

Plan Overview

A Data Management Plan created using DMPTool

DMP ID: <https://doi.org/10.48321/D1RH2Q>

Title: Superiority of intestinal lipoproteins (chylomicrons) for oral drug delivery: a screening platform for formulation candidates

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Funding opportunity number: PA-23-230

Template: NIH-FDP Pilot Template Alpha

Project abstract:

Oral drugs are often 70-90% metabolized during the first pass through the liver via the portal vein, rendering their tissue bioavailability correspondingly low. This results in many agents being administered intravenously or through inhalation. Mammals, including humans, have 2 distinct systems for absorbing nutrients into the blood after ingestion. Nutrients such as amino acids, sugars, salts, water and virtually all oral drugs are absorbed into the portal vein blood. The pathway through which fats (lipids) are exclusively absorbed is under-utilized for drug delivery.

Orally administered lipophilic drugs may be absorbed in conjunction with absorbed triglycerides in chylomicrons. Chylomicrons (CM) transit into the subclavian venous blood via the terminal lymphatics, thus avoiding first pass hepatic metabolism.

Systemic pharmacokinetics are the gold standard for quantitating exposure of a drug. However, differences in absorption during the first circuit through the body is not reflected in systemic PK.

Up to a 10-fold increase in the arterial vs venous levels of inhaled nicotine which has a 2 hour

plasma half-life, suggesting that “first circuit” removal is considerable. CM only have a 5-minute half-life and first circuit effects on the A/V ratio are likely much greater than observed with inhaled nicotine. Thus, drug absorbed via this route experience rapid delivery unreduced by metabolism. Because of the first circuit absorption effects, systemic pharmacokinetics are a poor measure of success. When we assessed the difference in CBD exposure in rats when comparing a formulation in medium chain triglycerides and one in long chain triglyceride (LCT) to 2 experimental formulations with a variety of LCT and surfactants added to promote solubility we observed a not statistically significant increase in AUC in the systemic circulation. In contrast, when portal blood and mesenteric lymph were collected, highly significant differences were seen with a 10x increase in portal blood levels and 100x increase in mesenteric (chylomicron carried) levels over the control formulations.

The proposed research in Phase I will focus on (Aim 1) Showing that oral lipophilic drugs (API) carried as cargo in chylomicrons have improved tissue distribution, metabolism and exposure over API absorbed directly into portal blood and (Aim 2) testing whether the degree of API enrichment of chylomicrons isolated from systemic blood is predictive of a formulation’s ability to partition API into chylomicrons in the enterocyte and can be used for screening formulation candidates. The data from these trials will form the basis for using the enrichment assay as a method for screening formulations to maximize chylomicron carriage of the API.

Start date: 04-01-2024

End date: 03-31-2025

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Superiority of intestinal lipoproteins (chylomicrons) for oral drug delivery: a screening platform for formulation candidates

PART I: General Information (To be completed by all applicants)

Type of Plan

- New

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Because of the first circuit absorption effects, systemic pharmacokinetics are a poor measure of success. When we assessed the difference in CBD exposure in rats when comparing a formulation in medium chain triglycerides and one in long chain triglyceride (LCT) to 2 experimental formulations with a variety of LCT and surfactants added to promote solubility we observed a not statistically significant increase in AUC in the systemic circulation. In contrast, when portal blood and mesenteric lymph were collected, highly significant differences were seen with a 10x increase in portal blood levels and 100x increase in mesenteric (chylomicron carried) levels over the control formulations.

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Plan Version Number. For example, 1.0.

1.0

Plan Submission Date, MM/DD/YYYY

09/05/2023

Project/Application/Protocol ID

I-N-001

Project Title

Superiority of intestinal lipoproteins (chylomicrons) for oral drug delivery: a screening platform for formulation candidates

Describe how compliance with the Plan will be monitored and managed, frequency of oversight, and by whom. List the name, title, roles and responsibilities of the contact PI and any other individuals on the project team who will be responsible for oversight of data management and sharing.

Vassili Kotlov and Ramon Seva listed on the grant proposal will implement and monitor the policy and the plan.

Will data management and/or sharing activities be facilitated by individuals outside of the project team?

- No

PART II: Human Derived Data (To be completed for projects managing and/or sharing data derived from humans)

Will the project be managing and/or sharing data derived from humans?

- No

**PART III: Data Management and Sharing Details (To be completed by all applicants)-
Project Level Information (Part III.A.)**

Describe project-associated documentation that will be made accessible to facilitate interpretation of the scientific data and where the document will be shared. Examples include study protocols and data collection instruments.

We will make available our protocols at the end of our 1 year study. Relevant quality controlled datafiles will be made available in SAS formatted databases when the study is completed.

Will you be performing secondary analysis of extant data to generate scientific data for this project?

- No

Will all scientific data generated by the research project be shared in a data repository that makes data available to the larger research community?

- Yes

**PART III: Data Management and Sharing Details (To be completed by all applicants)-
Data Type(s) (Part III.B.)**

Data Type Brief Description Organism, Model, or Other Sources Amount of Data Standards Shared Formats Data Repository Data Access Type *Define each data type add additional rows to describe multiple data types Summarize how the data of this type will be managed and prepared for sharing Projected number of participants or samples from which the data will be generated or other appropriate metrics to describe the scale of the data List the standards that will be applied to the scientific data and associated metadata if standards exist Formats of data to be submitted to the data repository Name the repository where scientific data and metadata will be preserved and shared Examples include open, registered, controlled or enclave*

Data Type	Brief Description	Organism, Model or other Sources	Amount of Data	Standards	Shared Formats	Data Repository	Data Access Type

**PART III: Data Management and Sharing Details (To be completed by all applicants)-
Timeline for Data Submission and Sharing (Part III.C.)**

Use this section to plan for data submission to and sharing from the repositior(ies) listed in the data type section. Consider publication timelines, performance period, and data repository review and release timelines when planning data submissions and communicate through Plan updates if there are major changes to planned timelines. Shared scientific data should be made accessible as soon as possible, and no later than time of an associated publication or end of the performance period, whichever comes first.

Data Repository Expected number and frequency of submissions

Projected timeline for first submission to repository Projected timeline for last submission to repository Target timelines for release Type of persistent IDs that will be used for data releases, to enable findability and citation of shared datasets If you will be contributing data to a dataset that is already registered with a data repository, provide that ID *Name the data repository described in the Data Type section. Add additional rows as necessary. Releases associated with data underlying publications, other scheduled releases, and remaining scientific data by the end of the performance period. Samples include dataset-level digital object identifier (DOI), accession number, globally unique identifier.*

Data Repository	Expected number and frequency of submissions	Projected timeline for first submission to repository	Projected timeline for last submission to repository	Target timelines for release	Type of persistent IDs that will be used for data releases, to enable findability and citation of shared datasets	If you will be contributing data to a dataset that is already registered with a data repository, provide that ID

**PART III: Data Management and Sharing Details (To be completed by all applicants)-
Tools, Software, and/or Code Sharing (Part III.D.)**

Briefly describe the tools, software, and/or code.

SAS or JMP software.

List the repository or location where researchers can access the tools, software and/ or code and how they can or will be accessed. Access examples include open source and freely available, generally available for a fee in the marketplace, available only from the research team.

Available only from the research team.

If not yet available, provide target timelines for sharing each tool, software, and/or code developed.

Within 1 year after the conclusion of the study.

PART IV: Additional Information

Use this section to provide additional information or context for readers and reviewers of

your Data Management and Sharing Plan. Optional Additional Information:

The data generated from these experiments will only be interpretable after QC and formatting into final databases.
