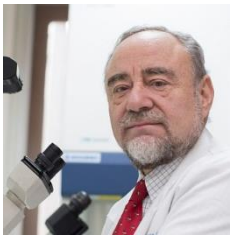
KEYNOTE LECTURE 5

Ana Martínez Gil, Ph.D.
Centro de Investigaciones Biológicas (CIB), Madrid, España.

PHARMACOLOGIC MODULATION OF TDP-43: A NEW FUTURE TO FIGHT AGAINST NEURODEGENERATION

Aggregates of the nuclear protein TAR DNA-binding protein 43 (TDP-43) were discovered in the spinal cord of amyotrophic lateral sclerosis (ALS) patients in 2006. Since then, the key role of TDP-43 in neurodegenerative diseases has been growed exponentially. Not only it is the main pathological hallmark in ALS but also in frontotemporal dementia, Alexander's disease, Perry syndrome and limbic-predominant age-related TDP-43 encephalopathy (LATE) usually misdiagnosed with Alzheimer´s disease (AD) as the clinical symptoms of both pathologies are similar. Additionally, TDP-43 pathology is a secondary feature of several other neurodegenerative disorders, including AD, or Parkinson's and Huntington's diseases. In those diseases, the presence of TDP-43 may aggravate the primary existing proteinopathy. Prominent TDP-43 cytoplasmic mislocalization and aggregation are evident in all these unmet neurodegenerative disorders. Thus, pharmacological modulation of TDP-43 post-translational modifications by small molecules offers a great opportunity in the discovery of efficient drug candidates for the future treatment of the fatal and severe ALS and many other unmet diseases. We have designed and optimized brain penetrant inhibitors of protein kinases involved in the in vivo phosphorylation of TDP-43. The better candidates of these series, emerged as valuable drug candidates able to restore TDP-43 homeostasis. They are able to decrease TDP-43 hyperphosphorylation and aggregation, recovering the nuclear localization and physiological function of this protein. Moreover, all these facts lead to motoneuron preservation in ALS in vivo models or cortical neuron survival in FTLD-TDP murine models. Only future clinical trials will reveal the therapeutic value of TDP-43 modulation by small protein kinase inhibitors in patients. TIDALS will start the recruitment before the end of the year.

KEYNOTE LECTURE 6



Nibaldo C. Inestrosa, Ph.D.
Centro de Excelencia de Magallanes (CEBIMA), Universidad de Magallanes, Punta Arenas y Centro de Envejecimiento y Regeneración (CARE UC), Pontificia Universidad Católica de Chile, Santiago Chile

ALZHEIMER´S DISEASE: ROLE OF WNT SIGNALING PATHWAY

Wnt proteins modulate cell proliferation and differentiation. In the adult brain, Wnt signaling is required for the development of neuronal circuits and it plays an important role in synaptic transmission and plasticity. Almost 20 years ago, we proposed that Wnt signaling activation might be neuroprotective against Alzheimer´s disease (AD). One mechanism involved could be the inhibition of glycogen synthase kinase-3b (GSK-3b) the enzyme that phosphorylate tau protein and control tau phosphorylation. b-and g-secretase cleave the amyloid precursor protein (APP) to release the amyloidogenic peptides (Ab) and the APP intracellular domain (AICD). Wnt signaling activation blocks b-secretase transcription decreasing the availability of Ab peptides and the APP intracellular domain AICD inhibits Wnt signaling by activating GSK-3b. Therefore, there at least two critical point of interaction between APP processing and Wnt signaling. Recently, we found that Wnt dysfunction results in memory loss, tau phosphorylation, Aβ production and amyloid deposition, indicating that Wnt dysfunction accelerated the onset of AD. More important, Wnt signaling loss in wild-type mice promoted cognitive impairment, tau phosphorylation and Aβ1-42 production, contributing to the development of an Alzheimer's-like neuropathology. We conclude that dysfunction of Wnt signaling pathway is sufficient to accelerate the onset of AD and could be considered a triggering factor for AD.