A Concise Guide to Jump Start Your Ramsay Research Proposal

2021 Cycle

Welcome to this introductory guide. We hope the information inside is useful as you develop your research proposal. The purpose of this toolkit is to:

- Provide a brief (by no means comprehensive) overview of the state of play in ME/CFS research
- Share what we know so far in the **new field of long-COVID** research
- Put forward intriguing disease models to be interrogated
- Outline key considerations and resources, including details of the You + ME Registry and Biobank
- List promising approaches to ME/CFS and long-COVID research that could accelerate progress to understand and treat these conditions

TABLE OF CONTENTS

ME/CFS

Myalgic encephalomyelitis (also known as chronic fatigue syndrome or **ME/CFS**) is a disease characterized by central nervous system and immune system disturbances, neurological and autonomic symptoms, circulatory abnormalities, and altered metabolism. Nearly 75% report that an infection preceded the development of their ME/CFS illness. The cardinal symptom is malaise and exacerbation of symptoms following minimal physical or mental exertion that is not relieved by rest or sleep, which can last days or even weeks. A remitting and relapsing disease course is common. Read more about the features of ME/CFS in the 2015 National Academy of Medicine Report.

Long-COVID

Although most recover from COVID-19, a subset of people (estimates suggest 10% or more) suffer from health impacts long after the expected recovery period, even months after the initial infection. Research into the phenomenon known as "**long-COVID**" is in nascent stages and much is unknown, but patient-led surveys demonstrate that long-COVID involves a multitude of respiratory, neurological, cardiovascular and gastrointestinal manifestations. A common feature of the illness are relapsing and remitting symptoms; patients improve, only to be struck back down again.

What's the connection between ME/CFS and Long-COVID?

Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, has acknowledged a number of long-COVID cases are "strikingly similar" to ME/CFS. This connection is not without precedent – a number of other pathogens have been connected to ME/CFS and post-viral illness. In a previous outbreak of a similar type of coronavirus infection called Severe Acute Respiratory Syndrome (SARS), persistent health impairments were experienced by a number of survivors.

It is imperative that we study the recovery period and the long-term impacts of COVID-19, including in those with mild or moderate illness in the acute stage. What we learn about the prevention and treatment of long-COVID may help further our understanding of ME/CFS and our ability to help those patients as well.
Read more >>> an opinion article from Dr. Anthony L. Komaroff and Dr. Cindy Bateman on behalf of the U.S. ME/CFS Clinician Coalition.

5 PROPOSED ME/CFS DISEASE MODELS

As outlined by Anthony L. Komaroff, MD at the April 2019 NIH conference on ME/CFS

For Dr. Komaroff's full slides click here

Watch a recording of his talk at 06:02:00 here

1

Excessive cellular senescence with generation of fatigue-inducing molecules

2

Cell danger response/incomplete healing

3

Sickness behavior/inflammation

4

Microbiome as the source of immune system activation and inflammation

5

Dauer/hibernation-torpor, in which energy-producing reactions are reduced to a minimum in response to some insult

ALSO. . . Check out some disease models proposed by Ramsay Investigators:

- Stimulation of microglia by mast cells in the hypothalamus Hatziagelaki et al.
- Infection-elicited autoimmunity Blomberg et al.
- Pathogen-induced dysfunction Proal & Marshall

ME/CFS RESEARCH LANDSCAPE

Understanding of the pathogenesis of ME/CFS has increased considerably in recent decades and a complex picture of the disease has emerged, implicating many systems and a variety of mechanisms >>>

GENETICS

- Clustering patterns are seen in families and there is need of genome-wide association studies to identify candidate SNPs
- There is growing evidence that epigenetic patterns are different between patients and matched healthy controls and research has shown differentially methylated pathways related to immune response, glucocorticoid receptors, and metabolism.
- In-depth investigation of epigenetic mechanisms other than DNA methylation are lacking in ME/CFS, but increased HDAC expression, an upregulation of microRNA related to cell cycle and immune regulation, and methylation changes associated with BDNF levels have been described.
- ME/CFS patients have also been found to meet the criteria for Ehlers-Danlos Syndrome (which often runs in families)

IMMUNOLOGY

- Research groups have found differences in ME/CFS blood cytokine signatures; some identifying patterns correlated with disease severity and others duration of illness. A recent paper pointed out the noisiness in peripheral cytokine data and urged caution in over-interpreting findings
- There is evidence of defective cell-mediated immunity, especially in NK cells, and increasing interest in T cell activation
- Mechanisms of autoimmunity have been explored; selective removal of autoantibodies has proved effective in small cohorts
- Altered B cell phenotypes have been uncovered
- Findings of deviations in the immune system are notably inconsistent, possibly due to patient heterogeneity and selection, the cyclical nature of the disease, and methodology

