Plan Overview

*Title:* Targeting Hepatic Mitochondrial Oxidation to Treat NAFLD, NASH and T2D

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*Affiliation:* Yale University (yale.edu)

*Funder:* National Institutes of Health (nih.gov)

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*Template:* NIH-Default DMSP

**Project abstract:**

Type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD) are emerging as two of the most critical global health challenges of the 21st century. NAFLD is estimated to affect up to one third of the general population, and NAFLD is nearly universally present in patients with T2D, with 75-100% of participants demonstrating hepatic steatosis, and with 50% and 19% demonstrating nonalcoholic steatohepatitis (NASH) and cirrhosis, respectively. Furthermore, NAFLD represents the most common cause of liver disease in children and adolescents. Studies by our group and others have shown a strong relationship between NAFLD, hepatic insulin resistance and T2D, however the cellular mechanisms that lead to hepatic insulin resistance and increased gluconeogenesis remain to be established. The studies proposed in this grant build on our previous studies that have shown that reduction of hepatic fat content through enhancement of hepatic mitochondrial lipid oxidation can reverse hepatic insulin resistance and diabetes in rodent and nonhuman primate models of NAFLD, NASH and T2D. The **Overarching Aims** that will be addressed in this grant will be to determine if rates of hepatic mitochondrial oxidation are altered in NAFLD, NASH and T2D and whether promoting chronic increases in rates of hepatic
mitochondrial fat oxidation by means of a chronic glucagon infusion delivered by minipump will reduce hepatic steatosis and hepatic insulin resistance in individuals with NAFLD. To address these questions we will apply a novel Positional Isotopomer NMR Tracer Analysis (PINTA) method that we have recently developed to: i) Assess rates of hepatic mitochondrial oxidation, pyruvate carboxylase flux and hepatic ketogenesis in participants with NAFLD, NASH and type 2 diabetes, ii) Assess the acute effects of a physiological increase in plasma glucagon concentrations, both in the presence and absence of compensatory hyperinsulinemia, on rates of hepatic mitochondrial oxidation, pyruvate carboxylase flux and hepatic ketogenesis in control and NAFLD participants and iii) Assess the effects of chronic glucagon treatment on rates of hepatic mitochondrial oxidation, pyruvate carboxylase flux, hepatic ketogenesis, hepatic fat content and hepatic insulin sensitivity in individuals with NAFLD. Taken together the results of these studies will provide important new insights regarding the role of altered hepatic mitochondrial function in the pathogenesis of NAFLD, NASH and T2D, which in turn will have important implications for the development of novel liver-targeted mitochondrial uncoupling therapies aimed at increasing hepatic mitochondrial fat oxidation to treat NAFLD, NASH and T2D, which are currently being evaluated in Phase 2b trials. The present study will also provide critical information regarding the acute and chronic effects of glucagon on hepatic mitochondrial oxidation, hepatic gluconeogenesis, hepatic insulin sensitivity and hepatic fat metabolism which has important implications for dual GLP-1/glucagon agonists and triple GLP-1/GIP/glucagon agonists which are now being evaluated in clinical trials for treatment of obesity, NAFLD, NASH and T2D.

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Targeting Hepatic Mitochondrial Oxidation to Treat NAFLD, NASH and T2D

Data Type

Types and amount of scientific data expected to be generated in the project: 

Summarize the types and estimated amount of scientific data expected to be generated in the project.

Describe data in general terms that address the type and amount/size of scientific data expected to be collected and used in the project (e.g., 256-channel EEG data and fMRI images from ~50 research participants). Descriptions may indicate the data modality (e.g., imaging, genomic, mobile, survey), level of aggregation (e.g., individual, aggregated, summarized), and/or the degree of data processing that has occurred (i.e., how raw or processed the data will be).

We will generate semi-targeted metabolomics and metabolic flux data, as well as physiological outcomes related to liver mitochondrial metabolism via the following methods: GC-MS, LC-MS/MS and NMR, COBAS, 1H MRS. We expect to generate the following data file types and formats during this project: .xlsx and .pzfx files.

Scientific data that will be preserved and shared, and the rationale for doing so: 

Describe which scientific data from the project will be preserved and shared and provide the rationale for this decision.

