MRC Human Genetics Unit

THE UNIVERSITY of EDINBURGH

12 April 2024

Dear ME/CFS Funders,

Re: Risks to future UK ME/CFS research

> *To be honest, there is no single area of research that could currently claim to provide a "strong research evidence base" for understanding CFS/ME. There are fragments of information and partial data sets, separated by large tracts of ignorance. The gaps are usually filled by enthusiastically held hypotheses that have yet to be evaluated or falsified. There is a wealth of unanalysed and unpublished data held by clinicians and patients which could be seen as a research base that could and should be tapped in, at the least, a hypothesis-generating way*. MRC CFS/ME Research Strategy, 2003.

Twenty years on, there has not been substantive change:

> *"…the working group identified key problems surrounding low capacity and capability to respond to research needs, low awareness of need of research in ME/CFS and low levels of funded research."* UK Government's Interim Delivery Plan for ME, 2023.

We are writing to urge the UKRI funders and charities to intervene decisively by interrupting the cycle wherein a low funding rate yields a low evidence base that hinders the competitiveness of project proposals.

MRC and NIHR have awarded £7.34m in ME/CFS research since 2013, including £3.2m to DecodeME (link). This is just **£2.67** per person with ME (pwME) per year. Charities fund just under **£2** per pwME per year (link). This compares with the UK's annual spend of **£74** per person on health research (link). Despite being at least twice as prevalent, ME/CFS receives approximately 20-times less research funding than multiple sclerosis (link). ME/CFS's annual cost to the UK economy is at least £3.3 billion (link); the cost of Long Covid to UK GDP is £1.5 billion annually (link).

This low level of research funding is not commensurate with disease burden: UK ME/CFS prevalence is at least 250,000, with an estimated 63,000 people in the UK are so severely affected that they are house-bound or bed-bound, with little functional capacity, often needing 24-hour care (link, link).

Collectively, since 2022, we have applied for over **£7.5m** for ME/CFS and/or Long Covid research without success. A £0.57m MRC Partnership bid stalled due to a slow response (~1 month) from MRC to multiple emails. Feedback from MRC panels include: their "concerns remained about the focus on the complex exemplar diseases of ME/CFS and long Covid and the challenges that this

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presented for the proposed approach" and "the programme lacked sufficient ambition and potential impact".

A recent application to the highlight notice, having taken into account advice from academic experts, UKRI funders and PPI groups about the imperative to align and synergise molecular pathogenesis approaches across both ME/CFS and Long Covid, and from an internationally recognised team with multiple relevant, recent publications in *Science*, *Nature* and *Lancet*, was declined with one referee allocating a score of '1/6; poor'. Another research team with a similar output profile has shelved all plans to work on ME/CFS after four attempts to obtain funding since 2020. Each application was revised in line with the feedback but then compromised by highly inappropriate reviews, two of which indicated that the reviewer had not read the grant (*e.g.*, by criticizing experiments that were not proposed anywhere in the application), and one of which indicated that the reviewer had little or no relevant knowledge (*e.g.*, by stating that there is a universal treatment for ME/CFS). Other reviews used earlier published research with conclusions based on highly questionable data to criticize the validity of the approach, which had already pinpointed a molecular signature of ME/CFS. This work remains unpublished without funds needed to push it through to completion.

A multi-centre proposal from one of us would have identified new ME/CFS cases and their aetiology from sampling hundreds of new COVID cases in six specialist ME centres across Europe for 3-5 years. This proposal was not reviewed. Another researcher among us was graded in the lowest quartile at the last Wellcome Discovery call.

Because of its historically low funding, we cannot, in good conscience, today recommend to early career researchers (ECRs) that they pursue a career in ME/CFS research. There are currently only 15 UK research groups undertaking ME/CFS research (link). The talent pool has dried up: there are only two ECR fellows researching ME/CFS in the UK. Reluctantly, without funding, researchers and their groups will need to refocus on other diseases.

Elsewhere, strategic ME/CFS funding has been provided recently: in the Netherlands (€28.5m; link), in Germany (€15m; link), in Australia $3m (link) for an NHMRC Targeted Call for Research for ME/CFS as well as AUS $6.4m from the Stafford Fox Medical Research Foundation (link), and in Austria (€0.6m [charity funds]; link). In the USA, the NIH funds ME/CFS about $15m annually (link). Calls for renewed investment in ME/CFS research will come again this year from the Research Working Group for the UK Department of Health and Social Care's ME/CFS Delivery Plan and the NIH's ME/CFS Research Roadmap.

We request a face-to-face meeting with the appropriate UKRI, NIHR and charity leadership, as we had previously for DecodeME, in order to discuss (i) strategic funding for ME/CFS and Long Covid, and (ii) more equitable review of ME/CFS grant proposals. We look forward to hearing from you.

Yours sincerely,

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