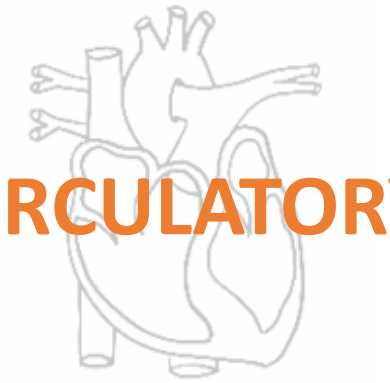
MICROBIOME

- Many patients report experiencing an infection preceding the development of ME/CFS and various pathogenic triggers have been considered, including HHV-6/7, EBV, enteroviruses, others
- Lacking clear evidence of chronic infection, researchers have focused on a "hit and run" hypothesis or viral reactivation
- Alterations in the gut microbiome composition of people with ME/CFS have been uncovered by different groups; it's hypothesized a "leaky gut" may trigger immune dysfunction and/or gut inflammation might disrupt bidirectional communication with the brain

NERVOUS SYSTEM

- There is considerable evidence demonstrating that ME/CFS has both structural and functional brain consequences, such as reduced functional connectivity and changes in cerebral blood flow, (CBF) including reductions in CBF during upright tilt table testing.
- Indicators of brain inflammation have been found in MRS and PET neuroimaging studies. The brainstem has been argued to be a target for future studies as it has explanatory power for autonomic dysfunction seen in patients and is a gap from previous research
- Inflammatory markers have been found in cerebrospinal fluid of patients
- Neuroendocrine changes, particularly HPA axis dysfunction, have been explored
- Findings from a small pilot study suggest that small-fiber polyneuropathy might underlie ME/CFS symptoms
- Mechanical causes of ME/CFS, such as craniocervical instability and cervical spinal stenosis have been described in patient recovery stories and case series

CIRCULATORY



- Cardiovascular symptoms and circulatory abnormalities, including impaired cardiac function and altered blood pressure regulation, have been described in ME/CFS
- The majority of studies in young people show a high prevalence of OI
- Reduced heart rate variability has been correlated with fatigue severity in patients
- Preload failure and indications of insufficient uptake of oxygen in the skeletal muscle cells have been observed in patients, which could be the result of circulatory problems or mitochondrial dysfunction
- A small study found evidence of endothelial dysfunction in large and small vessels

METABOLISM

- Mitochondrial dysfunction, AMPK impairment, and redox imbalance have all been associated with ME/CFS.
- The body of evidence points to irregularities in various metabolic pathways, including changes in lipid and amino acid pathways, nucleotide, nitrogen, and hormone metabolism. Overall, different groups have found evidence to support a hypometabolic state
- There has been some exploration whether metabolic dysfunction in immune cells could be driving problems with immune system functioning in ME/CFS patients.
- A recent study found bioenergetic defects in muscle cells, suggesting that energy production problems could be body-wide

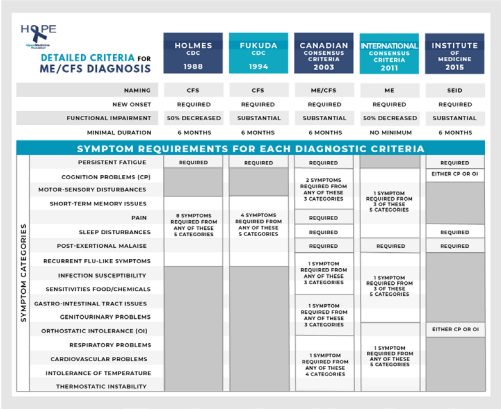
ME/CFS RESEARCH CONSIDERATIONS

ME/CFS PATIENT SELECTION

The ME/CFS field lacks an agreed upon research or clinical case definition.

Sample heterogeneity across research studies and disordered patient selection impedes replication and holds back progress in the search for biological markers and effective treatments.

Click the image to view an overview of case definitions from Open Medicine Foundation



We don't have the space to outline the arguments for one case definition over another in this guide, but this is unequivocal:

A well-designed study will **require the presence of post-exertional malaise (PEM)** in determining a case of ME/CFS.

