Ramsay Award Program
Application Instructions and Scope

MONDAY, JUNE 27, 2016

Background

It is now recognized that ME/CFS is a complex disease that has been disenfranchised and misunderstood, even stigmatized, for so long. Concordantly, the Institute of Medicine (IOM) was commissioned by several federal agencies including the NIH alongside AHRQ, CDC, FDA, SSA and others to establish clear clinical diagnostic criteria for ME/CFS and evaluate the current ‘state-of-the-science’. In 2015, the IOM released its 300-page report sounding the alarm regarding the dearth of investment and investigations in ME/CFS, pointing to the severe gaps in knowledge when it comes to this debilitating disease. The report underscored the complexity of ME/CFS as a multifactorial disease affecting up to 2.5 million Americans and advocated for the need of funding, collaborations, patient registries, and studies that investigate the Pathophysiology of ME/CFS. Notably, the report stated that the committee was “struck by the relative paucity of research on ME/CFS” and “was unable to define subgroups of patients or even to clearly define the natural history of the disease” to specifically recommending that “Studies aimed at assessing the natural history of the disease and its temporal characteristics (onset, duration, severity, recovery, and functional deficits) are essential for a better understanding of ME/CFS and also are important to further refine the diagnostic criteria proposed in this report.” In a press release on October 29, 2015 the NIH announced that is taking actions to bolster research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and NIH Director, Francis S. Collins, M.D., Ph.D., stated that “Of the many mysterious human illnesses that science has yet to unravel, ME/CFS has proven to be one of the most challenging.” He went on to say “I am hopeful that renewed research focus will lead us toward in identifying the cause of this perplexing and debilitating disease so that new prevention and treatment strategies can be developed.”

Scope of Solicited Research

Applications that address gaps in knowledge of energy system defects, biochemical processing of ATP-bound substrates, nutrients sensing and signaling mechanisms, neuro-inflammation, endocrine biology, cellular and systemic immunity, host/pathogen interaction, gut/brain axis, microbiome research, Post Exertional Malaise (PEM) and other characteristics of ME/CFS like Orthostatic Intolerance (OI), sleep abnormalities alongside environmental and biological risk factors are all encouraged. More specifically,

- **Bioenergetics-type projects** encompassing cellular and biophysical processes regulating energy production, the adaptation to metabolic and genotoxic stress conditions, mitochondrial dysfunction, aerobic and anaerobic bioenergetics, cellular signaling of substrate uptake, storage and processing (fat, glucose, amino acids and complex lipids), tissue oxygen delivery, REDOX biology, biochemical and free radicals toxicity, DNA damage response, reactive oxygen species (ROS), and other structures affecting ATP generation and utilization, including nutrient/gene interaction in the regulation of energy source acquisition transport, mobilization and expenditure are welcomed.
- **Neuroendocrine-focused investigations** addressing adrenergic and non-adrenergic pathways, the Hypothalamic-Pituitary-Adrenal axis (HPA), glucocorticoids regulation and signaling, Catecholamine’s energy ‘rheostats’ systems and energy balance like Leptin, Ghrelin alongside regulatory components of nucleotides, metabolites, substrates and precursors synthesis directly associated with energy production (mitochondriand and otherwise), as well as enzymes regulating glucose and fatty acid oxidation, glycolysis, TCA cycle biology, nutrient shuttle and shunting mechanisms and the transcriptional regulation of cell metabolism, hormonal response, feed-forward and feed-back adaptive response and the role of regulatory complexes (transcriptional, enzymatic and otherwise) important for the regulation of homeostatic energy systems across multiple tissues and organs are solicited.

- **Immunity and Inflammation** proposals including the area of immune-surveillance and immune-senescence biology are welcomed. That is in addition to studies addressing defined aspects of pathogen/host interaction, autoimmunity, immunotherapy and the pathologies of chronic inflammation in ME/CFS. Studies that will synergize, inform or complement existing national efforts at the NIH and the CDC (e.g., the intramural ME/CFS study at the National Institutes of Health and the clinical multisite study at the CDC) are welcomed.

In addition, investigations addressing hemodynamic changes (e.g., reduced blood volume in ME/CFS patients) and studies of **organ system physiology** nature particularly cardiovascular, cardiopulmonary, nephrology, exercise physiology, muscle contractility, neuromuscular, and associated functions as well as the detoxifying roles of the kidney and immune surveillance are welcomed. A better understanding of signaling pathways cross talk and integration between multiple organs functioning and organelles biology (e.g., ER, mitochondria) in ME/CFS using interdisciplinary studies will promote the knowledge of how cells sense and respond to genotoxic and environmental stresses or triggers. This will also identify system perturbation in the adaptive response to pathological insults that is likely deficient in ME/CFS. Furthermore, **possible determinants of heterogeneity** including endogenous and exogenous stressors such as toxic metals, pesticides and air pollution components as well as disease-associated genetic mutations (gain- or loss-of-functions), chromosomal deletions translocations, point mutations, polymorphism including Single Nucleotide Polymorphisms (SNPs) genetic variants, inherited traits and epidemiological studies that address the natural history of the disease using strong patients registries or large epidemiological studies are also invited. Studies that build on current knowledge in identifying biomarkers, innovative treatment modalities, and/or the modifiable risk and protective processes specifically targeted by preventive and/or treatment interventions are encouraged. Innovative platforms using modern investigative tools such as RNA interference, iPS, CRSPR, single-cell-analysis or large scale, high-throughput and deep-resolution profiling, identification and screening of metabolic, immune, genetic, pathogenic and phenotypic signatures in ME/CFS using imaging, NMR, mass spec, calorimetric and other technologies are welcomed. SMCI is interested in funding interdisciplinary research that will enhance our knowledge of the disease process and provide evidence based solutions to improve the diagnosis, treatment, and quality of life of all persons with ME/CFS.

**Administrative and submission details**

Please email full application as one PDF by July 29th, 2016 5:00 PM (PST) to research@solveCFS.org. Please include ALL of the following components, and in this order, with your application (use Arial or similar san serif font, 11 pt or higher):

1- Cover Pages - (Signature Page with Assurances and Certification, Contact Page, and General Audience Summary, provided)

2- Structured Technical Abstract........................................................................................................................................... 1 page

3- Budget and Justification...................................................................................................................................................... 2 page

4- Biographical Information of Applicant............................................................................................................................ Form provided

5- Biographical Information of Key Personnel .................................................................................................................. Form provided

6- Research Plan (up to 5 pages, excluding Facilities and References) ................................................................................
A. Specific Aims ........................................................................................................................................................................
B. Background and Significance ................................................................................................................................................
C. Preliminary Studies (if available) ........................................................................................................................................
D. Research Design and Methods ...........................................................................................................................................
E. Statement of ME/CFS Relevance .........................................................................................................................................
F. Facilities .................................................................................................................................................................................
G. References ...............................................................................................................................................................................

Appendix
- Subcontract Documentation/consortium agreement (if applicable)
- Letters of collaboration (if applicable)