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## **Metabolomics to Identify Neurological Modifying Metabolites in the Plasma and Urine of a Mouse Model of Tyrosinemia Type I**

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**METABOLOMICS** to Identify Neurological Modifying Metabolites in the Plasma and Urine of a Mouse Model of Tyrosinemia Type I.

**A Proposal for the Research and Creative Experience for Undergraduates (RCEU) Program, Summer 2017**

**Faculty Sponsors:** Bernhard Vogler, PhD, Chemistry, Gordon MacGregor, PhD, Biology. Beth Barnby, DNP, Nursing.

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***Project Summary:***

Introduction: Tyrosinemia Type 1 (TT1) is a genetic inborn error of metabolism affecting children throughout the world. This metabolic abnormality causes the buildup of toxic metabolites that have a catastrophic effect on the child's health, precipitating painful neurologic crisis and death without treatment. The drug used to treat TT1 is nitisinone (NTBC) and is marketed as Orfadin®. This drug is life saving for children with TT1, but has been associated with neurocognitive changes. Elevations of tyrosine can have neurological effects as these amino acids are precursors for the monoamine neurotransmitters serotonin, dopamine and norepinephrine. Tyrosine also competes with phenylalanine for reabsorption from the kidney and uptake by the brain, so high tyrosine levels can lead to low phenylalanine levels, which is also likely to cause neuro-behavioral symptoms.

***Research Plan:***

Our initial observations from mouse maze studies showed a robust alteration in learning, memory and behavior when the WT & TT1 mice are placed on NTBC. Here we plan to analyze the mouse plasma and urine, to look for altered levels or presence of a potential neuromodulatory metabolite that is altered in the treated or TT1 disease mice. We have preliminary NMR data indicating the presence of a number of small molecule compounds. We also have data showing increases in dopamine levels in the mouse plasma, which was acquired by ELISA, which is extremely expensive and time consuming, and can only measure one metabolite at a time. We propose to use HPLC MS, for quantitation purposes, and a continuation of the NMR studies(urine) to identify and quantify additional metabolic compounds and neurotransmitters. Most of the identified compound have been acquired, so that quantitative studies by both NMR and MS seem to be reasonable. This would allow to establish a difference in concentration levels for the key metabolites between the groups of mice. Thus we will have a chance to identify a therapeutic target to treat and address these issues, and re-evaluate the mice in the cognitive behavioral tests. Standard procedures will be adapted from protocols found at Metabolomics workbench (<http://www.metabolomicsworkbench.org>). These standard protocols need to be established and modified according to our local needs; for instance sample volume needs to be optimized; stability of sample between taking the sample from animal and measurement needs to be established. Storage capabilities need to be explored.

***Student Duties:***

Run NMR and MS samples; identify components and monitor differences between different samples.

***Tentative plan for the 10 week schedule:***

- week 1/2: familiarization with, LC-MS and NMR.
- week 3/4: building of reference data files, establishing concentration curves .
- week 5/6: familiarization with VNMRJ, MestreNova (NMR), and Tracefinder (MS) for data analysis.
- week 7/8: analysis of data sets.
- week 9/10: refine measurements.

***Manuscript preparation:***

Dr. Vogler encourages all undergraduate student researchers to write up their results in the form of a manuscript for publication. The RCEU participant, under the supervision of Dr. Vogler, will help prepare the manuscript(s), which may include data from other undergraduate or graduate students.

***Expected Student Background :***

Students should have good background in General Chemistry, knowledge of Organic Chemistry is advantageous, so typically students with a major in Biology, Chemistry, and or Chemical Engineering should be ok. Previous exposure to analytical instrumentation is a clear benefit. This is a continuation of a RCEU 2016 project.

***Expected results and deliverables:***

The student will be exposed to important instrumental techniques such as mass spectrometric analysis, NMR analysis, preparation of samples in smallest concentrations, error analysis, literature studies. Exposure to state of the art instrumental techniques will greatly enhance any students' career chances in chemistry or related disciplines. Instrumental skills are highly regarded.

***Faculty Supervision and Mentoring:***

NMR and LC-MS measurements will be supervised by Dr. Vogler. Manuscript preparation will be supervised by Dr. Vogler. We will hold regular group meetings weekly. The student will have access to the instructor at least once a day.

***Rational to choose the student:***

Flora Eason has completed all of the coursework relevant for this research topic. I know her since this summer, when she took Organic Chemistry II. Subsequently we engaged in an Honors paper about metabolic pathways that Flora completed this semester. I am very much looking forward to work with her in the summer.