International Conference

"Scientific Creativity to Understand Alzheimer´s Disease"

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Title: **A metabolic NGF deregulation in the Alzheimer's disease and Down syndrome.**

Keynote Speaker: **Dr. Claudio Cuello**

Pharmacology, Pharmacology and Therapeutics, McGill University, Montreal, PQ, Canada

We have demonstrated a novel brain metabolic pathway responsible for the release, maturation and degradation of NGF. This pathway has been validated pharmacologically, in vivo.

In Alzheimer's disease (AD) there is an apparent paradox in which the atrophy of NGF-dependent forebrain cholinergic neuron occurs with normal NGF synthesis and over-abundance of the NGF precursor (proNGF). We have resolved the paradox by showing that in the AD pathology there is a deregulation of the NGF metabolic pathway in which the conversion of proNGF to mature NGF is compromised and the NGF degradation facilitated. A similar situation was found in Down syndrome (DS) brains with AD pathology.

The above provides a rationale for the atrophy of NGF-dependent forebrain cholinergic neurons and loss of their terminal synapses. Both AD and DS develop a decades-long "silent" amyloid pathology resulting cognitive deficits and eventually dementia. The NGF metabolic deregulation opens new possibilities to investigate biomarkers indicating the "silent" AD pathology in populations at risk. Our studies in DS individuals evolving to DS/AD symptomatic in a longitudinal study has shown that one-year elevation of plasma proNGF correlated with severe cognitive decline in the following year.

Supported the Canadian Institutes of Health Research.

Title: **On the road to understand Alzheimer Disease, APP axonal transport and synaptic proteostasis defects.**

Keynote Speaker: **Dr. Tomás Falzone**
University of Buenos Aires, Faculty of Medicine.

Abnormal accumulation of proteins in Alzheimer disease (AD) is a key process for the formation of the distinctive pathological hallmarks of amyloid plaques and neurofibrillary tangles. Imbalances between protein production, distribution and clearance are at the core of pathology buildup. Therefore, local protein homeostasis in highly polarized neurons requires a regulated system of protein delivery by axonal transport and a coordinated action of protein removal by selective degradation. We have focused on the role and regulation of axonal transport in normal neuronal function and how defects in the proper distribution of proteins that are associated with Alzheimer's can be at the core mechanisms of disease progression. Using high-resolution live imaging systems to follow fluorescent axonal cargos such as APP and proteasomes, mature and polarized human derived neurons in culture, and the development of human 3D cerebral organoids models to study protein aggregation and pathology build up we propose to understand the relationship between axonal transport defects and protein degradation impairments. We envision to understand the mechanisms that govern axonal proteostasis and how impairments in these processes can give rise to the manifestation of Alzheimer disease.

Title: **Validation of neurotrophic effects of synthetic peptides of the active site of BDNF in neurons derived from dental pulp stem cell or iPSCs from familiar Alzheimer's disease patients.**

Keynote Speaker: **Dr. Maria del Carmen Cardenas-Aguayo**
Universidad Autónoma de México, Mexico DF

Disruption of growth factor signaling is a characteristic of many neurodegenerative disorders. The use of neurotrophic factors to modulate neuronal survival and synaptic connectivity is a promising therapeutic approach. Growth factors such as Brain derived neurotrophic factor (BDNF), a member of the neurotrophin family that also includes nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5), is of particular interest, since the signaling pathway of its receptor, tropomyosin-related kinase B (TrkB) is known to promote survival, differentiation and synaptic function. In Alzheimer's Disease (AD), BDNF expression levels are reduced, additionally BDNF levels diminish in Parkinson's disease, depression, stress, anxiety and aging; however, BDNF expression is increased in autism spectrum disorders. Since BDNF has short plasma half-life, and a poor Blood Brain Barrier (BBB) penetration, small molecules that could mimic its functions might be an alternative approach. Use of patient derived cells as a model to study human diseases has been shown to be a better approach to validate drugs than murine models. Differentiation on neural stem cells and cellular reprogramming are important tools to obtain patients- and disease- specific cells. The therapeutic potential of small molecules and its validation in human neuronal cultures from familiar AD patients will be discussed.

Title: **A novel translational approach to Neurodegenerative diseases: A small peptide derived from neuronal cell cycle kinase (Cdk5) provides a protective and restorative role in neurodegenerative diseases like Alzheimer disease (AD).**

Keynote Speaker: **Harish C. Pant**

Chief, Cytoskeletal Protein Regulation Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892. USA.

