

# A Concise Guide to Jump Start Your Ramsay Research Proposal

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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
- Put forward intriguing disease models to be interrogated
- Outline key considerations and resources
- List promising approaches to ME/CFS research that could move the field forward



# RESEARCH LANDSCAPE

Myalgic encephalomyelitis (formerly 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. People living with ME/CFS present with a range of debilitating symptoms. 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. 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 more 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](#) and an [upregulation of microRNA](#) related to cell cycle and immune regulation have been described.

- Research groups have found differences in ME/CFS blood cytokine signatures; some identifying patterns correlated with [disease severity](#) and others [duration](#) of illness.
- 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

## IMMUNOLOGY



## 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 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

- 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](#)
- 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
- [Circulatory abnormalities and an association with orthostatic intolerance](#) in ME/CFS has been described. The majority of studies in young people show a [high prevalence of OI](#)
- Neuroendocrine changes, particularly [HPA axis dysfunction](#), have been explored

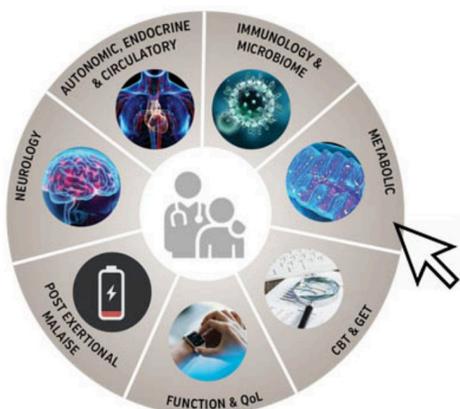


- [Mitochondrial dysfunction](#), [AMPK impairment](#), and [redox imbalance](#) have all been associated with ME/CFS.
- The body of evidence points to irregularities in various metabolic pathways, including changes in lipid and amino acid pathways, nucleotide, nitrogen, and hormone metabolism. Overall, 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

*But wait, there's more!*

## ADDITIONAL SOURCES OF INFORMATION

Solve ME's interactive research wheel summarizing promising original research by area of science, written by Rochelle Joslyn, PhD. You can access 2018 [here](#) and Q1 2019 by clicking the icon below:



Summary of the NIH April 2019 Conference "Accelerating Research on ME/CFS" by Anthony L. Komaroff, MD. Click the icon for the full slides. You can watch a recording of his talk at 06:02:00 [here](#)

### Accelerating Research On ME/CFS

Summary of the NIH meeting.... and reflections on how far we've come and still have to go

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Brigham and Women's Hospital, Harvard Medical School

April 5, 2019, National Institutes of Health

No significant conflicts of interest

# 5 PROPOSED 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 disease models proposed by Ramsay Investigators:

- Stimulation of microglia by mast cells in the hypothalamus  
[Hatzigelaki et al.](#)
- Infection-elicited autoimmunity  
[Blomberg et al.](#)

# CONSIDER:

## 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.

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.

## RESOURCES FOR PATIENT SAMPLES



## DATA COLLECTION INSTRUMENTS

### NINDS COMMON DATA ELEMENTS FOR ME/CFS

Start up resources from the NINDS CDEs can be accessed [here](#)



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

# Approaches to research that could move the needle

- Studies designed to **interrogate post-exertional malaise (PEM)**, the cardinal symptom of ME/CFS
- Studies aimed at identifying **subgroups**
- Provocation (**exercise protocol**) studies. Results from a recent research provide strong evidence that an exercise protocol has more value than measurements taken at rest to determine biological differences in ME/CFS
- **Longitudinal characterization** of the disease. Moving away from cross-sectional studies to the collection of information at multiple time points
- Include **disease controls** along with healthy controls. Comparison with related diseases (e.g. multiple sclerosis, Gulf War Illness, fibromyalgia) will clarify biological differences that are unique to ME/CFS pathophysiology, assisting in refining diagnostic criteria and developing targeted therapeutics
- **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**

Have any questions?

Want to get connected with an  
ME/CFS expert as you develop  
your proposal?

Need help identifying a  
collaborator?

Looking for access to patient and  
control samples from Solve ME's  
biobank?

*Email us at [research@solvecfs.org](mailto:research@solvecfs.org)*

