



University of Camerino
School of Advanced Studies
Chemical and Pharmaceutical Sciences
Scientific event 2010

**Location: Aula Magna del Polo di Alta Formazione
Palazzo delle Esposte**

**Wednesday, February 24th, 2010
5 – 6 p.m.**

The crystal structure of the adenosine A_{2A} receptor – implications for GPCR drug design

The adenosine class of G protein-coupled receptors mediates the important role of extracellular adenosine in many physiological processes including antagonism by caffeine, the most widely used pharmacological agent in the world. The crystal structure of the human A_{2A} adenosine receptor in complex with a high affinity antagonist, ZM241385, was determined to 2.6 Å resolution. Four disulfide bridges in the extracellular domain combined with a subtle repacking of the transmembrane helices relative to the beta-adrenergic and rhodopsin receptor structures defines a pocket capable of binding the antagonist in an extended conformation perpendicular to the membrane plane. The binding site highlights an integral role for the extracellular loops, together with the helical core in ligand recognition by this class of GPCRs. These findings question the use of rhodopsin or any other single receptor structure in homology modeling studies.

seminar

PROF. Adrian P. Ijzerman

Leiden/Amsterdam Center for Drug Research – Leiden, The Netherlands

Wednesday, February 24th, 2010
6 – 7 p.m.

Ex vivo pretreatment with melatonin improves survival, angiogenic/antifibrotic activities and efficiency of mesenchymal stem cells in ischemic heart

Le cellule mesenchimali del midollo osseo hanno dimostrato un grande potenziale nel campo della terapia cellulare cardiaca. L'effetto benefico di queste cellule é stato attribuito, in parte, a fenomeni di transdifferenziazione, d'altra parte, alla secrezione di citochine proangiogeniche. Uno dei problemi maggiori legati all'amministrazione intracardiaca delle cellule mesenchimali é la loro morte precoce dopo il trapianto. Nel nostro laboratorio abbiamo messo a punto una tecnica di condizionamento delle cellule mesenchimali del midollo osseo con l'ormone pineale melatonina. Questo ormone, in piu' dei suoi effetti fisiologici sulla regolazione del ciclo circadiano, ha anche dimostrato degli effetti protettivi su diversi organi. I nostri risultati hanno permesso di dimostrare che la melatonina aumenta la sopravvivenza delle cellule mesenchimali amministrate nel miocardio di ratto e maiale nella fase tardiva dell'infarto. Questo pretrattamento aumenta anche la secrezione di fattori proangogenici da parte delle cellule mesenchimali e amplifica le loro proprietà antifibrotiche. Questi effetti sono accompagnati da un miglioramento significativo della funzione ventricolare sinistra. Sulla base di questi risultati, abbiamo elaborato un protocollo clinico di terapia cellulare dell'insufficienza cardiaca per amministrazione transendocardica (sistema NOGA) di cellule mesenchimali (studio MESAMI). Questo protocollo di Fase 1, su 10 pazienti, ha ricevuto le autorizzazioni del Comitato Francese di Protezione dei Pazienti e dell'Agenzia Francese di Sicurezza Sanitaria. I primi pazienti sono stati trattati nel Novembre 2009 e, sulla base dei risultati d'innocuità, uno studio multicentrico, internazionale di Fase 2 sarà programmato per inizio 2011.

seminar

PROF. ANGELO PARINI

Institute of Molecular Medicine of Rangueil I2 MR – Toulouse, France

Thursday, February 25th, 2010
4 – 5 p.m.

On the Way to New Antiischemic Agents: Design and Synthesis of Poly(ADP-ribosyl) polymerase (PARP-1) Inhibitors

CPoly(ADP-ribosyl)ation is a transient post-translational modification which takes place in eukariotes in response to exposure to DNA-damaging agents involved in main processes related to the preservation of genomic integrity such as DNA repair, chromatin decondensation, and, under certain circumstances, cell necrosis, and apoptotis. Potent PARP inhibitors have been shown to be endowed with neuroprotective properties in experimental models of brain ischemia, thus representing a promising new class of anti-ischemic agents. By taking advantage of the X-ray structures of the catalytic domains of PARP-1 and PARP-2, in silico docking were carried out. The integration of these results with the structure activity relationships based on our potent thieno[2,3-c]isoquinolin-1-one derivative (TIQ-A), allowed the design and synthesis of a series of novel inhibitors which, tested for their ability to inhibit PARPs, showed high potency, selectivity and water solubility. Some of the new potent derivatives were selected for further characterization and found to be endowed with neuroprotective properties in animal models of cerebral ischemia.

seminar

PROF. EMIDIO CAMAIONI

Dipartimento di Chimica e Tecnologia del Farmaco – Università di Perugia

Thursday, February 25th, 2010
5 – 6 p.m.

Presence of Fusarium emerging mycotoxins in cereals

Beauvericin (BEA), fusaproliferin (FUS) and enniatins (ENs) are secondary toxic metabolites produced by *Fusarium* spp., with different toxicological activities on insect and cells.

BEA, FUS, and ENs were produced with fermentation on solid medium of corn operated by a strain of *Fusarium tricinctum*, and purified with a semipreparative liquid chromatography coupled to a fractions collector, followed by an analytical LC. The fractions containing the toxins were characterized by LC-MS/MS ion trap. The purified toxins obtained in this way were utilized as standards for the study of the contamination's level of different cereal samples purchased from local markets in Spain and Morocco.

For the control of these emerging mycotoxins, samples were extracted with a mixture of water/acetonitrile (85/15, v/v) by using an Ultra-turrax homogenizer and the mycotoxins were quantified with a LC with diode array detector (DAD). Positive samples were confirmed with an LC-MS/MS.

Analytical results showed that in the Spanish samples the percentage of contamination of ENs, BEA and FUS were 73, 33 and 7.8 %, respectively. The high levels found in analyzed samples were up to 814 mg/kg for ENA₁, 11.8 mg/kg for BEA and 6.6 mg/kg for FUS. Corn and wheat were more contaminated than barley. However, rice could be the best substrate for emerging mycotoxins production since higher contamination levels were found in the limited analyzed samples.

As regards the Morocco samples the percentage of contamination of ENs, BEA and FUS were 50, 26 % and 7.8 %, respectively. The high levels found in analyzed samples could represent a risk for the Moroccan population, considering that the cereals have a considerable contribution to the local diet.

It could be concluded that because of the absence of international legislation limits for this group of toxins, and due to the toxicological effects recently described, more research is needed to completely assess the situation especially on moulds species and factors responsible for their production.

seminar

PROF. Jordi Mañes Vinuesa

**Departament de Medicina Preventiva i salut pública – Universitat de València,
Spain**

Coordinator: Prof. Piero Angeli