DATA COLLECTION INSTRUMENTS

NINDS COMMON DATA ELEMENTS FOR ME/CFS

Start up resources from the NINDS CDEs can be accessed here

NINDS Common Data Elements
Harmonizing information. Streamlining research.

Please note a few things:

- a method for ascertaining and recording the presence or absence of PEM as a case defining symptom is imperative
- The DePaul Symptom Questionnaire should be considered as a core instrument over the Symptom Checklist
- The use of a method to assess functional status, like the Karnofsky score, should be used along with a quality of life assessment

LONG-COVID RESEARCH LANDSCAPE

Research into the phenomenon known as “long-COVID” is in nascent stages and much is unknown. It is imperative its features, trajectory, and biology are tracked and studied. Here are some key research efforts and observations so far >>>

- Multiple organs, in addition to lungs, are implicated in long-term damage and impacts of COVID:
  - There is evidence SARS-CoV-2 can infect the brain, causing neuroinflammation and neurological symptoms.
  - Clinical studies have pointed to cardiovascular consequences.
  - Damage across multiple organ systems has been observed even in non-hospitalized individuals

- Some patients are experiencing lingering symptoms even without evidence of organ damage. Patient-led surveys have documented:
  - A multitude of respiratory, neurological, cardiovascular and gastrointestinal symptoms that persist many months past the initial infection; even in those with mild or moderate illness in the acute phase.
  - Relapsing and remitting symptoms.
  - Experience of exertional intolerance and post-exertional malaise (PEM), a hallmark symptom of ME/CFS in which minimal activity triggers a relapse of exhaustion, cognitive problems, and other symptoms.

- Preliminary reports and data about long-COVID symptoms and patient experiences contain many similarities to other chronic illnesses known to be associated with viral triggers, such as: ME/CFS, postural orthostatic tachycardia syndrome (POTS), other forms of dysautonomia, and Mast Cell Activation Syndrome (MCAS), just to name a few.

RESOURCES FOR PATIENT DATA & SAMPLES

Resources available through Solve M.E. and other biorepositories. Click the logos to learn more>>>

You + ME

Study Subjects
2,003 ME/CFS
305 Healthy Controls
322 long-COVID

Available Data
The You + ME Registry questionnaires include Demographics, SF-36, Karnofsky Performance Scale, Multidimensional Fatigue Inventory, Symptoms Assessment (maps to ME/CFS case criteria), ME/CFS Disease History (ME/CFS only), COVID-19 History, Medications, Comorbidities, Beighton. A subset of participants track symptoms and other factors over time through a mobile app. All data are de-identified to protect participant privacy.

Biospecimens (collection planned on subset of total cohort in early 2021)
Dried Blood Spot Cards
Other sample types on request

Please email research@solvecfs.org for more information

SOLVE CFS BIOBANK AND PATIENT REGISTRY

Study Subjects
235 ME/CFS
110 Healthy Controls

Available Data
The questionnaires administered to the SolveCFS Biobank participants include Medical History, Demographics, Symptoms, Medications, SF-36, Fibromyalgia Impact Questionnaire-R. All data are de-identified to protect participant privacy.

Available Biospecimens
PBMC, Plasma

Please email research@solvecfs.org for more information

CURE ME
Leading research into ME/CFS

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

NINDS BioSEND

APPROACHES TO RESEARCH THAT COULD MOVE THE NEEDLE

- Studies designed to **interrogate post-exertional malaise** (PEM), a key feature of ME/CFS and a symptom that has already been observed in some long COVID patients
- Studies aimed at identifying **subgroups**
- Provocation (**exercise protocol**) studies. There is evidence that an exercise protocol has more value than measurements taken at rest to determine biological differences in people with ME/CFS. This might also be true for people with long COVID
- **Longitudinal characterization**. Moving away from cross-sectional studies to the collection of information at multiple time points
- Include **disease controls** (e.g. multiple sclerosis, Gulf War Illness, fibromyalgia) along with healthy controls, and design studies to compare ME/CFS, long-COVID and those who fully recovered from COVID
- **Cross-disciplinary research** that can dig into the multiple systems indicated in the disease
- **Stratification analyses** by age, sex, severity, duration, type of onset/triggering event, symptoms, comorbid conditions, functional status
- Utilizing high-powered methodologies, including **multi-omics** and **machine-learning** approaches, and novel techniques, like **examining exosomes**

Would you like help with:

- Connecting with a ME/CFS or long-COVID expert?
- Identifying a collaborator?
- Accessing patient and control samples from Solve ME's Registry & Biobank?

Email us with these and other questions at research@solvecfs.org