, i.e. designing ligands with enhanced affinity and/or selectivity. His lab participated in a team effort to determine the first X-ray crystal structures of P2Y receptors and agonist-bound A2A receptors in collaboration with Ray Stevens (USC).

Dr. Jacobson graduated from Reed College, Portland, Oregon, and received his Ph.D. (1981) at the University of California, San Diego, Department of Chemistry. He was a Bantrell Fellow in the Dept. of Organic Chemistry, Weizmann Institute of Science before joining the NIH. His laboratory is interdisciplinary; he has mentored >70 postdoctoral fellows, including organic chemists, computational chemists, and pharmacologists. Awards include, 2009 Pharmacia-ASPET Award, 2009 Sato Award, and 2014 Goodman and Gilman Award, 2017 Smissman Award, and 2018 Highly Cited Researcher in Pharmacology and Toxicology by Thomson Reuters (H-index 103, according to Google Scholar). He was Chair of the ACS MEDI Division and was inducted into the Division's Hall of Fame in 2009. He is an inventor on >50 patents.