Using Advanced Informatics Strategies to Identify Key Disease-Associated Metabolites and Provide Evidence for Infection in ME/CFS Patients

Grant Amount	£16,971
Location	The Rosalind Franklin Institute, the University of Oxford
Research Field	Biomarker discovery
Lead Researcher/s	Aleyna Lumsden, under the supervision of Dr Bela Paiza and Professor Karl Morten
Start Date	18/10/2024
Duration	3 years
Status	In progress
Latest Update	New funding awarded to PhD project that will identify key metabolites and infection markers in ME/CFS

BACKGROUND

The complex and poorly understood causes of ME/CFS has posed major obstacles to biomarker discovery. This creates a self-perpetuating cycle, where the lack of standardized diagnostic criteria leads to misdiagnosis, reinforcing scepticism and reducing both participation in research and investment in the field. However, the most distressing consequence is that currently no effective treatments exist for patients.

One promising approach to finding biomarkers is called 'omics', which looks at large sets of biological data to find disease-specific patterns that can inform diagnosis, prognosis, and therapeutic targeting. A newer branch of this is metabolomics, which focuses on metabolites – the small molecules your body produces as it carries out necessary biological functions, processes food, and fights disease. Since metabolites reflect what's happening in the body in real time, they're powerful indicators of disease and are ideal for biomarker discovery. (See more information: here.)

Metabolomics generates huge amounts of data using techniques like mass spectrometry (MS), which can detect even tiny amounts of metabolites. But while MS is highly sensitive, figuring out exactly what many of those detected molecules are – especially the unknown ones – is a major challenge. And some of those unknowns may hold the key to understanding ME/CFS.

The process of figuring out what those unknown molecules are is called structural elucidation. This means identifying the molecule's chemical structure based on how it behaves in our instruments. One common technique is Nuclear Magnetic Resonance (NMR), which gives very detailed information about how atoms are arranged in a molecule. However, NMR requires a large, concentrated sample, and many metabolites we are interested in are only present in tiny amounts – especially in complex mixtures like blood or urine. This makes NMR slow and inefficient for large-scale metabolomics studies. Other methods like microED and Raman spectroscopy also have strict sample requirements and aren't sensitive enough for many of the molecules we want to study. That's why we are turning to more advanced and flexible tools like advanced MS and chemical modelling to counteract these limitations.

PROJECT DETAILS

In this project, we aim to find potential biomarkers for ME/CFS by figuring out the structure and identity of unknown molecules that differ between patients and healthy individuals. This could help us better understand the disease and eventually guide new treatments.

By leveraging the unique platforms at the Rosalind Franklin Institute (RFI), Imperial College, and the National Phenome Centre (NPC), we can speed up the process of identifying unknowns without relying on slower, traditional methods. One powerful technique we are using is ion mobility mass spectrometry (IMS), combined with liquid chromatography and tandem MS (LC-MS/MS). This setup helps us separate and analyse molecules that are very similar in size or shape, making it easier to figure out their structures.

We're also using new computer modelling tools developed in-house at the RFI. These tools simulate how a molecule behaves in the mass spectrometer and predicts how it breaks apart – giving us a clearer picture of what each unknown compound might be. One such tool is the Universal Fragmentation Model (UFM) which uses quantum chemistry to predict the structure and fragments of a molecule.

By combining these experimental and computational methods, we aim to build a workflow that can rapidly identify and characterise ME/CFS biomarker candidates. We will then double check the identities of these molecules using other techniques, such as NMR or microED, depending on the sample. Then, we'll map these confirmed molecules onto biological

pathways to understand how they may be involved with the disease. This opens the door to designing new treatment strategies that target the disrupted processes we've uncovered.

IMPORTANCE OF FUNDING

- **Improves diagnosis:** By uncovering biomarkers, the research aims to make ME/CFS easier to diagnose—reducing misdiagnosis and speeding up access to care.
- **Supports targeted treatments:** Mapping disease-related molecules helps researchers identify pathways for developing effective, personalised therapies.
- **Drives innovation in biomedical science:** The project uses cutting-edge tools like metabolomics and molecular modelling to advance understanding of complex diseases.
- **Addresses an urgent health need:** Millions with ME/CFS and Long Covid live without effective treatment—this research is a step toward changing that.

N.B. The ME Association are providing a top-up in funding for this PhD project which is also being funded up the UKRI.