1-1-2015

Learning, Memory and Cognitive Studies in a Mouse Model of Tyrosinemia Type I

Gordon MacGregor
University of Alabama in Huntsville

Title

Learning, Memory and Cognitive Studies in a Mouse Model of Tyrosinemia Type I

Faculty and Research Mentor

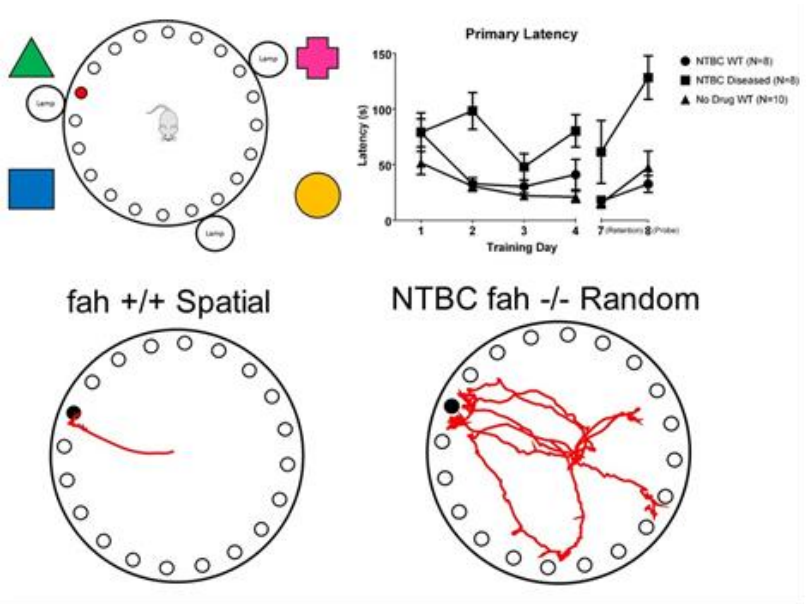
Mentor: Gordon MacGregor PhD

E-mail: gordon.macgregor@uah.edu **Phone:** 256-824-4925

Contact: Dept. of Biological Sciences, 301 Sparkman Drive, SC 369-H, Huntsville, AL, 35899

Project Summary

Tyrosinemia Type 1 (TT1) is an autosomal recessive disorder that is caused by a deficiency of the FAH enzyme that serves as the terminal enzyme in the tyrosine catabolic pathway. This deficiency results in the buildup of toxic metabolites that can eventually cause death without treatment. The only pharmacologic treatment currently available for those with TT1 is Nitisinone (NTBC), which blocks the tyrosine catabolic pathway above the enzyme deficiency. This drug saves the lives of children with TT1, yet has recently been associated with neurocognitive changes and learning deficits. Based on this association, we are using mice as a model to unravel to contribution of the disease itself or the treatment, NTBC, to these alterations in cognitive function. We will use classic models to study mouse learning, memory and anxiety, such as elevated plus maze, Barne's maze, open field maze, hole-board and social interaction analysis. We will also quantify any differences in neurotransmitter levels in mouse urine and plasma.



Tyrosinemia type I mice have altered spatial learning and memory in the Barnes maze model of testing.

Student Duties

The student is critical to this project as firstly, they will learn correct animal handling skills. The mice need to be comfortable with the person who usually works with them, so that they are not excessively stressed when it is time to be tested. The mice should react solely to the maze and not to the stress invoked by unfamiliar handling. One of their daily duties is to check on the mice, confirm their well-being, and have them be familiar with handling. Secondly, the student will genotype the knock-out mice litters. This will involve DNA extraction, PCR, agarose gel electrophoresis, and restriction nuclease fragment analysis. The third and largest part of the students duties will be for them to develop their own protocols for the testing of mouse cognitive abilities, anxiety and memory, using several mouse tests and mazes and to develop tests of mouse gait and neuro-motor skills. The tyrosinemia mouse, and NTBC treated mouse have not been studied in this way before so all data will be novel. As well as developing the testing protocols, the student will analyze their own data, determine its significance and present it correctly for publication.

The student will learn to use state of the art Noldus Ethovision animal tracking and analysis software. The student will be provided with an individual copy of Graphpad Prizm software for data plotting and analysis. The student will perform ELISA quantifications for neurotransmitters in mouse plasma and urine and use 96 well fluorescence and absorption spectrophotometer plate readers.

Mentor Supervision and Interaction

My goal is to allow the student independence enough to develop, perform and analyze their own experiments. I will guide them, and point them in the correct direction and solve problems that they can't resolve on their own. I will be in the lab fulltime on a daily basis for interaction and bouncing ideas off. I aim to introduce the students to research methodology, correctly performed data analysis, and techniques for correct amalgamation of their data for presentation in the form of a poster or oral presentation for use at a conference.

This project will require full time presence in the lab for 32-40 hours per week, for 10-12 weeks.