Appropriate measures will be used for data de-identification and sharing, and informed consent forms will reflect those plans. In this proposed project, the cleaned, item-level spreadsheet data for all variables will be shared openly, along with example quantifications and transformations from initial raw data. Final files used to generate specific analyses to answer the Specific Aims and related results will also be shared. The rationale for sharing only cleaned data is to foster ease of data reuse.

Metadata, other relevant data, and associated documentation: Briefly list the metadata, other relevant data, and any associated documentation (e.g., study protocols and data collection instruments) that will be made accessible to facilitate interpretation of the scientific data.

Documentation and support materials will be compatible with the clinicaltrials.gov Protocol Registration Data Elements.

Related Tools, Software and/or Code
State whether specialized tools, software, and/or code are needed to access or manipulate shared scientific data, and if so, provide the name(s) of the needed tool(s) and software and specify how they can be accessed.

The data obtained from this study will not require the use of specialized tools to be accessed or manipulated.

**Standards**

State what common data standards will be applied to the scientific data and associated metadata to enable interoperability of datasets and resources, and provide the name(s) of the data standards that will be applied and describe how these data standards will be applied to the scientific data generated by the research proposed in this project. If applicable, indicate that no consensus standards exist.

Data will be stored in common and open formats, such as .xlsx and .pzfx files. Information needed to make use of this data along with references to the sources of those standardized names and metadata items will be included wherever applicable.

**Data Preservation, Access, and Associated Timelines**

Repository where scientific data and metadata will be archived: Provide the name of the repository(ies) where scientific data and metadata arising from the project will be archived; see [Selecting a Data Repository](http://example.com).

Aggregate clinical trial data generated from this study will be available in clinicaltrials.gov. All other data will be archived through the Common Fund-supported Open Science Framework.

**How scientific data will be findable and identifiable:** Describe how the scientific data will be findable and identifiable, i.e., via a persistent unique identifier or other standard indexing tools.

The Open Science Framework provides metadata, persistent identifiers (unique URL), and long-term access. This repository is supported by the Common Fund and dataset(s) are available free of charge to any user.
When and how long the scientific data will be made available: Describe when the scientific data will be made available to other users (i.e., no later than time of an associated publication or end of the performance period, whichever comes first) and for how long data will be available.

Shared data generated from this project will be made available as soon as possible, and no later than the time of publication or the end of the funding period, whichever comes first. The duration of preservation and sharing of the data will be a minimum of five years after the end of the funding period.

Access, Distribution, or Reuse Considerations

Factors affecting subsequent access, distribution, or reuse of scientific data: NIH expects that in drafting Plans, researchers maximize the appropriate sharing of scientific data. Describe and justify any applicable factors or data use limitations affecting subsequent access, distribution, or reuse of scientific data related to informed consent, privacy and confidentiality protections, and any other considerations that may limit the extent of data sharing. See Frequently Asked Questions for examples of justifiable reasons for limiting sharing of data.

There are no anticipated factors or limitations that will affect the access, distribution or reuse of the scientific data generated by the proposal.

Whether access to scientific data will be controlled: State whether access to the scientific data will be controlled (i.e., made available by a data repository only after approval).

Controlled access will not be used. The data that is shared will be shared by unrestricted download.

Protections for privacy, rights, and confidentiality of human research participants:
If generating scientific data derived from humans, describe how the privacy, rights, and confidentiality of human research participants will be protected (e.g., through de-identification, Certificates of Confidentiality, and other protective measures).

In order to ensure participant consent for data sharing, IRB paperwork and informed consent documents will include language describing plans for data management and sharing of data, describing the motivation for sharing, and explaining that personal identifying information will be removed.

To protect participant privacy and confidentiality, all shared data will be de-identified by removing
the association between a set of identifying data and the data subject following HIPAA guidelines.

Oversight of Data Management and Sharing

Describe how compliance with this Plan will be monitored and managed, frequency of oversight, and by whom at your institution (e.g., titles, roles).

Dr. Gerald Shulman (ORCID ID: 0000-0003-1529-5668) and Dr. Kitt Petersen (ORCID ID: 0000-0003-2664-670X) will be responsible for the day-to-day oversight of lab/team data management activities and data sharing. Broader issues of DMS Plan compliance oversight and reporting will be handled by the Co-PIs and Co-I team as part of general Yale School of Medicine stewardship, reporting, and compliance processes.