State of the Knowledge Workshop

# Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research

**April 7–8, 2011**

National Institutes of Health
Bethesda, Maryland

# Workshop Report

*Sponsored by*

**the Office of Research on Women's Health**
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*In collaboration with*

**the Trans-NIH ME/CFS Research Working Group**

The Office of Research on Women's Health gratefully acknowledges the support and assistance of the Trans-NIH ME/CFS Research Working Group, members of the HHS Chronic Fatigue Syndrome Advisory Committee, and patients/advocates in the planning of this workshop. A list of the Workshop Planning Committee members can be found in Appendix 4.

The Workshop was held on April 7–8, 2011, in Building 31C, Conference Room 10, on the Bethesda main campus of the National Institutes of Health. The conference was videocast live on the Internet, and an archive of this transmission can be found on the NIH VideoCast Past Events page:

Day 1 (April 7): **http://videocast.nih.gov/summary.asp?Live=10098**
Day 2 (April 8): **http://videocast.nih.gov/summary.asp?Live=10114**

The Trans-NIH ME/CFS Research Working Group Web site is available at: **http://orwh.od.nih.gov/CSF%202011/CFS_home.htm**
A current list of resources for research investigators can be found on this Web site.

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# Executive Summary

The core symptom of chronic fatigue syndrome (CFS), sometimes referred to as myalgic encephalomyelitis (ME) or ME/CFS, is fatigue, a common experience associated with many other illnesses. Additional symptoms range broadly and can be confused with manifestations of acute viral infections, chronic illnesses, or the mere impact of daily living. They include impaired memory, concentration problems, enlarged/tender nodes, sore throat, headaches, stiff head and neck, muscle pain, multijoint pain, unrefreshing sleep, and general weakness.

Individuals with ME/CFS, their families, and their caregivers have gone through untold suffering and difficulties from a disease that is poorly understood and for which there is relatively little to offer in the way of specific treatments. There is no question that this disorder needs further definition, and it is possible that ME/CFS may encompass more than one etiology. As research continues across body systems to uncover the underlying mechanisms and manifestations of ME/CFS, moving toward a more interdisciplinary, collaborative approach may be the most effective way to investigate this complex illness.

The Office of Research on Women's Health, in collaboration with the Trans-NIH ME/CFS Working Group, hosted an NIH State of the Knowledge Workshop on ME/CFS on April 7–8, 2011, to bring together patients, advocates, and scientists from across the Nation to review and discuss the opportunities and gaps in ME/CFS research. The Workshop was broken into overlapping categories to address the interdisciplinary nature of this illness including: infectious diseases, systems biology, immunology, neurology, exercise physiology and energy metabolism, diagnosis and biomarkers, treatment, and opportunities for communication.

The cause of ME/CFS is unknown, yet an **infectious disease** etiology is plausible because of to the frequent abrupt onset of the illness with a classic viral-like syndrome and the similarity of the chronic symptoms to other prolonged infections. Multiple viruses have been studied in connection with ME/CFS, including Epstein-Barr and a host of other herpes viruses, enteroviruses, and a virus of debatable origin, XMRV. Studying viruses and the body's response to them over time is a complex process, beginning with where and how to gather clinical specimens. The level of virus in the blood may not be indicative of continued infection or inflammation, yet other body tissues, such as muscles, organs, or the brain stem, may be harboring virus proteins and responding to their presence.

How the immune system interacts with other body systems, such as the central or peripheral nervous system, is an area of deep interest. In researching the **immunology** of ME/CFS, many possible models can be considered. One of these, as presented in the Workshop, is that pathogenesis for ME/CFS comes from a genetic predisposition combined with a triggering event or infection and, in many cases, mediators (immune, endocrine, neuroendocrine, sleep disorder, psychosocial, viral reactivation or persistence) creating, in effect, the perfect storm resulting in ME/CFS. Studies suggest immune abnormalities consistent with chronic viral infection, such as immune activation, poor antiviral cell function, cytokine regulatory disruptions, and abnormalities of neuropeptide Y and cytokines that interface with autonomic, endocrine, and neurologic mediators. Some of these studies point to reasonable biomarkers for disease presence and severity, possibly leading to future therapeutics.

There is some controversy regarding the immune system research focus for ME/CFS based on a lack of consistency in research findings, suggesting only some patients diagnosed with ME/CFS have an immune dysfunction, while others primarily have something else wrong, possibly with their nervous system. **Neurology** is an active area of research for ME/CFS. Studies look at chronic pain pathways; autonomic nervous system dysfunction, such as orthostatic intolerance; the process of central sensitization and the impact of stress on immune function. There is also extensive focus on the brain as the possible source or residence of the illness, and functional neuroimaging studies are looking at changes in brain structure and function in people with ME/CFS.

Postexertional malaise is a signature symptom of ME/CFS. Researchers interested in **exercise physiology and energy metabolism** are able to study the capacity of the cardiovascular system to supply oxygen to active

muscles and the pulmonary system's ability to clear carbon dioxide from the blood via the lungs, which give a quantifiable measure of clinical stress and the metabolic cost of doing work. In the case of ME/CFS, these capabilities are a means to objectively assess fatigue and postexertional malaise, with studies looking at recovery time in patients with ME/CFS who exercise.

**Systems biology** is a research approach that integrates and analyzes complex data from multiple sources using interdisciplinary tools and computational biology. It is a particularly useful approach for complex disorders, such as ME/CFS, that appear to involve a dysregulation of multiple body systems, such as the immune, endocrine, and nervous systems. Using a computational biology approach, researchers can determine the degree to which a single protein or gene (biomarker) communicates with a broad range of other biomarkers that form a network profile in patients compared with healthy controls.

