

2023 NEOMED Summer Research Fellowship Program

- 1. Title:** TGR5 & Alcohol-associated liver disease
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Location: NEOMED, Department of Integrative Medical Sciences, Laboratory F-205A
- 2. Abstract:** Bile acids are the natural ligand for Takeda G protein-coupled receptor 1 (TGR5), an anti-diabetic and anti-inflammatory receptor expressed in the liver, intestine, and brain. It is also a potential therapeutic target for obesity, non-alcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (AALD). *Tgr5^{-/-}* mice have significantly increased expression of fibroblast growth factor 21 (FGF21) upon administration of alcohol via unknown mechanisms. FGF21 is a growth factor involved in suppression of carbohydrate consumption, including ethanol and sugar. FGF21 was shown to be induced after alcohol consumption in rodents and primates/humans, and administration of FGF21 significantly reduces alcohol consumption. However, it is unknown whether the increased Fgf21 in *Tgr5^{-/-}* mice affects alcohol consumption or nutrient preference. The aim of this study is to determine the role of TGR5 in FGF21 signaling, and to determine if *Tgr5^{-/-}* mice have altered preference for ethanol consumption.
- 3. Significance:** Our data indicates that in *Tgr5^{-/-}* mice, alcohol induces changes in fibroblast growth factor 21, a hormone involved in mediating preference for carbohydrate and ethanol consumption. *Tgr5^{-/-}* mice also have changes in leptin signaling, involved in the control of food intake and satiety, in the white adipose, liver, and brain, though the mechanisms by which this occurs are unknown. Studying how TGR5 is involved in ethanol and nutrient preference could lead to novel therapeutic targets for metabolic syndrome or AALD.
- 4. Goals and Objectives:** The proposed research will further uncover the role of FGF21 and TGR5 in alcohol consumption and nutrient preference. The goals for the summer research student are to learn scientific technique and experimental design, data analysis and interpretation, and to demonstrate professional presentation of scientific results.
- 5. Research Methods:** Wild type control or *Tgr5^{-/-}* mice will be subjected to 2-bottle-choice study (10% ethanol or water control), and tissue will be collected for: qPCR to determine changes in gene expression, Western blotting to determine changes in protein expression, lipid and bile acid analyses, and tissue histology.
- 6. Data Analysis:** Appropriate statistical tests (Student's *t*-test, one-way ANOVA, etc.) using GraphPad Prism Software will be performed to determine statistical significance ($p < 0.05$).
- 7. Contribution of Findings:** It is expected that the findings obtained from this project will lead to better understanding of the role of TGR5 signaling under normal and pathophysiological conditions and will be an instrumental base in further studying the role

of TGR5 and FGF21 liver injury, nutrient preference, and alcohol consumption during the pathogenesis of AALD.

8. Student Fellow Training/Mentoring Plan: The training plan for the student encompasses individual and group mentorship from Dr. Ferrell (mentor), postdoctoral fellow, senior lab manager and a lab technician who will be available to help instruct the student learn the techniques necessary to complete this research. The student will become familiar with the research topic by reading primary and review journal articles. Basic lab techniques will be introduced through one-on-one instruction and will progress to independent work when appropriate. In addition to lab work, the student will be expected to keep records of the experiments and will learn to interpret the data collected. These results will be discussed with the mentor as necessary and during weekly lab meetings. Additionally, lab members participate in biweekly Diabetes, Obesity, and Metabolism Research Focus meetings, which include data and journal article presentations by graduate students, post-docs and staff. The student will attend these meetings and will have the opportunity to present research results at the end of training program. Lastly, the student will prepare and present a poster of their work at the Summer Research Fellow Poster Day. All the resources required to complete this work are available, and the student will receive laboratory safety training. The research will be conducted at NEOMED in F-205A.