

ME/CFS/SEID Biomarker Discovery Grants

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Response to reasons NIH refused to accept grant applications, Ronald W. Davis, PhD

Two pre-proposals were sent to NINDS. The first pre-proposal was for a P01 grant for \$1,000,000 per year for 5 years. Below are the reasons given for not considering funding and my responses.

1. *NIH: It was not clear that the proposal falls within the mission of NINDS since there was no mention of collection of CSF or of analysis of cognitive or other nervous system function of the individuals with ME/CFS/SEID.*

Response: The mission of NINDS is to study diseases with a neurological component. CFS is clearly such a disease. The mission is not defined by what data is collected. It is not possible or necessary to collect either CSF or cognitive data from severely ill patients in their homes. It is very clear in the proposal that we are going to study severely ill (bed-bound) patients. We also state, “Although many of the symptoms suggest a neurological

basis, molecular biomarkers that reflect the underlying mechanism may be present in the blood, saliva, sweat, urine and/or stool. Identification of biomarkers in these easily assayed fluids can be convenient and inexpensive, and could be conducted on the estimated 25% of patients who are currently house-bound or bed-bound.” Also, bed-bound patients cannot visit a clinic where an MRI or other imaging can be performed. They are frequently unable to speak, unable to be spoken to and unable to read. Cognitive testing is thus also impossible. It is already clear that there are cognitive impacts in these patients. Cognitive testing will not contribute to anything this study seeks to address. Further, we cannot do a spinal tap (CSF) and the IRB would correctly never approve of taking CSF from a severely ill patient in a home.

2. *NIH: Everyone agrees that this research needs to be done for ME/CFS/SEID, but that you would be more successful in review if you narrow the focus of the application to focus on the very ill population and appropriate controls (for example) and submit an R01 with a budget of less than \$500,000 for any year of the application.*

Response: This comment is mystifying. The entire proposal is written to study severely ill patients already. This comment made me wonder if they had even read the proposal. The proposal is already very focused, and we do propose to focus on the very ill. Reducing the proposed research budget by half will reduce the number of patients by half and reduce the statistical significance. This will likely cause the R01 proposal to be rejected in review because they will correctly judge that there are too few patients studied to identify the false positive biomarkers. This was clearly articulated in the grant. Further, we cannot “narrow the focus” by reducing the number of tests. The heart of this proposal is to assay a very large number of molecular species all from biological samples collected at the same time. This is essential for reducing variance and for enabling us to correlate the various types of data from one point in time. This is what makes this a groundbreaking study.

3. *NIH: There was a lack of clear hypotheses to be tested and many felt there was a lack of detail provided in the proposal.*

Response: There is not a clear hypothesis because this is not a hypothesis-testing proposal but a hypothesis-generating proposal in the form of observations. The scientific method starts with **observation**, then **hypothesis**. Without first observation you cannot formulate a good hypothesis. I’m extremely surprised that NIH does not know this. Furthermore the Human Genome Project had no hypothesis and was one of the most important projects accomplished by NIH in its history. The lack of detail was intentional. This was a pre-proposal and not a completely detailed grant. I clearly stated what we were proposing to do but not exactly how we were going to do it. The exact details are not for NIH to review because they lack the experience and expertise. That is the job of a peer review study section.

4. *NIH: There was agreement that a large biomarker study is needed in ME /CFS/SEID, but that perhaps there needs to be an RFA that spells out what NIH would like to fund, with agreement between several institutes so that appropriately powered studies would be submitted and provided with sufficient funding to accomplish the studies.*

Response: Why would NIH not consider an excellent large biomarker study from a very experienced team when they state a “*large biomarker study is needed*”? Our proposed study could help NIH “*spell out what NIH would like to fund*”. Ill patients have already waited 30 years for NIH to decide what to fund. 30 years is long enough.

The second pre-proposal was for an R01 grant for \$800,000 per year for 5 years. The rejection is given below and is essentially the same as the P01 rejection:

NIH: “I am writing to inform you that the NINDS Extramural Science Committee did not approve your request to submit an R01 application with a budget over \$500,000 to NINDS. The Committee was concerned that the grant does not fall in the NINDS mission since it will measure markers and biomarkers in the peripheral blood from individuals with ME/CFS and there are no neurological outcomes in the grant. They also suggested that the application is more appropriate for NIAID, so I suggest you contact Program staff at NIAID to discuss whether or not the application is appropriate for their Institute.”

Response: I believe they don’t want to fund either grant and are pushing us to another Institute even though NIAID has publicly stated they will not support research on ME/CFS/SEID. The IOM report has made it clear that there are cognitive issues with this disease. The fact that many of our severe patients cannot talk, listen to spoken words or read should indicate neurological involvement possibly similar to stroke, which they clearly support. Furthermore, there is considerable research looking for blood biomarkers for stroke patients. I am mystified why if they support stroke and other neurological diseases, they refuse to support ME/CFS/SEID research. The IOM and P2P reports both state the urgent need for research support. This research proposal addresses many of the critical needs specified in these reports. This should be viewed as an opportunity for NIH to show leadership and quickly initiate research activity.