A critical piece in identifying biomarkers involved in a complex illness is getting an accurate phenotype of the patient. As more objective measures of ME/CFS become known, identifying **biomarkers** that can be used for **diagnosis** and treatment will be within reach. Although investigators are eager to find genetic markers of ME/CFS, the complexity of this disease makes such discoveries difficult. A number of biomarkers have been described but need to be validated in ME/CFS patients, including natural killer (NK) cell function, perforin, cell membrane dipeptidyl peptidase-4 (CD26 antigen), and levels of various individual cytokines. Workshop panelists strongly encouraged continued research in identifying biomarkers for ME/CFS.

The **treatments** available to people with this illness can be broken into two categories: symptom alleviation and disease-targeted interventions. The first step, however, is making an accurate diagnosis, which includes learning everything about the patient, understanding how he or she fits into the various case definitions, and determining where overlapping comorbidities exist. Some underutilized and understudied approaches to this illness are worth continued interest, including self-management, which refers to all of the ways people cope with a chronic condition to manage the symptoms, as well as cognitive behavioral therapy. Pharmacologic approaches depend on illness course and symptoms. However, the biggest barrier to treating patients, according to Workshop participants, is lack of informed clinicians and limits to the amount of time physicians can spend with a patient to understand and address the complexities of this illness. Workshop panelists discussed opportunities to expand awareness of ME/CFS.

Throughout the Workshop, participants identified opportunities for advancement in the current research paradigm for ME/CFS, beginning with a need to define and standardize the terminology and case definitions. They suggested more cross-system research, as seen in the systems biology approach. Creating more coordinated and collaborative systems for sharing research included developing standard operating procedures for the field, within and across labs, as well as common data elements. The Workshop pointed to gaps in the ME/CFS field, including study design, types of studies, outcome measures, reproducibility, and animal models. ME/CFS requires an interdisciplinary approach ranging from the cellular to the clinical level, and, as one participant suggested, reverse translational research, starting from the bedside and looking back to the bench.

## Introduction

The **NIH State of the Knowledge Workshop: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research** brought together 32 investigators from a wide variety of scientific disciplines to discuss ME/CFS research. The goals of the Workshop were to: (1) evaluate what is known about this disease, recognizing what is scientific fact and what is still theory; (2) identify gaps in the many research areas that deal with ME/CFS; and (3) look for outstanding opportunities where science and technology might lead to improvements in medical care for these patients who have suffered far too long. The Workshop helped to build an interdisciplinary foundation that the Trans-NIH Working Group members can use to understand the complexity and details of this disease. [Note: *NIH supports highly meritorious research on CFS or ME and does not distinguish between the two names. Therefore, in this Workshop report, the disease will be referred to as ME/CFS.*]

## Overview

Chronic fatigue syndrome (CFS), sometimes referred to as myalgic encephalomyelitis (ME) or ME/CFS, is a debilitating disease that lacks a universally accepted case definition, etiologicagent, diagnosis, or treatment. Its core symptom is fatigue, a ubiquitous human experience and a symptom associated with many other illnesses. Other symptoms, which range broadly and depend on the case definition used, include a selection of the following: impaired memory, concentration problems, enlarged/tender nodes, sore throat, headaches, stiff head and neck, muscle pain, multi-joint pain, unrefreshing sleep, and general weakness. People with this illness generally exhibit more severe symptoms after exertion, even if modest.

In the plenary overview of the Workshop, the presentations focused on the experience and presentation of this illness and the criteria used in diagnosis. In a study of 444 patients at Brigham and Women's Hospital in Boston who met the Centers for Disease Control and Prevention (CDC) diagnostic criteria for CFS between 1983 and April 2011, 74 percent of the patients were women, with an average age at onset of 33 years. The youngest patient was 10 and the oldest was 77 years of age at the onset of illness. In these patients, the duration of symptoms ranged from 0.8 to 50 years, with a median of 21 years. The severity of fatigue at its worst has left 27 percent bedridden and 29 percent shut in, with social consequences leaving half unable to work full-time and 21 percent unable to work at all. Of these patients, 66 percent cannot meet responsibilities of the family and 86 percent had to curtail their social life. ME/CFS started suddenly in 78 percent of these patients with a flu, virus, or bad cold, with symptoms including sore throat, fever, cough, swollen glands, headache, diarrhea, and aching muscles.

Many of the core symptoms of ME/CFS are similar to what people experience now and then in the course of their lives, with or without other illnesses. Determining how these symptoms are different from the symptoms of ME/CFS is critical to the study and treatment of the illness. A study published in the *American Journal of Medicine* in 1996 compared the frequency of ME/CFS symptoms in people with ME/CFS and healthy controls, as well as people with multiple sclerosis (MS) and major depression. All patients were evaluated using the same instrument. ME/CFS symptoms are reported much more frequently in people with ME/CFS than in healthy controls. ME/CFS symptoms are reported more often than in patients with MS, except for forgetfulness and arthralgias (joint pain). ME/CFS symptoms also are reported more often than in patients with depression, except for impairment of concentration, awakening unrested, and myalgias (muscle pain).

Three major case definitions are used in diagnosing and studying this illness. These include the following:

**Myalgic encephalomyelitis (ME)** is a case definition developed in Great Britain[1] in 1988 that involves (1) muscle fatigability after minimal exertion plus a delay in recovery of muscle power, often lasting up to 5 days; (2) involvement of the central nervous system, including cardinal features such as impaired memory and concentration, disturbed sleep, and other signs of autonomic dysfunction; and (3) circulatory impairment (e.g., cold extremities, a grey pallor preceding reports of feeling unwell, and hypersensitivity to climate change).

A **chronic fatigue syndrome (CFS)** working case definition[2] also was developed in 1988 in the United States in which individuals need to report 6or more months of persistent or relapsing debilitating fatigue that did not resolve with bed rest. Also, participants were required to report at least 8 of 11 minor symptoms. This definition was revised in 1994[3] with sponsorship from CDC, requiring the concurrent occurrence of four or more of eight symptoms: sore throat; tender cervical or axillary lymph nodes; muscle pain; multiple joint paint without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; postexertional malaise lasting more than 24 hours; and persistent or recurring impairment

in short-term memory or concentration. In 2005, an empiric CFS case definition was developed[4] again by CDC to provide more guidelines and specific criteria.

