A Rosetta Stone to decode post-viral sequelae in Long Covid and ME/CFS

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Lead Researcher/s	Professors Daniel Altmann and Rosemay Boyton
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Latest Update	Rosetta Stone Study – Summary: Three month update

IMPORTANCE OF FUNDING

The ME Association (MEA) has committed **£1.175 million** to a major new research project – its largest ever investment, and the biggest amount any charity has committed to Long Covid (LC) or ME/CFS research.

Since the Covid-19 pandemic began, huge amounts of research have gone into understanding Covid-19 and Long Covid. The MEA has consistently argued that ME/CFS should have been included in this work, because the two conditions show many similarities. The new **Rosetta Stone** project will finally allow researchers to study them side by side, on a scale never attempted before.

This study brings together leading experts from **Imperial College London (WILCO)**, the **University of Edinburgh (DecodeME)**, the **London School of Hygiene & Tropical Medicine (UK ME/CFS Biobank)**, and **Brunel University London (HHV)**. The MEA first approached the Imperial team in November 2024, and the proposal has been carefully reviewed over the past year to ensure strong scientific foundations and good management of this major investment.

Over **three years**, the project will closely examine the immune systems and biology of people with Long Covid and people with ME/CFS. Their results will be compared with those from healthy individuals and people who have fully recovered from Covid-19. Because it involves large groups of

participants and advanced technologies, the findings will be more reliable and informative than those from smaller early-stage studies.

The study will also investigate several important biological questions, including whether:

- **Proteins in the blood** (measured using SomaScan proteomics) reveal shared disease patterns or underlying mechanisms in LC and ME/CFS.
- **Immune function**, including autoimmune antibodies, autoimmune T cells, different immune cell types, and their metabolic activity, shows common changes that could help explain symptoms.
- **Human herpesviruses**, such as EBV, HHV-6B, and HHV-7, are reactivating in these conditions, and how virus levels and T-cell immune responses relate to illness.
- **Gut microbiome disturbances**, already suspected in both LC and ME/CFS—including changes involving bacteria like *Faecalibacterium prausnitzii*—are linked to particular symptoms, immune changes, or metabolic abnormalities.

By combining these findings, the research team aims to identify **shared biological pathways** between Long Covid and ME/CFS. This will deepen understanding of how these diseases develop and may highlight promising targets for future treatments that could be tested in clinical trials.

Importantly, the Rosetta Stone project is not looking at single findings in isolation. Instead, it is designed to identify **consistent patterns across multiple biological systems**, giving a more complete and trustworthy picture of what is driving illness in both conditions.

BACKGROUND

Long Covid (LC) has triggered a new focus on the wider question of post-viral sequelae (a condition resulting from an infection), notably, similarities to another poorly characterised disease, ME/CFS.

Together, they comprise a considerable disease burden, (UK prevalence of 1.35M), a challenge to healthcare, and an estimated loss to the economy of over 3% of the contributory workforce.

It seems likely there are similar defects in molecular and cellular processes which constitute triggers for specific pathologies in LC and ME/CFS. This suggested there would be added value for both patient communities from a bespoke study that allowed detailed, side-by-side, mechanistic comparison.

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PROJECT OVERVIEW

The aim of this project is to understand what is happening in the body at the cellular and molecular level in people with LC and ME/CFS. We will do this by directly comparing biological samples from people with these conditions to those from healthy individuals.

By studying these groups side-by-side, we hope to identify the key biological changes that may explain symptoms, offer a guide to future treatments, and supply serum markers to be used both in referral pathways and in stratification for clinical trials.

Recruitment will build on well characterised cohorts from the NIHR 'WILCO Study', the MRC/NIHR DecodeME study, and the UK ME/CFS Biobank, with representation of all illness severities.

250 individuals will be recruited into each cohort, comprising ME/CFS, LC, and 'Covid-19 with full recovery within 4wks and showing symptoms of neither LC nor ME/CFS'. The UK ME/CFS Biobank will provide further comparison with pre-Covid-19 healthy controls.

