PI: Tomas Guilarte

Grant Number: R01ES007062

Grant Title: Peripheral BDZ Receptor Biomarker of Neurotoxicity

Background/Context:
The main focus of this grant is to investigate Translocator Protein 18 kDa (TSPO) as a potential biomarker of neurotoxicity, neuroinflammation and neurodegeneration. Interestingly, Tomas has extended this investigation to also look at this as a biomarker of neuroinflammation/brain atrophy of former NFL players.

Key Translational Milestones

- Translocator protein 18 kDa (TSPO) is a biomarker of neurotoxicity, neuroinflammation and neurodegeneration
- Identification of TSPO interaction with NADPH oxidase (NOX2) that links the generation of reactive oxygen species (ROS) to the induction of an antioxidant response to maintain redox homeostasis (bacterial and plants?)
- Investigate protein as a biomarker of neuroinflammation/brain atrophy of former NFL players
- Studies in primary microglia from Nrf2 knockout mice will be crucial for understanding the role of Nrf2 as a transducer of the putative TSPO–NOX2 interaction for cell-autonomous protection from ROS and other toxic products generated by activated microglia.
- Testing of biomarker (Implied ?)
- Biomarker validation (Implied ?)
- Will ultimately explore the potential ability to detect neuro-degeneration prior to clinical expression of disease.

Starting Point:

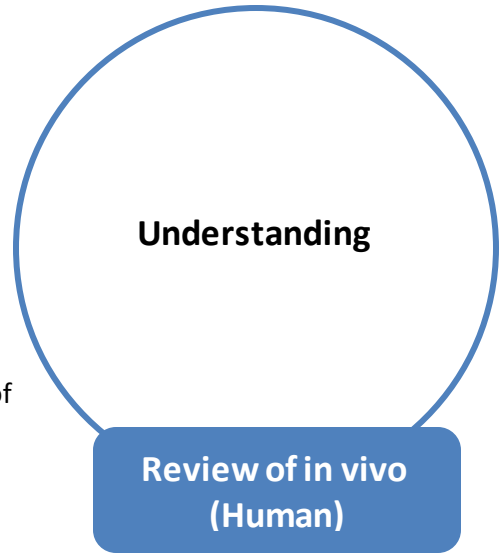
- Translocator protein 18 kDa (TSPO) is a biomarker of neurotoxicity, neuroinflammation and neurodegeneration.

Fundamental Science Interactions Ring:

Driver: Mechanistic understanding

Experimental Setting: Review of in vivo

Organism: Human



Timeframe: circa 2006-2014

Collaborators:

- Working group for renaming the PRB, with support by Novartis Pharmaceuticals
- JHU Neurotoxicology & Molecular Imaging Laboratory, Department of Environmental Health Sciences
- Australian Group

Citations:

V. Papadopoulos, *et al.* Translocator protein (18 kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. Trends Pharmacol. Sci., 27 (2006), pp. 402–409.

G-J. Liu, *et al.* The 18 kDa translocator protein, microglia and neuroinflammation. Brain Pathol., 24 (2014), pp. 631–653.

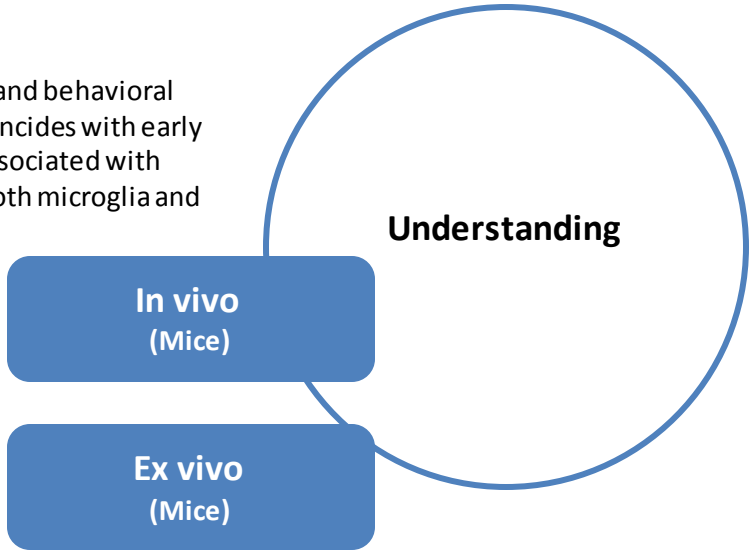
M-K. Chen, T.R. Guilarte. Translocator protein 18 kDa (TSPO): molecular sensor of brain injury and repair. Pharmacol. Ther., 118 (2008), pp. 1–17.

Translational Narrative:

What led to the next step?
How did the idea evolve?
Who was involved?
What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?
How did you know what to do next?

Translational Research Milestone 2:

- TSPO levels markedly increase prior to physical and behavioral manifestation of disease. TSPO upregulation coincides with early neuronal GM2 ganglioside aggregation and is associated with ongoing neurodegeneration and activation of both microglia and astrocytes.



Fundamental Science Interactions Ring:

Driver: Mechanistic understanding

Experimental Setting: In vivo, Ex vivo

Organism: Mouse

Timeframe: ? – 2015?