Finally, Canadian criteria were developed in 2003, known as **myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)**. This case definition[5] requires specific symptoms including postexertional malaise, unrefreshing sleep, two or more neurocognitive manifestations, and at least one symptom from two of the following categories: autonomic manifestations, neuroendocrine manifestations, and immune manifestations.

These case definitions present a number of problems according to plenary presenters. For example, the lack of consistency in using one definition across the world is a major impediment to replicating findings in research and makes it exceedingly difficult to identify biomarkers for the disease. In addition, some of the case definitions lack explicit criteria for what meets threshold to be counted as one of the symptoms. As a consequence, some investigators use the occurrence of symptoms, rather than severity and frequency, to identify whether a person meets the threshold. Moreover, the most commonly used definition across the world, CFS/Fukuda,[6] is a "polythetic criteria," meaning that not all symptoms are needed to make a diagnosis. Rather, researchers and clinicians can select any four of eight symptoms instead of requiring a core common group of symptoms for a diagnosis. Finally, how a question is asked and how the data is collected can affect diagnosis.

The largest source of diagnostic unreliability is criterion variance. If the rules for identifying who is a patient and who is not differ, then problems will occur, not only for a patient seeking an accurate diagnosis, but for the entire scientific enterprise. According to presenters, working toward a single, more usable, and accurate case definition for this illness would create a more solid foundation for research and ultimately benefit people living with this illness. For any illness still defined exclusively by symptoms, the question remains: What is the underlying biological basis for this illness? Much of the current research is what one presenter coined "reverse translational research" whereby scientific hypotheses about the biology of the illness are generated on the basis of clinical observations ("from bedside to bench") and then tested scientifically. Accordingly, many intriguing possibilities garnered from clinical observations could influence future research.

## Infectious Diseases

Despite ongoing controversy about the etiology of ME/CFS, an infectious disease ideology is plausible and worthy of continued research, based on a number of factors, including

- the frequent abrupt onset of the illness with a viral-like syndrome in many patients;
- the temporal association between that acute illness in previously healthy and energetic individuals and the evolution of the symptoms that characterize ME/CFS;
- the similarity of the chronic symptoms to other prolonged infections such as EBV-induced infectious mononucleosis, which can last for 6months, a year, or more; and
- the occasional clustering of cases suggesting an infectious spread.

Three theories define possible pathways by which infections could lead to ME/CFS. The **single agent theory** suggests the patient is exposed to an agent that causes acute illness and then may or may not persist but initiates an overwhelming abnormal host inflammatory response. The **immune theory** proposes that any one of a number of infectious agents, or a co-infection of two or more agents, may trigger an inappropriate autoimmune response that persists. Finally, since only a small minority of people exposed to microbial illnesses develop ME/CFS, the **genetic susceptibility theory** contends that those individuals who develop a postinfectious inappropriate autoimmune response are genetically predisposed to respond in this manner.

Several viruses, bacteria, and parasites have been linked to ME/CFS, yet none have been confirmed as being consistently associated or causative. These include Chlamydia, mycobacteria, giardia, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), enteroviruses, and xenotropic murine leukemia virus-related virus (XMRV). Evidence of association includes antibodies to microbial proteins, isolation of the infectious agent or some of its proteins, and nucleic acid identification. Infections with these microbes are quite common, and they can be isolated in healthy individuals as well as those with diseases other than ME/CFS. The way in which these microbes might cause ME/CFS remains to be determined.

Stress is a potential co-factor in viral pathogenesis of ME/CFS. For example, stress is reported to reactivate latent EBV infections through activation of the production of stress hormones (e.g., glucocorticoids) and neuropeptides via the hypothalamic-pituitary-adrenal medullary axis. These hormones play significant roles

in immunomodulation. Furthermore, reactivation of latent viruses results in the release of complete virus particles, incomplete particles, and "naked" viral proteins. The bioeffects of such viral components on disease pathogenesis are not fully understood. Latent virus activation may be involved in the transactivation of endogenous retroviruses and the subsequent stimulation of immune components. The anti-EBV antibody patterns are distinctly different from each other in individuals with infectious mononucleosis, Burkitt's lymphoma, nasal pharyngeal carcinoma, and ME/CFS, the first three of which have a definite association with the virus.

Human enteroviruses, including poliovirus, coxsackievirus, and echovirus, are another group of viruses that have been speculated to have a role in the etiology of ME/CFS. These viruses are capable of infecting and persisting in many organs where viral proteins and genetic mutants can be produced for extended periods. The possible role of enteroviruses in ME/CFS remains under investigation and will benefit from advances being made in molecular virology.

Evidence of infection with XMRV, a gammaretrovirus, in ME/CFS patients from geographically disparate regions has produced wide excitement in the ME/CFS communities. A 2009 paper[6] presented research that detected XMRV proteins, nucleic acids, host antibodies, and intact virus particles significantly more often in patients than in healthy controls. Subsequent research[7] reported that a high proportion of CFS patients harbored polytropic and modified polytropic murine leukemia viruses (MLV) distinct from XMRV. Polytropic MLV gag sequences were detected in some patients more than 15 years after their initial detection although they were only distantly related to the initial isolate.

The interest in the XMRV association with ME/CFS has been mitigated by numerous failed attempts to replicate the results from the original paper. In addition, studies of mouse genomes identified two different endogeneous proviruses that contained portions of the XMRV genome (*preXMRV-1* and *preXMRV-2*). These parts are believed to have recombined as XMRV in human prostate cancer cells during repeated passage through immunologically defective nude mice between 1992 and1996. Furthermore, XMRV has been detected in laboratory reagents that also tested positive for mouse mitochondrial DNA, indicating the presence of contaminating mouse DNA.

