19 APRIL AT 2:30 P.M.
ROOM B107 | POVO 2

CIBIO EXTERNAL seminar

SELECTIVE CASPASE-2 INHIBITORS AND THEIR USE IN ALZHEIMER'S DISEASE

Etienne Jacotot

Faculté de Pharmacie,
Université Paris Cité

For many years Casp2 was considered as a redundant apoptosis initiator and/or effector and consequently was initially not considered as a priority target for drug development. However, in the context of Alzheimer's disease, a role for Casp2 was proposed more than 20 years ago and later confirmed in animal models of Alzheimer's disease and of frontotemporal dementia. Casp2 specific inhibitors have not yet been tested in humans. Currently, there are no commercially available selective Casp2 inhibitors. The standard Casp2 inhibitors that are marketed for research use (e.g. Ac-VDVAD-CHO and z-VDVAD-fmk) are non-selective. They have poor biodisponibility and strong inhibitory effects on Casp3. The pharmacological targeting of Casp2 has been considered challenging because of the structural similarity between caspase catalytic domains. Specifically, Casp2 shares the closest cleavage specificity similarities with Casp3 and Casp7, and to a lesser extent with Casp8. Therefore, designing selective inhibitors for Casp2 has been difficult. We have designed and evaluated a series of peptidomimetics derived from the canonic pentapeptide VDVAD and combined potent irreversible warhead (proven to be safe in human) with non-natural structures conferring Casp2 specificity and biodisponibility. The most potent peptidomimetic, LJ2a, inhibits human Casp2 with an extremely high inactivation rate. LJ3a is the most selective inhibitor, with close to 1000 times higher inactivation rate on Casp2 as compared to Casp3. Structural analysis of LJ3a shows that spatial configuration of Cα at the P2 position determines inhibitor efficacy. ß-amyloid oligomers (Aß) are central pathogenic proteins in Alzheimer's disease. Aß induces synapse loss and neuronal death through rapid Casp2 activation. The neuronal death pathways implicate Bim and c-Jun expression increase, Casp3 activation. In primary hippocampal neurons treated with ß-amyloid oligomers (Aß), submicromolar concentrations of LJ2a and of LJ3a prevent synapse loss. At higher (micromolar) concentrations, Aß induces Bim expression increase, Caspase-2 activation, and hippocampal neuron death, all of which are inhibited by cell-penetrant siRNA targeting Casp2 (PensiRNACasp2) as well as LJ3a, but not by Pen-siRNACasp3, nor by necroptosis inhibitors. Furthermore, LJ3a similarly inhibits cell death induced by Aß in human embryonic stem cellderived neurons. These data argue for further investigation of LJ2a/LJ3a in the treatment of AD.

DEPARTMENT OF CELLULAR, COMPUTATIONAL AND INTEGRATIVE BIOLOGY - CIBIO
VIA SOMMARIVE, 9
38123 - POVO (TN)
COMUNICAZIONE.CIBIO@UNITN.IT

UNIVERSITÀ DI TRENTO
Department of
Cellular, Computational and Integrative Biology - CIBIO