**CNS and peripheral metabolomics of calorie restriction in a mouse model of Alzheimer’s disease – a RTI RCMRC Pilot Study**

Metabolomics Analysis: NIH Eastern Regional Comprehensive Metabolomics Resource Core (RTI RCMRC)

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**Abstract:**

Alzheimer’s disease (AD) is a devastating neurodegenerative disorder that robs people of their memory and cognitive function. Currently, no successful treatment or preventative measure exists for AD. Calorie restriction (CR) is a dietary regimen posited to suppress genetic programs of aging and reduce AD-related pathology. CR is known to enhance longevity and mitigate aging phenotypes in multiple model species. Mechanisms underlying the benefits of CR remain unknown, particularly in areas of the brain selectively vulnerable to age-related AD pathology such as the hippocampus, a region crucial for learning and memory. Moreover, AD pathology can be influenced by changes in diet, metabolism, and immunity, indicating that factors distant from the brain may play a role in pathogenesis. The intestinal microbiota, composed of trillions of microbial cells, influences host metabolism, immunity, and cognitive function, and is posited to be linked mechanistically to AD pathobiology, but a specific role remains to be adequately tested. We hypothesize that mechanisms underlying the benefits of CR are cell-type and organ specific, involving the gut-brain microbiome throughout the lifespan, this requiring subregional analysis in the brain, as well as coordinated assessments of key peripheral targets including the liver, fecal pellets, and plasma. Thus, CR is proposed to be a viable treatment option that may ameliorate the development of AD-related pathology, and importantly, reveal mechanisms that attenuate age-related expression changes in vulnerable cells.

This pilot metabolomic study will evaluate brain specimens from an established mouse model of AD, the Tg2576 mouse model of cerebral amyloid overexpression (APP), in comparison to their non-transgenic (NTG) littermates. These animals were either on a CR or *ad libitum* (AL) diet, and specimens were collected at two time points (5 and 15 months of age). Tissue from this cohorts of mice have already undergone microbiome analysis, and await coordinated brain and peripheral tissue assessments. Future analysis will include metabolomics, RNA-seq, and microarray data to assess the gut-brain microbiome system in neurodegenerative disorders.

**Sample Description:**

A total of 71 coded brain samples were shipped to the NIH RTI-RCMRC on dry ice and immediately stored at -80 °C after being logged in for metabolomics analysis.

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

Procedures: 1. GINSBERG Brain Metabolomics Procedures.docx

Study Design Tables: 2. GINSBERG Brain Metabolomics Study Design Table.xls

Metadata: 3. GINSBERG Brain Metabolomics METADATA.xlsm

Processed Data: 4. GINSBERG Brain Metabolomics Normalized Binned Data.xlsx

Raw Data: 5. GINSBERG Brain Metabolomics NMR Raw Data.zip

**Notes:**

Full sample preparation and analysis procedures are available in the accompanying document entitled **1. GINSBERG Brain Metabolomics NMR Procedures.docx**.

Descriptions of abbreviations for factors are available in the Variable Dictionary in the accompanying file no. **2. GINSBERG Brain Metabolomics NMR Study Design Table.xls**.

The phenotypic and normalized data are available in the accompanying files: **4. GINSBERG Brain Metabolomics NMR Normalized Binned Data.xlsx** for normalized binned NMR data. Sample ID and factors can be found in the first 5 columns and other columns in the spreadsheet contain sample metadata and the normalized binned data. If the statistical program does not allow variable names to begin with a number then add a prefix to the column names, for example, bin\_8.98 instead of 8.98.

The Sample ID serves as the unique identifier (Graphical ID) of the individual samples and is used as the NMR folder name in the raw NMR data file **5. GINSBERG Brain Metabolomics NMR Raw Data.zip**.