Two large NIH-funded projects are underway to help resolve the debate around XMRV association with ME/CFS. A study coordinated by the National Heart, Lung, and Blood Institute (NHLBI) is distributing panels of XMRV positive and negative serum and cells to five laboratories for testing. In the other study supported by the National Institute of Allergy and Infectious Diseases (NIAID), new blood samples from ME/CFS patients and healthy controls are being collected at six different geographic sites to be evaluated for XMRV/MLV at the Food and Drug Administration (FDA), CDC, and a private research institute.

## Systems Biology

Systems biology is a research approach that integrates and analyzes complex data from multiple sources using interdisciplinary tools and computational biology. It is a particularly useful approach for complex disorders such as ME/CFS that appear to involve a dysregulation of multiple body systems, including the immune, endocrine, and nervous systems. Research is revealing how these systems work in a closely coordinated fashion, each system with its own dynamics as well as dynamics coupled across systems. Using a computational biological approach, researchers can determine the degree to which a single protein or gene (biomarker) is connected to a broad range of other biomarkers that form a network profile in patients versus healthy controls.

The temporal expression profiles of specific antibodies, cytokines, hormones, chemokines, lymphocyte subsets, cell receptors, neuropeptides, and mRNAs may reveal patterns that can stratify ME/CFS patients as well as differentiate them from healthy individuals. For example, certain immunologic biomarkers in ME/CFS patients tend to cluster and form networks that can be shown, both visually and statistically, to be different from healthy individuals or subjects with other diseases. An example shown at the Workshop indicated that ME/CFS patients had a unique pattern of responses before, during, and after exercise challenge than did healthy controls or Gulf War illness patients. These responses also were able to distinguish male from female patients, suggesting possible sex differences in pathogenesis. Such network analyses may lead to early diagnostic tests and new treatments for ME/CFS, as well as a better recognition of dysfunctional pathways that may be associated with this illness.

Communication within and between the immune, neuroendocrine, vascular, and muscle systems is critical to maintaining health and appears to be disrupted in ME/CFS. The immune system communicates with the brain through three known pathways: the humoral pathway (through the blood), the neural pathway (through the

nervous system), and the cellular pathway (where activated cells migrate into the brain). An understanding of these modes of communication can help to explain how infection and inflammation lead to changes in appetite, mood, and energy level; sensitivity to pain; and deficits in learning and memory. In a series of acute infection experiments in mice, levels of cytokines (e.g., interleukin-1, interferon gamma, tumor necrosis factor) increased in the brain and were associated with transient behavioral changes lasting approximately 1 day. However, with chronic infection, there appeared to be a switch to mood and cognitive symptoms indicative of depression-like behavior, with the mice becoming less mobile and no longer preferring sugar water. To test the theory that chronic infection affects mood and cognition, researchers treated the mice with an antibiotic to limit infection and the production of proinflammatory cytokines, which resulted in reductions in both sickness-related behaviors and later mood changes. Further experimentation showed that blocking the immunomodulatory enzyme indoleamine 2,3-dioxygenase (IDO) prevented the development of depression in the mice without having an effect on the infection. Additional research in pre-clinical animal models may lead to potential interventions for patients with ME/CFS. Possible interventions for chronic infection/inflammation effects on the brain include antibiotics, cytokines, inflammatory cytokine blockers, omega-3 fatty acids, IDO blockers, neutraceuticals, moderate exercise, and behavioral interventions to increase parasympathetic tone.

CFS involves a large number of genes and a highly heterogeneous phenotype, which means the probability of finding the genetic basis of the disease is very small right now. This raises a number of questions. Should researchers focus on DNA when the heritability of the disease is unknown, or on RNA and proteins to understand the expression signatures? Moreover, where should the samples come from? In the absence of specific anatomic lesions, researchers are left only with blood samples to study, yet tissue samples are proving to be important. If research needs to be tissue dependent, what kind of tissue should be used? Finally, other research constraints include the duration and onset of the illness, which are major barriers for genomic studies, and samples sizes.

In looking across the past 10 years of genomics research on ME/CFS, the broad range of studies often lack comparable elements. Research on gene expression profiles of ME/CFS has inconsistent study designs or measurements, including different platforms, sample collections, and analytical techniques. Most studies looking for biomarkers and DNA susceptibility genes have been focused on the immune system, the hypothalamic-pituitary-adrenal axis, and the neurotransmitter serotonin.

Investigators are now pursuing a host of studies on integrated convergent functional genomics. Amassing the results from various genomic studies (single nucleotide polymorphisms, mRNA transcription, and DNA methylation) using different types of assay platforms, microarrays, or deep sequencing is helping to better define the ME/CFS phenotype. Such studies are revealing potential candidate genes and markers, such as *GRIK2* and *NPAS2*, associated with some of the hallmark symptoms of ME/CFS, namely fatigue, impaired memory, and unrefreshing sleep.

Another line of genomics research pertinent to the study of ME/CFS is endophenotyping, a process that essentially deconstructs the phenotype of an illness into its underlying parts. These subphenotypes, also known as internal phenotypes, are generally seen as patterns of symptoms that are physiologically or biochemically distinct and therefore likely have select underlying genetic associations. In ME/CFS, multiple subphenotypes are worth further study, with inflammation appearing as the most likely common underlying mechanism. Looking forward, research is beginning to uncover pathways focused on the genetic evaluation of immune- and inflammation-related genes, which may reveal functionally relevant polymorphisms associated with symptoms of ME/CFS.

## Immunology

The response of the immune system to a particular illness is complex to study and interpret. The immune system is not an independently acting system but communicates and works in collaboration with the endocrine and central nervous systems. Immune reactions are initiated in response to infections, tissue damage, dead and dying cells, and small disruptions in the integrity of the gut lining, or epithelium. Many different immune responses can happen at the same time in a single host. Immune alterations occur in ME/CFS, but it is not clear what they are or their cause and effect. ME/CFS research has shown evidence of immune activation and inflammatory responses, poor antiviral cell function, cytokine regulatory disruptions, and abnormalities consistent with chronic viral infections or postviral sequelae.

