Dr. William Blaner

SUMMARY
This exploratory project will test the hypothesis that chronic alcohol consumption impairs the thermogenic capacity of brown adipose tissue (BAT), and that this impairment is associated with alcohol's effect on BAT retinoid metabolism. The project has two Specific Aims, the first is designed to assess the functional impairment associated with chronic alcohol consumption on BAT, and the second will provide mechanistic insight into the effects of alcohol in this tissue. The results of this project will be of broad significance to 3 research areas: research on alcoholism, BAT physiology, and retinoid homeostasis.

The concept that BAT has physiological functions in adult humans represents a paradigm shift in the field of BAT research, and has led to an increased interest in this hitherto underappreciated tissue. Our preliminary data reveal that chronic alcohol consumption is associated with a dysregulation of body temperature maintenance, as well as a very marked decrease in BAT mass. In Specific Aim 1 the functional consequences of chronic alcohol consumption on BAT thermogenesis will be systematically investigated. Through a series of alcohol-feeding studies, we will assess the effects of alcohol-feeding on BAT morphology and function. The thermogenic capacity of alcohol-fed mice will be tested using 2 established techniques: responsiveness to cold exposure, and responsiveness to a norepinehprine challenge. We expect to establish that chronic alcohol consumption has a negative impact on the thermogenic capacity of BAT in adult mice.

While Specific Aim 1 is designed to characterize the effect that alcohol feeding has on BAT function, Specific Aim 2 is designed to provide a mechanistic insight into this effect. Specifically, in Specific Aim 2 we will test the hypothesis that alcohol-induced dysregulation of retinoid metabolism contributes to alcoholinduced alterations in BAT physiology. This hypothesis has its origins in the established effects that retinoids have on BAT differentiation and function, as well as our preliminary data which indicates that BAT of alcohol-fed mice has altered tissue retinoid levels, as well as changes in the gene expression levels of genes important in retinoid metabolism. We plan to undertake a comprehensive analysis of retinoid metabolism in BAT of alcohol-fed mice; we will also perform alcohol-feeding experiments in which the dietary retinoid content has been altered. We expect that the data obtained from these experiments will confirm our hypothesis that alcohol consumption disrupts BAT retinoid homeostasis, with a consequent effect on BAT function.

In summary, the research proposed in this R21 application will explore the novel concept that chronic alcohol consumption affects the body's ability to produce heat through its effect on BAT. The data generated regarding these innovative hypotheses will impact general concepts regarding the effects of alcohol consumption on tissues other than the liver (specifically BAT), as well as provide mechanistic understanding of these changes.