1ª. ISN CAEN visit by the applicant to another laboratory

REPORT

Victor Bodart Santos, PhD student
Federal University of Rio de Janeiro, Brazill
Visitor at Tanz Centre for Neurodegenerative Diseases from University of Toronto – Toronto, Canada from November/2018 to March/2019

Dear Dr. Alessandro,

Begin the report thanking you for the excellent opportunity given to me by ISN and ratifying how much this experience contribute for my PhD and life. It is very important to emphasize how important is this ISN support, allowing students from countries where science is experiencing a difficult time, such as Brazil, to have a better opportunity in other countries. Due to ISN's support, I had the experience of working with Dr. Paul Fraser at the Tanz Center for Neurodegenerative Diseases, a center of excellence in neuroscience on Canada. In addition to a friendly personality and all the technical and financial support, I was able to learn a lot under Dr. Fraser's supervision and develop an innovative work.

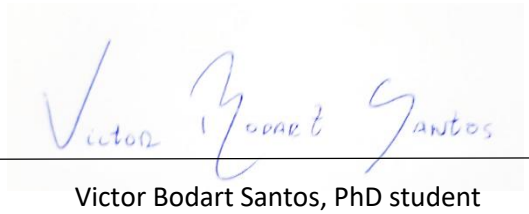
CAEN funds was used to fund my flight from Rio de Janeiro/Brazil to Toronto/Canada and the living expenses (accommodation, meals and transportation) during my stay in Toronto between November, 2018 and March, 2019.

The main purpose of my collaborative visit to Dr. Fraser was to harness the expertise and availability of transgenic animals to study the role of tau protein in neurodegenerative diseases such as Alzheimer's disease. With adaptations to the original design, due to the availability of animals and the opportunity to access samples from tauopathies patients, that is not a reality for me in Brazil, we evaluated in this study the role of brain-derived extracellular vesicles (EVs) from tauopathies in the propagation of tau pathology in a transgenic mice expressing human tau in the absence of murine tau (hTau/TauKO).

The EVs are nanomeric size particles secreted by cells in several tissues, and plays a key role on intercellular communication through the transfer of bioactive molecules like

RNA, proteins and lipids. From the post mortem brain cortex of patients with Alzheimer's disease (AD), fronto-temporal dementia (FTD) and progressive supranuclear palsy (PSP), we isolate (Fig. 1) and characterize the EVs as to their size, concentration, morphology, EVs markers and tau protein levels (Fig. 2). We then inject the vesicles into the hippocampus of 7-8-month-old hTau / TauKO transgenic mice (Fig. 3) to study the propagation of tau pathology. Our data indicate that infusion of EVs from patients with AD and FTD promote a memory impairments when these mices were evaluated in the novel object recognition test (NOR) (Fig. 4), in the Barnes Maze test (Fig. 5) and fear conditioning test (Fig. 6), but did not present anxious behavior when evaluated in the Zero Maze test (Fig. 7). Despite the memory loss, these animals do not exhibit a synaptic loss, but there is a tendency to increase phosphorylated tau levels in the hippocampus of animals injected with DA and FTD-EVs (Fig. 8).

In conclusion, we show for the first time that EVs derived from DA and FTD brains are enriched in tau protein and may promote memory impairment in hTau/TauKO transgenic mice. This highlights an important role of EVs in the propagation of tau pathology and points to a still under-explored field to understand how tau protein can propagate between different brain regions during the progression of tauopathies such as Alzheimer's disease.



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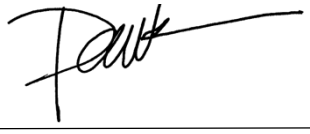

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