In researching the immunology of ME/CFS, one can consider many possible models. For example, Workshop presenters suggested that pathogenesis for

ME/CFS could come from a combination of a genetic predisposition combined with a triggering event, such as an infection, resulting in the release of immune, endocrine, or neuroendocrine mediators that can eventually result in ME/CFS. Two types of cells known to function abnormally in patients with ME/CFS are natural killer (NK) cells and cytotoxic T cells (CD8). Both function in a similar way to rid the body of virally infected cells. Both recognize infected cells, attach and deliver cytolytic enzymes to the cell, and move onto a new target. The difference between them is in cell recognition: the more primitive NK cells look for "nonself", whereas cytotoxic T cells clonally expand to create large numbers of antigen-specific cells. Both NK and CD8 cells require perforin, a molecule necessary for the killing of virus-infected and tumor cells. Perforin appears to be low in NK and CD8 cells in people with ME/CFS, relative to healthy controls. Both of these lymphocytes, as well as many other immune cells, can respond to viral nucleic acids in their cytoplasm. Polymorphisms in the genes encoding these viral response molecules, and the pathways they activate, may represent one area in which genetic predispositions can lead to ME/CFS.

Another path of research is the analysis of gene expression and cytokine production in people with ME/CFS. Studies collecting data tagged as "good day" or "bad day" from patients with ME/CFS or comparing symptoms of ME/CFS with those of Gulf War illness (GWI) before, during, and after exercise are beginning to point to immune abnormalities consistent with chronic viral infection. These include immune activation; poor antiviral cell function; cytokine regulatory disruptions; and abnormalities of neuropeptide Y and cytokines that interface with autonomic, endocrine, and neurologic mediators. Cytokines such as interleukins 5 and 6, soluble CD26, and neuropeptide Y are emerging as potential biomarkers for disease presence and severity. Injection of pro-inflammatory cytokines into animal models reproduces some of the symptoms of ME/CFS. These data suggest that blocking the release of inflammatory cytokines (e.g., tumor necrosis factor inhibitors) or preventing activation of immune cells while preserving antiviral immunity may have potential therapeutic benefit.

The characterization of immune alterations in ME/CFS has led to inconsistent results. A literature review conducted in 2002 on the immunology of ME/CFS pointed to a high level of discrepancy, and the only consistent results were a positive antinuclear antibody test, which indicates a possible autoimmune reaction, and reduced NK cell count and activity. A number of possible reasons could account for discrepant results across studies, including unmatched controls, statistical errors, patient pool heterogeneity, single timepoint studies, or assaying the wrong immune variable. A more thorough analysis of immune parameters using high-throughput techniques to study well-matched patients has the potential to address some of these discrepancies. Other data point to the possibility that ME/CFS may not be an immune dysfunction disorder but rather a primary dysregulation in the nervous system, with some data suggesting an encephalopathy. It is possible that the immune dysfunctions observed in ME/CFS are in response to neurologic damage rather than the cause of this damage.

## Neurology

The nervous system is considered to play a significant role in ME/CFS in concert with other body systems, genetics, and the environment. Research in animal models has been invaluable to the study of how the nervous system works in humans, both in health and disease. However, because the cellular and molecular mechanisms involved in the major symptoms of physical and mental fatigue of ME/CFS are quite poorly understood, the development of relevant animal models has been difficult. Nevertheless, mouse models used in the study of chronic muscle pain have reported that at least two molecular ion channel receptors must be activated concurrently to detect muscle fatigue and muscle pain. These receptors, thought to be part of a sensory ion channel receptor complex, detect a unique combination of lactate, overall pH levels, and adenosine-5'-triphosphate (ATP) levels that are produced by muscle activity. Additional research in animal models has pointed to purinergic 2X receptors, especially *P2X4*, as receptors of potential significance to ME/CFS research because they appear to be involved in chronic pain.

Applying these findings to the study of people with ME/CFS, researchers are looking at gene expression associated with postexertional malaise in patients with ME/CFS alone, fibromyalgia (FM) alone where pain is the primary symptom, ME/CFS with comorbid FM, MS when fatigue was a primary debilitating symptom, and healthy controls. Using a stationary bicycle with moving arms with participants who had not exercised for 48 hours, researchers administered a moderate, 25-minute exercise task in the morning that raised the participants' age-predicted maximum heart rate to 70 percent. They drew blood before the exercise and at 30 minutes, 8 hours, 24 hours, and 48 hours after the exercise. Gene expression (mRNA) assays on leukocytes measured levels of three different catego-

ries of biomarkers: sensory ion channel receptors, the adrenergic receptors and enzymes, and cytokines and cytokine receptors. These genes are thought to be part of a co-regulated, complex genetic pathway.

Findings from this study point to increases in expression of the entire gene profile 30 minutes after exercise, with ion channel receptors significantly greater in ME/CFS patients versus controls across the 48-hour period. The interacting ion channel receptors are up-regulated after exercise. The adrenergic genes also are significantly increased, as well as those for IL-10 receptor. As a biomarker for ME/CFS, only four of these genes are needed to very clearly differentiate patients from controls: *P2X4*, alpha 2A and beta 2 adrenergic receptors, and cytokine IL-10.

An area of potential interest to ME/CFS is the role of autonomic nervous system (ANS) dysfunction on the symptoms associated with ME/CFS. Such neurologic dysfunction is characterized by orthostatic hypotension, tachycardia, cold extremities, episodes of sweating, pallor, sluggish papillary responses, constipation, or increased frequency of micturition. These changes lead to lightheadedness, dizziness, weakness, fatigue, and cognitive slowing—all symptoms associated with ME/CFS. Reports hypothesize that immunologic damage to the nerves following an acute viral illness may be responsible for ANS dysfunction.

