

## Report – ISN-CAEN Award Category 1A, April 2016 Round

**Awardee:** Rafaella Araújo Gonçalves da Silva

**Subject:** Alzheimer's Disease, Tau protein and diabetes

**Home laboratory:** Laboratory of Investigation of Alzheimer's Disease, Institute of Medical Biochemistry, Federal University of Rio de Janeiro, Brazil.

**Home Supervisor:** Dra. Fernanda G. De Felice

**Host Laboratory:** Tanz Centre for Research in Neurodegenerative Diseases, The Krembil Tower, University of Toronto, Canada.

**Host Supervisor:** Dr. Paul Fraser

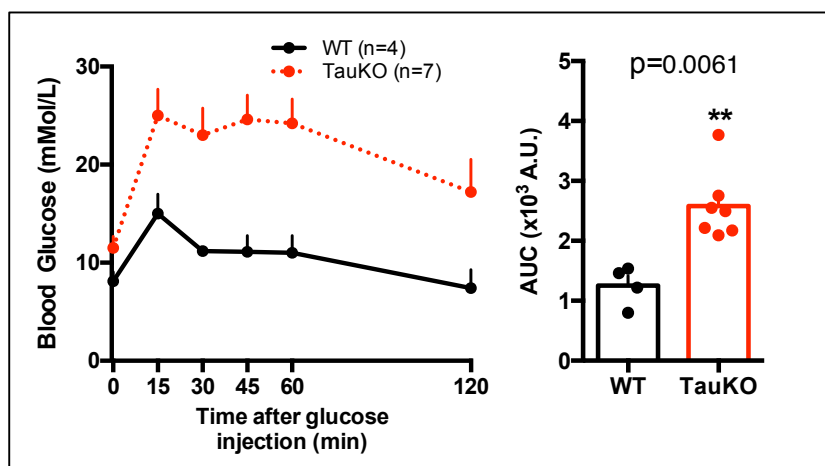
**Dates of Fellowship:** October 2016 to June 2017

I would like to thank the ISN-CAEN Award Committee for supporting my visit on Dr Fraser's laboratory which was of great importance for my career. From this experience a collaboration started between my lab in Brazil and Dr Fraser's lab at the The Krembil Tower, Toronto Western Hospital. During my stay in Canada I was able to perform a variety of experiments which greatly contributed to my MSc research project.

The period initially proposed was of 6 months which would be funded by the IUBMB and ISN fellowships. However, due to additional funding from my host lab in Canada I could extend my stay to a total of 8 months.

### • **Research proposal**

Considering the clinical and epidemiological evidences correlating Alzheimer's Disease (AD) and Type 2 Diabetes (T2D) in patients and animal models<sup>1; 2; 3; 4 5; 6 7</sup>, we initially proposed to investigate the molecular mechanisms underlying the correlation AD-T2D with focus on hypothalamic inflammation and peripheral metabolic alterations in a mouse model that expresses the wild-type tau protein (hTau) and develop tau pathology. Therefore, hypothalamic inflammation, impaired insulin signaling and peripheral metabolic dysregulation would be investigated in mice expressing human WT tau protein in the absence of murine tau. However, after the identification of glucose intolerance in the TauKO mice (the control of our hTau mice), we decided to explore this result and focus on the role of Tau protein deletion on peripheral glucose homeostasis.



**Figure 1. TauKO mice is glucose intolerant.** Blood glucose levels during Glucose Tolerant Test (GTT) performed after 4 hours fasting. Blood was collected at different time points (15,30,45,60,120 min) from tail incision after intraperitoneal (i.p.) injection of 1.5g/kg body weight of glucose.

- **Summary of the project developed in host lab**

Microtubule associated protein tau assist in polymerizing and stabilizing microtubules and tau loss of function has been particularly implicated in Alzheimer's disease<sup>10</sup>. Expression of tau outside the central nervous system, including skeletal muscle and pancreatic beta cells, is documented<sup>11</sup> and abnormally phosphorylated tau, a prominent hallmark of Alzheimer's pathology in the brain<sup>12</sup>, has been found in pancreas tissue of type 2 diabetes patients<sup>13</sup>. These findings suggest tau may correlate with impaired peripheral glucose homeostasis. It is known that constitutive deletion of tau in mice does not lead to lethality or neurodegeneration, presumably due to compensatory mechanisms in the brain<sup>14; 15; 16</sup>. However, the effects of tau on peripheral metabolic regulation is not known. In the present study, we investigated the role of tau in hypothalamic insulin signaling and peripheral metabolic parameters using a tau knockout mouse. Glucose and insulin tolerance tests were performed. Fasting plasma insulin and leptin were measured by Elisa. Levels of hypothalamic proteins components of insulin signaling pathway were quantified by Western Blot. The findings from this study demonstrate that at early age (4-5 months) systemic tau deletion leads to glucose intolerance, increased fasting plasma leptin levels and increased body weight. No changes in fasting plasma insulin were observed. At a later age TauKO mice becomes insulin resistant (1 year). These results suggest tau protein may play a role in whole body glucose homeostasis. In addition to the results above we also performed GTT and ITT with TauKO mice on High Fat Diet and we collected tissues for future biochemical analysis.

- **Chronogram of activities**

ACTIVITY	Previous 3 mon	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8
Breeding and aging of mice, and feeding HFD	X								
Mandatory Courses of Biosafety and Laboratory Animal Housing in the host institution + pilot experiments		X							
Behavioral experiments with 1 year old male mice (Glucose Tolerance Test, Insulin Tolerance Test and food intake) on Chow diet + euthanasia and tissue collection			X						
Biochemical analysis of hypothalamus from 1 year old mice			X	X					
<b>Group 1</b> - Behavioral experiments with 4 months old male mice (Glucose Tolerance Test, Insulin Tolerance Test and food intake) on Chow diet					X				
<b>Group 1</b> - Euthanasia and tissue collection of 5 months old male mice on Chow diet						X			
<b>Group 2</b> - Behavioral experiments with 4 months old male mice (Glucose Tolerance Test, Insulin Tolerance Test and food intake) on Chow diet						X			
<b>Group 2</b> - Euthanasia and tissue collection of 5 months old male mice on Chow diet							X		

Behavioral experiments with 7 months old male and female mice on HFD (Glucose Tolerance Test, Insulin Tolerance Test)					X				
Euthanasia and tissue collection of male and female on HFD (8 months old)						X			
Biochemical Analysis of collected tissue (5 months old male mice on chow diet)								X	X

- **Publication that may result**

- A manuscript with me as a co-author is submitted for review.
- A review with me as a co-first author is submitted.
- A second manuscript will be prepared with the remaining set of results I obtained in Dr. Paul Fraser's lab. To be able to finish this second part I will go back to Dr. Paul Fraser's lab for additional months this year.
- One chapter of my MSc dissertation in Brazil will cover all the data I obtained in Dr. Paul's Fraser lab.

- **References**

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**Lab members in my farewell lunch**

From left – Nadeeja (Postdoc), Rosemary (Technician), Myself, Zhilan (Technician), Kathy (Technician), Kyung (Technician), Feng (Technician), Dr. Anurag Tandon (Principal Investigator of another lab), Dr. Paul Fraser (Host Supervisor), Kanayo (Postdoc), Monica (Retired Technician).