Participants will provide blood, saliva, and stool samples. These samples will allow the team to investigate several biological features that may help explain what causes symptoms in LC and ME/CFS. Specifically, they will study:

- **Proteins in the blood (proteomics):**
  They will examine whether detailed measurement of blood proteins can reveal biological changes that are consistently linked with these diseases.
- **Immune system function:**
  This includes looking for signs of autoimmunity involving antibodies and T cells and assessing how different types of white blood cells—especially lymphocytes—produce and use energy. These analyses may help identify features of the immune system that distinguish people with LC and ME/CFS from healthy individuals.
- **Herpesvirus activity:**
  They will investigate what role virus levels and immune responses to reactivated herpesviruses (such as Epstein–Barr virus) may play in driving symptoms. This will help determine whether viral reactivation contributes to disease processes.
- **Gut microbiota (gut bacterial communities):**
  By analysing stool samples, they will explore whether disruptions in gut bacteria are

involved in both conditions, and whether these disruptions are linked to shared immune patterns and disease features.

Since some individuals will improve during this longitudinal study, there is the potential to uncover not just disease markers, but markers of recovery.

By comparing samples from people with Long Covid, ME/CFS, and healthy, as well as recovered, controls side-by-side, this project aims to identify key biological changes – known as disease correlates – that may help explain symptoms and guide the development of future treatments.

DETAILED EXPLANATION

Long Covid (LC) shares many symptoms with ME/CFS, including extreme fatigue after exertion, problems with thinking and concentration, and issues with the autonomic nervous system such as dizziness, heart-rate changes, and postural orthostatic tachycardia syndrome (POTS). A large review showed that almost all symptoms linked to ME/CFS (25 out of 29) have also been reported in studies of LC. These similarities reflect a broader pattern seen after many viral infections.

ME/CFS has long been recognised as a condition that can develop following a wide range of infections, including pandemic flu (H1N1), varicella-zoster virus (VZV), enteroviruses, and the original SARS virus. In a similar way, many people with Long COVID remain unwell for several years – some now into their fifth year of illness – just as people with ME/CFS often experience long-lasting symptoms. Historical reports of “Long-SARS” after the 2003 SARS outbreak also show that some individuals saw little improvement even after decades.

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- **Herpesvirus activity:**

  There is growing evidence that reactivation of common herpesviruses may play a role in LC. Studies have found that Epstein–Barr virus (EBV) can reactivate in some people and may be linked to persistent symptoms. EBV reactivation can disturb the immune system by increasing certain T cells that target the virus and activating B cells, which produce antibodies. Similar findings have been reported in ME/CFS, where higher levels of other herpesviruses (HHV-6B and HHV-7) were observed in saliva compared with healthy individuals.

- **Long-term immune changes and cell metabolism:**

  In LC, researchers have focused on whether T cells show signs of "exhaustion," where cells become less effective after prolonged activation. In ME/CFS, studies have examined changes in natural killer (NK) cells and MAIT cells. Some of these immune disturbances may be driven by chronic herpesvirus reactivation.

  In addition, the energy-producing machinery of immune cells appears to be altered in ME/CFS, with T cells showing reduced mitochondrial function and lower glycolysis. In this project, the team will compare energy use in immune cells from people with LC and ME/CFS using a specialised technique called Seahorse analysis, which measures how cells generate and use energy in real time.

- **Gut microbiota (gut bacterial communities):**

  Changes in gut bacteria, or "gut microbiota dysbiosis," may be an important shared feature of LC and ME/CFS.

  In LC, certain bacteria such as R. gnavus and B. vulgatus are more abundant, while beneficial species like Faecalibacterium prausnitzii are reduced. Many of these beneficial bacteria produce butyrate, a compound that supports the immune system by promoting regulatory T cells, which help control inflammation.

  Similar patterns are seen in ME/CFS, where reduced levels of F. prausnitzii and butyrate are linked to persistent symptoms. Studying these gut microbiome changes side-by-side may help identify shared disease mechanisms and point to potential therapeutic strategies.

Together, these findings suggest that immune disturbances, viral reactivation, altered cellular metabolism, and gut microbiome changes may all contribute to the persistent symptoms seen in

LC and ME/CFS. By studying these factors in parallel, we hope to uncover common biological patterns that could guide future treatments.