Another relevant research path for ME/CFS is the study of central sensitization. In healthy patients, if there is inflammation somewhere in the body, the peripheral sensory system activates spinal cord and brain immune cells (microglia) that work to regulate the amount of pain a person feels. In neuropathic pain or centrally mediated pain, this activation leads to hypersensitivity, with a disruption of inhibitory interneuron activity and outgrowth and activation of large sensory neurons that innervate the same and surrounding tissue regions as the small type-C fibers. As a result, even the slightest touch causes tremendous pain, known as allodynia.

The change that occurs in central sensitization is thought to be primarily on the post-synaptic neurons, which receive signals from multiple molecular messengers, including substance P, calcitonin gene-related peptide (CGRP), glutamate, and brain-derived neurotrophic factor (BDNF). The down-regulation of the inhibitory neurotransmitter gamma amino butyric acid (GABA) levels reduces its normal inhibitory effects on these cells, previously activated by excessive glutamate and other neurotransmitters. Proposed as a mechanism for migraines, central sensitization may lead to cognitive problems, fatigue, and sensitivity to light, pain, noise, and odors—all symptoms associated with ME/CFS. Recent research has pointed to a high prevalence of migraines, almost 80 percent, in patients with ME/CFS.

## Exercise Physiology and Energy Metabolism

Exercise, and even simple physical activity, involves nerves, blood flow, hormones, metabolism, and physical movement. Studying how muscles function reveals this multisystemic process. Looking specifically at a voluntary muscle contraction, the pathway of force production begins in the central motor system and delivers a signal to the peripheral nervous system where activation of the muscle occurs. Energy metabolism provides the necessary fuel, as well as producing byproducts that can inhibit contractile function.

Research does not point to notable differences in muscle strength and muscle fatigue in people with ME/CFS versus healthy controls. Some evidence points to impaired central motor drive and delayed recovery of force in ME/CFS, but overall, findings indicate normal muscle fibers with respect to histology and biochemistry. A number of reports indicate that at the same relative workload in a single muscle group, there is a higher rating in perceived exertion in people with ME/CFS. This finding also appears to translate into whole body exercise in ME/CFS patients where exertion is higher and work capacity lower.

Knowledge gap areas highlighted at the Workshop include the following: (1) whether the central motor impairment is primary or secondary; (2) what the relationship is between impaired central motor drive, perceived exertion, and exercise capacity; (3) how physical activity is managed in ME/CFS patients; and (4) what the mechanisms are for impaired recovery from exercise. Contributing to these gaps are research design issues, uneven collection of information about the individual being studied, and lack of standardized clinical data needed to allow comparison of results from one study to the next. One Workshop presenter suggested an integrative approach, from cell to person, looking across systems, and study designs that address covariates and include potential biomarkers in sufficiently powered group sizes.

Exercise science is concerned with the capacity of the cardiovascular system to supply oxygen to active muscles and the pulmonary system's ability to clear carbon dioxide from the blood via the lungs. Cardiopulmonary exercise testing (CPET) with gas

exchange is both a quantifiable measure of clinical stress and a means to objectively assess fatigue and postexertional malaise in ME/CFS. High-effort CPET testing is unique in its ability to quantify the reduction in efficiency with measures of both workload and the metabolic cost of doing work. The amount of time a person takes to recover is where there seems to be a clear difference between ME/CFS and controls. In one study, most of the control group recovered in a day. For the ME/CFS group, the average recovery time was more than 4 days, and some had not recovered by 7 days. In the posttest questionnaires, the ME/CFS group reported a significantly larger number of symptoms, which also appeared to be aligned with the Canadian ME/CFS case definition.

Probing further into postexertional malaise, one Workshop presenter developed a unique protocol using a double test paradigm doing maximum effort tests 2 days in a row. Analyzing the data from the CPET using a multivariate technique with several univariates, there was no significance on day one between the ME/CFS group and the controls. Both groups gave maximal effort. On day two, however, there were significant differences in variables in the univariates, some of which may be related to metabolic anomalies, indicating autonomic dysfunction. Plotting the oxygen consumption at the anaerobic threshold, the controls in this study do as expected, and some even improve on the second day, suggesting a learning factor. For the ME/CFS patients, they are nearly equal with controls at the start, but they get worse in anaerobic threshold, and there is a huge decrease in efficiency in the amount of work that they produce for the same sort of oxygen delivery.

These data suggest that the CPET with gas exchange is an objective measure of fatigue in ME/CFS, especially compared with other tests such as the 6-minute walk test. Furthermore, single exercise tests may be insufficient to distinguish between ME/CFS and sedentary controls. If postexertional malaise is a true artifact of ME/CFS, a 2-day test should show increased symptoms, whatever the underlying etiology is. As discussed in the Neurology section of the Workshop, research also has found that orthostatic intolerance is strongly associated with ME/CFS. There appears to be an overlap in symptoms of two common forms: postural orthostatic tachycardia syndrome (POTS) or neurally mediated hypotension (NMH). Patients with ME/CFS at all ages consistently have a worsening of the ME/CFS symptoms within minutes of upright posture, and usually long before changes in heart rate and blood pressure became evident. In one study of adults, the patients had rates of 95 percent reporting worse ME/CFS symptoms during upright tilt. Studies have pointed to additional stressors associated with orthostatic intolerance that bring on or exacerbate significant fatigue in ME/CFS patients, only one of which was physical exertion. Others included hot showers, prolonged standing, and a warm environment. Moreover, in a subset of patients with ME/CFS, treatment of orthostatic intolerance is associated with improvement in ME/CFS symptoms and function. One Workshop presenter suggested that recognition and treatment of orthostatic intolerance provides an avenue for pragmatic individualized treatment of symptoms in those with ME/CFS.

## Diagnosis and Biomarkers

Biomarkers are becoming the essence and pillar of research into human disease, in large part due to their capacity to reduce the cost and time required to conduct epidemiologic and clinical studies. While some major questions are currently being raised in the biomedical field as to what makes a biomarker and how to identify one, for ME/CFS, there is movement toward this research, with suggestions from Workshop participants to stratify biomarkers into four broad categories: (1) diagnostics, (2) predictive and preventive, (3) metabolism biomarkers to determine how a patient metabolizes a particular medication and to help with dosing and schedule, and (4) outcome biomarkers to forecast the disease response itself.