During the course of our studies on the compartment specific phosphorylation of cytoskeletal proteins in the neurons, we discovered a novel kinase, Cdk5, a cell cycle like kinase, in the brain. Though it binds with cyclins, however, its activity is primarily restricted to neurons due to its binding and regulation by neuron specific molecules p35, p39 and p67 KDa molecular weight. Cdk5, by virtue of its tightly regulated, multifunctional role in neuronal development, migration, synaptogenesis, synaptic activity, memory / learning and survival. It targets a large number of different types of neuronal proteins and has emerged as a major player in nervous system function in health and disease. However, due to neuronal insults and stress (e.g., Aß, glutamate, oxidative, mutational, neuroinflammation and intra / extra cellular stresses), Cdk5 is hyperactivated and deregulated, induces a number of neurodegenerative disorders. Although our studies continue to unravel the role of Cdk5 in neurogenesis and synaptic function but our most exciting recent results have been related to its role in neurodegeneration and our success in developing compounds that protective and restorative to neurons from deregulated Cdk5 pathology, neuro-inflammation, and apoptosis in vitro and in AD and other neurodegenerative disease (ALS, ALS,PD) model mice. Hence, our current and future work include a major emphasis on the efficacy of our newly modified 24 aa peptide, TFP5, (carrying a fluorescent marker at the N-terminal end and a TAT PTD sequence at the C-terminal (to facilitate penetration into tissues) and pass blood brain barrier, as a therapeutic candidate for AD, ALS and PD using model mice. Currently, most therapeutic approaches targeting the deregulated Cdk5/p25 complex and other kinases in neurodegenerative disorders have focused primarily on drugs like roscovitine that inhibit kinase activity by interfering with the ATP binding domain of the kinase. Most of these drugs, however, lack sufficient specificity, since all kinases including cell cycle Cdks, are vulnerable at the ATP binding site targeted by drug molecules and are toxic. TFP5/TP5 inhibited hyperactive Cdk5/p25 and rescued cortical cells in vitro from abnormal AD-like phenotypes. It did this without affecting the function of the normal Cdk5/p35 without toxicity. In addition, the

Intraperitoneal injection (IP) of TFP5 ameliorated ALS and PD phenotypes in model mice. Precise regulation of synaptic integrity is essential for neuronal network connectivity and proper brain functions. The structural and functional changes of excitatory synapses are often accompanied by changes in dendritic spine number, shape and neurotransmitter receptor contents. These events are exclusively regulated during synapse development and subsequent plasticity in the adult brain. Aberrant dendritic spine morphology or surface abundance of neurotransmitter receptors are associated with nervous system disorders, with Alzheimer's disease, Parkinson's disease, schizophrenia, mental retardation and autism.

Studies from several laboratories have confirmed that Cdk5, plays an essential role in synapse development and functions. It can act as a positive and or negative regulator of synapse development and functions; that is highly dependent on the phosphorylation of specific substrates. In this talk, I will provide an increase in the dendritic spine number and TRVP1 channel density in the cultured rat cortical neurons treated with TFP5 /TP5 peptide compared to scrambled peptide. We also noted increase in the Rab11 positive recycling endosomal vesicles in the axons of TP5 treated cortical neurons. However, we did not observe these changes in scrambled or untreated cortical neurons. These studies elucidate the role of TP5/TFP5, in regulating the neuronal morphology and spine density of cultured rat cortical neurons, thus provide a protective and restorative role.

Title: **"Nutraceuticals: Opening new windows to future medicine in Alzheimer´s Disease"**

Local Speaker: **Nicole Cortes**
International Center for Biomedicine (ICC)

Alzheimer´s Disease (AD) is the most prevalent neurodegenerative disease worldwide, affecting deeply to society and world economy. The AD produces in the patients a progressive and severe cognitive damage, together with alterations in mood and behavior. Despite of the giant efforts to find a cure or a treatment for AD after more than 40 years of rigorous scientific research, the Food Drug Administration (FDA) has approved only 4 drugs to treat the disease, which only decrease the severity of some symptoms in a reduced group of patients. Considering this context, **nutraceuticals appear as a viable option** to improve the cognitive and behavioral skills affected in AD patients. Nutraceuticals are defined as natural nutritional products with strong bioactive properties that benefit human health. In this way, it has been demonstrated for example that curcumin as well as extracts of *Rosmarinus officinalis* and *Moringa oleifera* exert neuroprotection in different cellular and animal models of AD. Moreover, there is an advanced group of evidence-based nutraceuticals (EBNP) supported by preclinical studies and clinical trials. A novel natural product, the Andean Compound, a basis for the formula known as Brain Up-10® has shown significant beneficial properties in AD subjects. Its mechanism of action resides in its strong effect in blocking tau self-aggregation. Nowadays an advanced phase 2 randomized placebo controlled clinical trials is underway to validate it as an EBNP. We have also investigated a new molecule from grapes and berries called malvidin, showing its nutraceutical potential with overwhelming results in preventing tau aggregation, a trademark of AD. Thus, nutraceuticals emerges as a natural option, opening new possibilities to control AD (Research financed by Innova CORFO grants on High technology to the ICC)

