2026 NEOMED Summer Research Fellowship Program

1. Title: TGR5 and FGF21 in altered sugar preference and associated metabolic outcomes.
PI: Dr. Jessica Ferrell, PhD; jfrancl@neomed.edu; x6468; Assistant Professor
Location: NEOMED, Department of Biomedical Sciences, Laboratory F-205A

2. Abstract: Takeda G protein-coupled receptor 1 (TGR5) is a receptor activated by bile-acids endogenously, known for its anti-diabetic and anti-inflammatory properties. TGR5 is expressed in the liver, intestine, and brain and represents a potential therapeutic target for obesity, metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (AALD). *Tgr5*$^{-/-}$ mice have significantly increased expression of fibroblast growth factor 21 (FGF21) upon administration of alcohol. These mice may also have altered leptin and adiponectin signaling from brain. FGF21 is a liver-produced hormone that is induced by carbohydrate consumption 9including ethanol and sugar), which negatively feeds back to the brain to suppress of carbohydrate consumption. We previously demonstrated that voluntary alcohol consumption is reduced in *Tgr5*$^{-/-}$ mice, possibly due to highly elevated FGF21. The aim of this study is to determine if FGF21 is upregulated in *Tgr5*$^{-/-}$ mice exposed to voluntary drinking of sucrose-water, if it will contribute to a reduction in their sweet-taste preference through canonical FGF21 signaling.

3. Significance: It has been reported that alcohol preferring animals tend to consume more sweet solutions. As FGF21 is induced by both sugar and alcohol consumption and acts to inhibit further intake, this study will determine if elevated FGF21 in *Tgr5*$^{-/-}$ mice reduces sweet taste preference alongside alcohol consumption. We will use mice models with voluntary intermittent access to sucrose water with and without alcohol. These voluntary drinking models will portray alcoholic human-like drinking behavior which can be a valuable tool to investigate the role of TGR5 and FGF21 in controlling human drinking and sweet taste preferences, and the metabolic consequences.

4. Goals and Objectives: The proposed research will further uncover the role of TGR5 in nutrient preference. The goals for the summer research student are to learn scientific techniques and experimental design, data analysis and interpretation, and to demonstrate professional presentation of scientific results.

5. Research Methods: Different cohorts of chow diet fed wild type (WT) and *Tgr5*$^{-/-}$ female mice will be subjected to an established 2-bottle-choice protocol with intermittent access of either 1% sucrose or 1% sucrose+10% ethanol along with water control for 4 weeks in the following manners:
   - WT and *Tgr5*$^{-/-}$ female mice with 1% sucrose solution or water control (sucrose given every other day).
   - WT and *Tgr5*$^{-/-}$ female mice with 1% sucrose mixed with 10% ethanol or water control (ethanol mixed with sucrose given every other day).

Liver, white adipose, brown adipose, ileum, colon and brain tissues (hypothalamus, prefrontal cortex, hippocampus, nucleus accumbens) will be collected for: qPCR to determine changes in liver and

brain gene metabolism, Western blotting to determine changes in protein expression, and serum analysis of metabolism (lipids, AST, ALT, etc.)

6. Data Analysis: Appropriate statistical tests (Student's *t*-test, one- and two-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 liver injury, nutrient preference, and alcohol consumption during the pathogenesis of AALD.

8. Student Fellow Training/Mentoring Plan: The student will complete safety and lab training modules prior to the start date. The training plan for the student encompasses individual and group mentorship from Dr. Ferrell (mentor), and Ph.D. students who will be available to help instruct in 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. This work will be conducted at NEOMED in F-205A.