Biomarkers for at-risk populations can be as simple as retrospective studies looking at the severity of an acute illness as a predictor of who will remain ill years later and represent potential at-risk population definers. Some markers define ill populations and subgroups, and other markers measure the autonomic/immune domains associated with disease. A number of biomarkers have been tested and might potentially be used in ME/CFS:

- NK cell function is useful as a biomarker for severity of disease, but methodological issues limit its widespread use.
- Perforin assayed by flow cytometry is reproducible and can be a surrogate for NK cell function.
- Dipeptidyl peptidase-4 (CD26) is an excellent cell membrane biomarker candidate with clear distinction between controls and ME/CFS patients. It may have a direct role in disease persistence.
- Neuropeptide Y bridges autonomic and immune function and is directly affected by soluble CD26. It correlates with severity of illness.
- New cytokine multiplex methods can look at individual cytokines and patterns of cytokine

abnormalities. Panels point to pro-inflammatory cytokine elevations, TH2 cytokine elevations, and drops in anti-inflammatory cytokines in ME/CFS. Statistical analyses point to cytokines as some of the best putative biomarkers to define the patient population. The patterns of cytokine elevation also suggest directed therapies to down-regulate the inflammatory cascade.

- Genomic studies have great promise in identifying putative biomarkers and pathways and helping to explain this multisymptom illness. Genomics studies also are beginning to identify at-risk populations.

Continued research on biomarkers for ME/CFS, including biomarkers that are mediators of the illness, has the potential to aid in diagnosis, and treatment, and prevention.

A critical factor in identifying genes involved in a complex illness is getting an accurate phenotype. This can be difficult for some illnesses, such as ME/CFS, in which there are multiple case definitions and the illness course can ebb and flow quite dramatically. To further facilitate research progress, cell line and tissue repositories available to researchers around the world are needed as a permanent resource.

Looking to research in other illnesses also can provide insight. For instance, one Workshop presenter discussed the example of responses to the HIV virus and the multiple variables along the way, beginning with the fact that not everybody exposed to HIV gets AIDS or certainly not at the same rate. A whole constellation of various outcomes can occur in some patients with an AIDS-defining condition and not others, at varying rates. As drugs and vaccines continue to be developed, not everyone will respond to those agents equally. Early research on AIDS discovered a mutation in the *CCR5* gene, the major co-receptor for HIV, which led to a whole new class of anti-HIV pharmaceuticals either blocking the receptor or blocking the region where HIV binds to the receptor. Taking these findings further, researchers were able to show, through survival analysis, how these genes and other genetic factors affect the rate at which people get the disease, identifying genetic factors involved in disease progression. This kind of time-dependent analysis could be applied more in chronic diseases, such as ME/CFS, to look beyond who gets a disease to studying the rate at which it progresses.

Turning to functional neuroimaging to find biomarkers for ME/CFS, one Workshop presenter discussed how grey matter volume is reduced or atrophied in patients versus controls and parallels performance status measures. One study looked at the influence of cognitive behavior therapy (CBT) on grey matter volume and found increases in grey matter in the dorsal lateral prefrontal cortex bilaterally that were significantly and positively related to cognitive processing speed and improved cognitive performance.

Studies using functional neural response to look at cognitive functioning during auditory monitoring found that ME/CFS patients had a much more diffuse and widespread neural response to cognitive task. In controls, response is often unilateral and very discrete. In contrast, in the ME/CFS patients, it becomes bilateral and more diffuse, indicating they are using more resources to perform the task. The ME/CFS patients perform the tasks as accurately, although a bit slower, than the controls, suggesting that they have to recruit more brain resources to maintain the same level of performance as a healthy control. Functional neuroimaging allows researchers to find possible objective representation of the subjective experience of patients.

## Treatment

Current therapeutic approaches to ME/CFS cover a broad spectrum that can be broken into two categories: (1) symptom alleviation and support, including treatments used to address fatigue or pain, and (2) disease-targeted interventions, such as antiviral and anti-inflammatory medications, agents directed at autonomic dysfunction, and stress management techniques. There are currently no established or mutually agreed-upon treatment parameters, nor are there reliably effective therapies. Even with the best of care, patients may have only some moderation of their symptoms and sometimes spontaneously improve. Workshop presenters reviewed what is known about the efficacy of certain treatments and pointed toward new treatment directions.

The first step to treating someone with ME/CFS is making a correct diagnosis, or group of diagnoses. This step includes learning everything about the patient and understanding how he or she fits into the multiple case definitions, as well as considering potential overlaps with comorbid diseases such as fibromyalgia (FM). Patients in different categories respond to treatment differently. If a clinician can make an accurate diagnosis and identify the symptoms, finding appropriate treatments is much easier. The clinician can begin to pick away at the various presentations of the illness, for example, disordered sleep, pain, physical conditioning, despair, and depression. However, this

type of supportive care medicine is a labor-intensive process that is generally not covered by health insurance parameters.

Self-management, which refers to all of the ways people cope with a chronic condition to manage the symptoms, treatment, psychosocial consequences, and lifestyle changes, has not received much attention in the behavioral literature. Yet studies show that patients prefer to self-manage their illnesses using a variety of the following techniques, both intuitive and learned:

- Pacing, to avoid over-exertion and collapse
- Cognitive coping, to lessen frustration over limitations and learn more tolerance
- Low-level exercise, for stress reduction and to increase effort tolerance
- Focused relaxation, to reduce stress
- Consistently engaging in low-effort pleasant activities.

