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TITLE: Novel Dynamic Proteomics Approaches to Investigate the Systems Level Pathology of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)

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CONTRACTING ORGANIZATION: University of Nottingham, Derby, UK

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14. ABSTRACT
ME/CFS is a severely debilitating condition characterised by unexplained, persistent and relapsing chronic fatigue of unknown pathology, typically lasting in excess of 6 months, which is significantly exacerbated by bouts of exertion/exercise. Despite its widespread nature (effecting ~1-2% of the world's population), little is still known regarding the underlying pathology driving these debilitating symptoms. The overall aim of this project is to use a novel dynamic proteomics approach to provide a real time measure of changes in metabolism across multiple tissues; blood, skeletal muscle and CSF, of ME/CFS patients at rest and following an acute exercise stressor designed to elicit symptoms. This will provide potential new therapeutic targets for translational to the clinical settting in the near future. This report provides an update of progress to date, highlighting the issues with volunteering particularly. We are currently struggling to recruit to the healthy volunteer group, however have had more interest within the ME/CFS group, with 4-5 potential volunteers due to be screened in the next few months hopefully.

15. SUBJECT TERMS
ME/CFS Proteomics

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1. INTRODUCTION:

ME/CFS is a severely debilitating condition characterised by unexplained, persistent and relapsing chronic fatigue of unknown pathology, typically lasting in excess of 6 months, which is significantly exacerbated by bouts of exertion/exercise. Believed to effect ~ 1-2% of the worldwide population, this condition is endemic across all ages, social, ethnic and economic strata, with a tendency for a greater prevalence in females than males (3:1 ratio). For those afflicted, symptoms can persist for years, with recovery rare, and health-related quality of life reported as worse than in many other common non-communicable illnesses or diseases (ie. Cancer, Stroke). Despite its widespread, very little is known about the underlying pathological causes of ME/CFS. The unknown aetiology means that there are no effective treatments currently available for this life altering condition. There is therefore a deep clinical, as well as societal, need for a better understanding of the complex aetiology underlying ME/CFS. The overarching aim of this project is to use a dynamic proteomics approach to provide a novel insight into the changes in metabolism present across multiple tissues; blood, skeletal muscle and CSF, of ME/CFS patients at rest and following an acute exercise stressor designed to elicit PEM. We believe that by taking this unique approach we will be able to show disturbances in turnover of key proteins involved in the regulation of immune, endocrine and central nervous system function (aspects of metabolism already believed to have key roles in disease development), in addition to key proteins involved in the regulation of metabolic networks previously unknown to ME/CFS pathophysiology.

2. KEYWORDS:

ME/CFS, Proteomics, Metabolism, Pathophysiology

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Approval and Set-up for Human Volunteer Studies

Subtask 1: Institutional Ethics Approval for the Project (Month 1 – 4) – **100% Complete**

Subtask 2: HRPO Approval Granted – (Month 4 – 6) – **100% Complete**

Subtask 3: Healthy Volunteer Group Recruitment Completed as per quarterly targets – (Month 6 – 12) – **0% Complete as of 12th August 2022.**

Subtask 4: ME/CFS Group Recruitment Completed as per quarterly targets – (Month 9 – 18) - **0% Complete as of 12th August 2022.**

Major Task 2: Completion of Volunteer Data Collection – (Month 6 – 18) – **0% Complete as of 12th August 2022.**

Major Task 3: Data Analyses and BioInformatics – (Month 6 – 24) - **0% Complete as of 12th August 2022.**

What was accomplished under these goals?

During the first 12 months of this project the following was accomplished:

- Institutional Ethics Approval was received
- HRPO Approval was granted following receipt of Institutional Ethics Approval.

Based on the agreement statement of work, I have been unable to meet the required goals of recruitment for subtask 3 of Major Task 1 as per the quarterly targets. I have struggled to recruit healthy volunteers for this project as many are unwilling to take part due to the invasive nature of the sampling required for each study. It may be a case that to successfully recruit the healthy volunteers needed is for the design of the study to be less invasive through the removal of the CSF sampling. This would be a shame as it is an important measure, however many people approached to volunteer do not wish to have a lumbar puncture procedure.

Although ME/CFS group recruitment for subtask 4 of Major Task 1 is at the same stage as the healthy volunteer group, I have had more interest in volunteering within this group. I currently have 4 potential volunteers that I am trying to arrange screening for with the clinicians over the next few months. ME/CFS volunteers seem less averse to the invasive nature of the study sampling.

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period I hope to accomplish the remaining goals of recruitment and data collection from my SoW. To achieve these, as described in the section above I may have to remove the CSF sampling from the study design. This seems like a significant obstacle to recruitment at the moment particularly in the healthy volunteer group, ME/CFS recruitment is looking more promising than the healthy volunteer, and I have less concern regarding this goal.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines? .

Nothing to report. However the techniques being utilised in these studies – Dynamic Proteomics – have widespread application across a number of other disciplines beyond ME/CFS. They can be a useful tool for understanding the biological factors driving health and disease, and could in the long term contribute to the translation to new and effective treatment in disease.

What was the impact on technology transfer?

Whilst there is nothing immediate to report to date. As above the technologies being used in this work could result in the identification of new and/or novel therapeutic targets for the treatment of ME/CFS. Leading directly on to translational future work for the development of new therapeutics based on these novel targets.

What was the impact on society beyond science and technology?

As above section there is nothing immediate to report to date, however effective treatments for ME/CFS are severely lacking and if we are able to identify potential new targets for therapeutic development, this could have wide ranging impact on improving the quality of life in this patient group.

5. CHANGES/PROBLEMS:

Nothing to report - No major or significant changes in the project or its direction have occurred.

Actual or anticipated problems or delays and actions or plans to resolve them

As with any human research there are always difficulties in recruiting volunteers to detailed mechanistic studies such as these, the presence of COVID-19 and intermittent lockdowns and changes to rules to prevent transmission have been especially challenging. In addition to this, the lack of interest of healthy volunteers due to the invasive nature of CSF sampling has caused some problems and delays to meeting my expected targets. In order to overcome these, I may need to make the study less invasive by removing these samples from the study protocol altogether. I believe this approach will improve my chances of successful recruitment. In addition, colleagues of mine from my research group have said that they are happy to help try to recruit volunteers should I need them to.

Changes that had a significant impact on expenditures

Nothing to report – As no studies have been completed, there have not been any changes to expenditure.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

No significant changes to the project have been made, however we have had the following minor amendments requested and approved by our local IRB

Amendment 1: 24.08.2021: Change of wording of Consent Form to fit to requirements of HRPO and agreement for annual ethical re-review

Amendment 2: 20.12.2021: Addition of another named Clinician to the research team

Amendment 3: 25.04.2022: Minor changes to sample number and timings to reduce participant burden and better fit with the named clinicians existing clinical commitments

Annual re-review of the project was completed on 16th May 2022 and a favourable ethics opinion was renewed for another year by the IRB and this was forwarded to HRPO.

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agent

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations** .

Journal publications.

Nothing to Report

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

Nothing to Report

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Dr Daniel Wilkinson
Project Role: PI
Researcher Identifier: 0000-0001-8808-8243 (ORCID iD)
Nearest person month worked: 2
Contribution to Project: Dr Wilkinson completed Ethical Approval Paperwork for the project and all HRPO documentation to enable recruitment to the project to begin. Dr Wilkinson has been trying to recruit volunteers for the project over the last 6 months.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

I am Co-I on a recently awarded Medical Research Council Experimental Medicine Grant with total time on the grant at 2%FTE.

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

N/A

9. APPENDICES:

N/A