Collaborators:

- Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University
- Department of Psychiatry and Behavioral Sciences, Johns Hopkins Medical Institutions
- Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Medical Institutions

Citations:

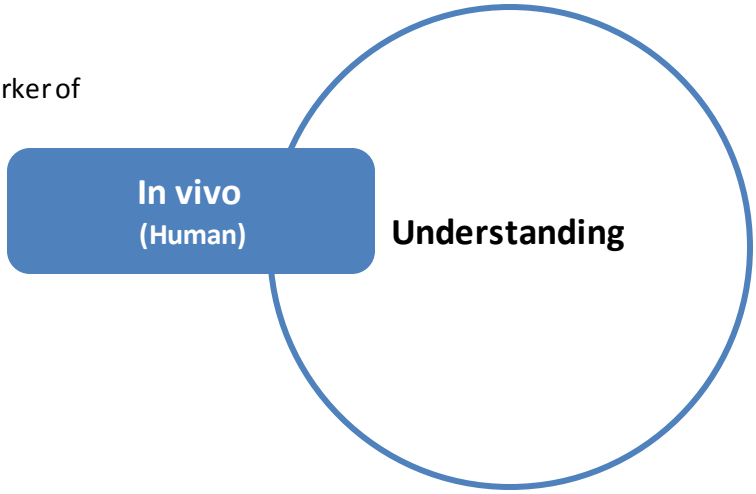
Loth et al. 2016. TSPO in a murine model of Sandhoff disease: presymptomatic marker of neurodegeneration and disease pathophysiology. Neurobiol Dis. 2016 Jan;85:174-86. doi: 10.1016/j.nbd.2015.11.001.

Translational Narrative:

What led to the next step?
How did the idea evolve?
Who was involved?
What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?
How did you know what to do next?

Translational Research Milestone 3:

- Future studies to investigate protein as a biomarker of neuroinflammation/brain atrophy of former NFL players



Fundamental Science Interactions Ring:

Driver: Mechanistic understanding

Experimental Setting: In vivo

Organism: Human

Timeframe: Still to be done

Collaborators:

Source:

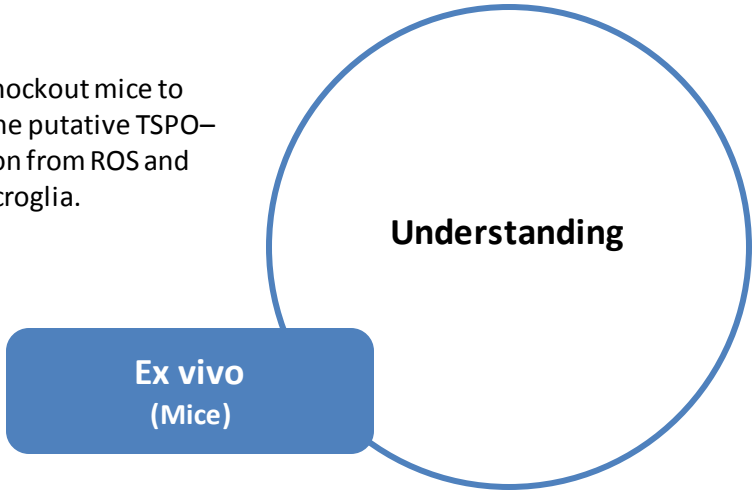
Coughlin J.M., Wang Y., Munro C.A., Ma S., Yue C. et al. (2015). Neuroinflamation and brain atrophy in former NFL players: An in vivo multimodal imaging study. Neurobiology of Disease; 74:58-65. doi: 10.1016/j.nbd.2014.10.019.

Translational Narrative:

What led to the next step?
How did the idea evolve?
Who was involved?
What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?
How did you know what to do next?

Translational Research Milestone 4:

- Future studies in primary microglia from Nrf2 knockout mice to understand the role of Nrf2 as a transducer of the putative TSPO–NOX2 interaction for cell-autonomous protection from ROS and other toxic products generated by activated microglia.



Fundamental Science Interactions Ring:

Driver: Mechanistic understanding

Experimental Setting: Ex vivo

Organism: Mice

Timeframe: Still to be done

Collaborators:

Source:

Grant proposal

Translational Narrative:

What led to the next step?

How did the idea evolve?

Who was involved?

What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?

How did you know what to do next?

Translational Research Milestone 5:

- Future studies might include some controlled testing of the biomarker in humans.

Other Controlled Testing

Controlled Testing Ring: Other controlled testing

Timeframe: Still to be done

Collaborators:

Source:
Grant proposal

Translational Narrative:
What led to the next step?
How did the idea evolve?
Who was involved?
What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?
How did you know what to do next?

Translational Research Milestone 6:

- Would this project ultimately pick up biomarker validation as it progresses?

Biomarker, Screen, Assay Validation

Real World Testing Ring: Biomarker validation

Timeframe: Still to be done

Collaborators:

Source:
Grant proposal

Translational Narrative:
What led to the next step?
How did the idea evolve?
Who was involved?
What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?
How did you know what to do next?

Translational Research Milestone 6:

- Potential ability to detect neurodegeneration prior to clinical expression of disease.

Practice Ring: Clinical Guidelines

Clinical Guidelines

Timeframe: Still to be done

Collaborators:

Source:
Grant proposal

Translational Narrative:
What led to the next step?
How did the idea evolve?
Who was involved?
What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?
How did you know what to do next?