Title: **"Innovative Biomarkers towards pre-symptomatic detection of Alzheimer's disease: A need for efficient therapeutic approaches"**

Local Speaker: **Dr. Andrea Gonzalez**
International Center for Biomedicine (ICC)

One of the biggest drawbacks to diagnose Alzheimer's disease (AD) is that currently there are no reliable biomarkers that allow detection at early stages (preclinical). Currently, biomarkers for AD are obtained mainly from cerebrospinal fluid (CSF) samples and using positron emission tomography (PET) imaging. However, CSF method is very invasive (since it requires a lumbar puncture) and PET scans are very expensive. Thus, the latter make these exams inaccessible to the elderly, and a routine procedure for the follow-up of patients is of utmost relevance.

Findings from our laboratory indicate that tau protein, used as a marker in CSF, is also present in platelets, which could be used as a biomarker. This is based on the fact that the platelet tau protein with the higher degree of oligomerization (HMWtau) has a high correlation with the cognitive status of patients, measured by neuropsychological tests and recently by MRI based on cerebral atrophy.

We have shown in the ICC Lab under leadership of Dr. Maccioni, that different anti-tau monoclonal antibodies are functional and recognize HMW-tau and low molecular weight (LMWtau) in western blot. The reason HMW/LMWtau significantly increases in AD patients as compared to controls due to a higher degree of tau oligomerization. Nevertheless, western blot is not a routine clinical laboratory technique, thus currently we are testing tau from plasma as a marker to be assessed by ELISA. Our anti-tau 51 monoclonal antibody recognizes tau from human plasma after precipitations with ammonium sulfate. In summary, we have developed an innovative biomarkers approach for early detection and as a diagnostic tool for Alzheimer´s disease.

Title: **Naturally occurring compound avoid oligomers formation via cysteine interactions**

Keynote Speaker: **Dr. Alberto Cornejo**
Universidad Andres Bello, Santiago, Chile

Neurodegenerative disorders including Alzheimer´s disease and Tauopathies involved hyperphosphorylated forms of tau protein in vivo. Tau protein physiologically participates in neuronal transport associated with microtubules. However, once tau became detached from microtubules, it starts to form toxic aggregates. Since oligomer´s toxicity reside in their β sheet content, we considered essential to avoid this type of secondary structure by using small naturally occurring compounds.
A naturally occurring compound was evaluated as tau inhibitor by ThT fluorescence, dot blot assays and total internal reflection fluorescence (TIRF). Our results suggest that a remodeling occurs after treatment of soluble oligomers. Moreover, by fluorescence labeling of cysteine inside of the microtubule-binding domain (4R), thus we showed a reduction of oligomers progression by inhibiting Cysteine interaction.

Title: **Neuroimmunomodulation and behavioral disorders in Alzheimer´s disease**

Keynote Speaker: **Prof. Dr. Ricardo B. Maccioni**

Professor of Neurology, Faculty of Medicine & Professor of Neuroscience, Faculty of Sciences, University of Chile. Director of the International Center for Biomedicine ICC. Member of Dana Alliance for Brain Initiatives, DABI.

Alzheimer's disease (AD) is a progressive neurodegenerative disease, characterized by behavioral disorders, loss of memory and cognitive impairment affecting more than 49 millions worldwide. Cumulative evidence shows that innate immunity participates in the pathogenesis of AD. According with our neuroimmunomodulation theory, microglial activation modifies the cross-talks between microglia and brain neurons. Thus, glial activation by the so called "damage signals" triggers a cascade of pathological events leading to hyperphosphorylation and oligomerization of the tau protein, associated with cognitive impairment. This activation depends on the type and intensity of the stimulus. The "big-bang" in AD seems to be the tau unfolding that lead to the explosive tau-tau self-aggregation In AD, a persistently active microglial condition could generate neuronal damage and neurodegeneration favored by ApoE4, causing the release of pathological tau toward the extraneuronal environment. Released tau would subsequently cause reactivation of microglial cells, thus promoting a positive feedback and generating continuous cell damage. However, from the pathophysiological point of view, AD is significantly more complex that just inducing a loss of memory. As initial events in the pathogenesis of this neurodegenerative disease, alterations in the dopaminergic pathway together with serotonin depletion in the elderly lead to late onset depression according with recent evidences. These events seem to occur together with immunomodulatory alterations that lead to tau oligomerization in the course of formation of neurofibrillary tangles. Interestingly, mood disorders are followed by neuroinflammatory processes and structural/functional alterations that lead to cognitive impairment in the context of AD (supported by Innova Corfo and the ICC).