Plan Overview

A Data Management Plan created using DMPonline

Title: Circadian regulation of liver energy metabolism: translational studies in diabetes and obesity

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Funder: Medical Research Council (MRC)

Template: MRC Template

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Project abstract:

Background Circadian clocks are an essential adaptive feature allowing our physiology and behaviour to predict day/night transitions. In mammals, the circadian timing mechanism is present in most cell types and establishes local cycles of gene expression and metabolic activity. These distributed tissue clocks are synchronised by the hypothalamic suprachiasmatic nucleus. The circadian clock is an influential regulator of energy metabolism allowing key pathways to be tuned across the 24hr cycle as metabolic requirements vary. Some core clock components (CRY, REVERB) also play essential roles in energy metabolism, and inflammation. Our studies reveal that these proteins regulate glucocorticoid receptor (GR) function, a major drug target and crucial regulator of liver energy metabolism. Strikingly, two recent studies reveal that shiftwork, which disrupts liver circadian rhythmicity, predisposes to type II diabetes, a highly prevalent human metabolic disease. Hypothesis Circadian control mechanisms in the liver are essential for energy homeostasis. Their disruption results in hepatosteatosis, inflammation and cancer. Plan This project capitalises on recent innovations which permit human liver organoids to be used as a translational model for diabetes and metabolic dysfunction. The microlivers will be challenged with lipogenic, high-energy culture medium, to drive lipid accumulation within the hepatocytes. The impact of this challenge, the mechanism underlying human hepatosteatosis, on the core circadian clock will be assessed by tracking the PER2-luc output, and by measuring gene expression profiles through the optimised circadian time-series model described above. The deep phenotyping of these microlivers with high throughput ‘omics technology platforms, cell based assays and systems microscopy allows entirely novel biology to be revealed in this important human disease with new insights, high-impact publications, and potential therapeutic advances. We will build on unique strengths coupling circadian biology and metabolic science, and will use CRISPR, and genetic engineering approaches to investigate novel pathways regulating liver phenotype, and metabolic flux. We can couple this genetic approach to chemical biology interventions, such as those we have recently pioneered to target circadian clock components (5). Outputs There is an expectation that the project will result in publications in high-impact journals, present at international meetings, drive project

progression, and capitalise on the joint academic/pharma stakeholders. There is considerable scope to pursue exciting new biological pathways emerging from the discovery platforms.

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Circadian regulation of liver energy metabolism: translational studies in diabetes and obesity

0. Proposal name

0. Enter the proposal name

Circadian regulation of liver energy metabolism: translational studies in diabetes and obesity

1. Description of Data.

1.1 Type of Study

Cell and organoid models
RNA-SEQ, proteomics and metabolomics for deep phenotyping
some animal studies for validation

1.2 Types of Data

RNA-SEQ
proteomics
metabolomics
cell imaging
in-vivo animal physiology

1.3 Format and scale of the data

GEO gene expression data
spreadsheets for proteomics and metabolomics
physiology will be low n, and multiple parameter measurements

2. Data collection / generation

2.1 Methodologies for data collection / generation

platform analysis technology for RNA, protein and metabolomics

microscopy, for cell biology
protein expression and modification by immunoblot (images)

2.2 Data quality and standards

data quality will be assessed by using internal QC controls, and by measuring variance between repeated measurements.

3. Data management, documentation and curation

3.1 Managing, storing and curating data

all data needs to be stored on a safe, backed up electronic platform, accessible to the investigators, and made available to the community, and to the journals when the data is published.

standard RNA-SEQ data and annotation standards.

3.2 Metadata standards and data documentation

all methods, and annotation will be captured in e lab books, and cross-referenced to the stored data.

all analysis of the data and code will also be stored, and linked to the primary data.

3.3 Data preservation strategy and standards

Data will be stored in Oxford until publication, and dissemination.

All platform technology data eg RNA profiles, will be uploaded to eg GEO database, and unlocked concident with publication.

4. Data security and confidentiality of potentially disclosive personal information

4.1 Formal information/data security standards

N/A

4.2 Main risks to data security

N/A

5. Data sharing and access

5.1 Suitability for sharing

GEO

5.2 Discovery by potential users of the research data

links to databases are included with publications, and where possible we will publish the data online with the journals concerned.

5.3 Governance of access

The PI will determine access, until the data is published, or the embargo on access eg GEO is passed.

5.4 The study team's exclusive use of the data

exclusive use until publication, then made available to the community.

5.5 Restrictions or delays to sharing, with planned actions to limit such restrictions

no restrictions.

5.6 Regulation of responsibilities of users

n/a

6. Responsibilities

6. Responsibilities

Just the PI

7. Relevant policies

7. Relevant institutional, departmental or study policies on data sharing and data security

Policy	URL or reference
Data Management Policy and Procedures	
Data Security Policy	
Data Sharing Policy	
Institutional Information Policy	
Other	
Other	

8. Author and contact details

8. Author of this Data Management Plan (Name) and, if different to that of the Principal Investigator, their telephone & email contact details

David Ray