**Metabolomic profiling of influenza: a 2009 pandemic H1N1 influenza in lean and obese mice (genetically-induced obesity)**

Metabolomics Analysis: RTI RCMRC

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**Abstract:**

During the 2009 H1N1 influenza pandemic outbreak, obese individuals were reported to be at greater risk for morbidity and mortality from pandemic infection. However, the mechanisms contributing to greater influenza severity in infected obese individuals remain unclear. Given that one in ten individuals is obese, and worldwide influenza outbreaks are a consistent public health burden, garnering a better understanding of the pathways and mechanisms contributing to greater influenza severity in the obese is essential for limiting influenza infection mortality in this at-risk population. Closely paralleling pH1N1 infection outcome in humans, obese mice exhibit increased morbidity and mortality following pH1N1 infection. In mice, obesity impairs the function of natural killer cells, dendritic cells, macrophage, B cells and memory T cells. Further, several analyses of lung antiviral responses revealed that obese mice have greater lung damage, lung immune cell infiltration and impaired lung healing after infection. Nevertheless, it remains unclear how altered immune cell function contributes to greater lung damage and increased infection severity in obese mice. This study utilized metabolomics as a novel method to dissect the metabolic consequences of obesity on the immune response to pH1N1 infection, where we compared metabolic profiles of lung-specific and peripheral samples from uninfected and infected lean and obese mice during early and late phases of influenza immunity. In addition to using metabolomics for generating mechanistic hypotheses and guiding future research, we propose to use metabolomics as a potential diagnostic tool for human influenza virus infection in non-invasive biofluids. Taken together, this proposal will provide novel information regarding the enhanced pathogenesis of influenza infection in the obese and directly translational information that can be applied to modifying clinical approaches and methods of infection treatment in the obese.

In addition to the dietary studies (see BECK\_Lung-Diet\_RP), a genetic model of obesity was utilized to strengthen analysis by eliminating effects of differences in the diets and focusing only on the impact of obesity. In this genetic model of obesity, leptin receptor signaling is disrupted in the hypothalamus, resulting in chronic hyperphagia and ultimately obesity. At approximately 15 weeks of age, lungs from uninfected and day 8 pH1N1 infected LepRHfl/fl (lean) and LepRH-/- (obese) mice were obtained for metabolic profiling (n=5-6 per group, see BECK\_Lung-Genetic\_RP). Additionally, urine samples at D0 and at D2 from a subset of LepRHfl/fl and LepRH-/- mice were collected from the same mice on both days.

This metabolomics study was conducted to provide data on the metabolic changes differentiating the response to pandemic influenza A (pH1N1) infection in mice that are genetically lean or genetically obese. Information about the metabolomic profile of urine from mice who are genetically lean or obese will be used to determine if metabolomic analysis of non-invasive biofluids can reveal a unique metabolic signature that reflects disease processes in the lung and influenza lethality.

The data required for the metabolomics analysis can be found in the accompanying files:

Procedures: 1. BECK\_Urine-Genetic\_HILIC Metabolomics Procedure.docx

Study Design Table: 2. BECK\_Urine-Genetic\_HILIC Study Design table.xlsx

Metadata: 3. BECK\_Urine-Genetic\_HILIC MetaData and Analytical Metadata.xlsx

Processed Data: 4. BECK\_Urine-Genetic\_HILIC Phenotypic and Normalized Data.xlsx

Raw Data: 5. BECK\_Urine-Genetic\_HILIC Raw LC-MS Data.xlsx

Archived Raw Data: 6. BECK\_Urine-Genetic\_HILIC Zipped LC-MS Data.xlsx