A review of the literature on self-management points to good outcomes for many patients and very few, if any, adverse outcomes. Determining how people actually manage their lives in their own homes could provide insight into future self-management techniques. In cognitive behavioral therapy trials, 4out of 10 patients are helped. This therapy is not equivalent to recovery, but patients do improve and the treatment appears worthwhile. However, patient-reported outcomes for subjective parameters (such as symptoms) are commonly used as the primary outcomes for these types of treatment studies, and many of these are not controlled studies; for both reasons, the reliability of these findings is unknown. Some panel members discussed the need for controlled research with objective and subjective outcome parameters for future studies on potential ME/CFS therapies.

In considering treatment options for people with ME/CFS, some researchers are looking at co- morbidities seen in the illness and symptoms that appear to overlap with other illnesses. For example, approximately 25 percent of patients with ME/CFS have postural tachycardia syndrome (POTS), the disorder discussed in the Neurology and Exercise Physiology and Energy Metabolism sections. Conversely, 50 to65 percent of POTS patients meet criteria for ME/CFS. ME/CFS and POTS patients may have a distinct underlying disease or be pieces of a spectrum of disease. When patients stand up, their heart rate increases by 50 beats per minute, and they have low-frequency blood pressure variability, leading to sympathetic overactivity. One potential target for treatment for these patients is exercise conditioning in a reclining position or in the water to control the tachycardia, which may improve the overall symptoms of fatigue. Other studies are looking at beta blockers, alone and in combination with exercise, being mindful of the side effects, which include fatigue, decreased blood pressure, and lower exercise capacity. Research to gain a greater understanding of the role of POTS in contributing to symptoms in different groups of ME/CFS patients also was suggested to determine which patients might be helped by these therapies.

Treating the presumed mechanisms and physiology of ME/CFS, such as autonomic and hypothalamic-pituitary-adrenal (HPA) axis dysregulation, is successful in some patients. Hormonal manipulation also can work, but care needs to be taken in its administration because the impact on the HPA-axis can potentially have long-term adverse outcomes for the patient. Infection and immune mechanisms, such as latent viral low-grade infections and nonspecific immune dysfunction, respond to treatments with varying success, again depending on clinical presentation in individual patients. Additional research was recommended to understand the role of each of these treatment targets in different groups of ME/CFS patients, to help determine the potential applicability of these treatment approaches.

One Workshop presenter expressed interest in the effects of tricyclic antidepressants in treating people with ME/CFS and hypothesized that, in addition to the labeled effect of these drugs, tricyclic antidepressants affect some immune function, specifically inhibiting mass cell activation. Mass cells were previously thought to be involved primarily in allergic reactions, but research has revealed numerous triggers of mast cells, with approximately 50 different mediators. There is no question that mast cells are involved in inflammation. Indeed, mast cell degranulation is central to numerous pathologic conditions. Levels of substance P, a neuropeptide localized throughout the body, are elevated in people with ME/CFS and are known to be a trigger of mast cells. Increasing substance P concentration also causes mitochondrial DNA to be secreted extracellularly during mast cell activation. Mitochondria, evolutionarily, were originally microbial pathogens that became symbiotic over millions of years. If they leave the cell, they may be mistaken as a pathogen, and the body will mount an immune response. Whether this complicated process is related to ME/CFS is not clear. Further research measuring free-floating mitochondrial DNA in the blood of ME/CFS patients is needed. Currently, treatments are being tested to stop or block mast cells, including

a flavanoid called luteolin. In animal models, luteolin administration affects postexercise fatigue, increasing exercise capacity five times.

## Opportunities for Communication

Although there never has been a time of higher visibility for ME/CFS, greater scientific interest, or stronger leadership and engagement, there is still much misunderstanding about this illness and discrimination against patients as well as researchers who want to study it. Opportunities to improve communication exist and must be part of the overall research agenda. The Workshop presenters talked about best practices for communicating with all stakeholders, the stigma of ME/CFS research on faculty at academic institutions, the overall funding for research, the pace of scientific discovery and clinical implementation, and the establishment of Internet communities that share ideas, frustrations, and support. Informing patients of research progress is a challenge that NIH is addressing through several Internet-related resources, such as Web pages and email distribution lists. Panelists concurred that information presented in scientific papers can be confusing and that reporting of ME/CFS research by the popular media must ensure that coverage is accurate, understandable, and appropriate.

## Reactions by Agencies

NIH is one of the Federal agencies associated with the U.S. Department of Health and Human Services (HHS) and is an ex officio member of the HHS CFS Advisory Committee (CFSAC) to the Assistant Secretary of Health. Reactions to the workshop were presented by several other CFSAC ex officio members to give viewpoints related to their agency missions.

**The Agency for Healthcare Research and Quality (AHRQ)** has a mission to improve the organization and delivery of healthcare services and translate research into clinical practice. Support for research includes connecting researchers, clinicians, patients, and consumers. New health care reform initiatives involve comparative effectiveness or patient-outcomes research in which treatments are compared with one another. Potential AHRQ support for ME/CFS research includes an updated and thorough review of the literature, a national guideline clearinghouse that captures patient information in one accessible location, and learning and clinical networks to bring clinical ideas into the practice of primary care and improve educational outreach.

The **Food and Drug Administration (FDA)** is involved in the regulation of drug products and biologic products for the treatment and prevention of diseases. In the case of ME/CFS, if investigators or sponsors are interested in bringing forward products, they would approach the FDA for assistance with the process through the preclinical development stages; phases 1, 2, and 3 clinical trials; and finally with the hoped-for outcome of receiving a new drug application and deciding to make new products available to patients. Recognizing the importance of centralizing these activities, FDA has determined that all the products intended for CFS will be handled by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to create a coordinated and consistent process for review of products in development. In addition, the consolidation to one division will allow an efficient and effective review and develop expertise within the group. Guidances are available on the FDA Web site to help investigators and sponsors put together ideas for developing biomarkers or end points for this disease **(http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm)**. Investigators and sponsors are encouraged to contact DPARP to submit an investigational new drug application, and to request a meeting that provides advice and guidance in bringing a product forward.

The representative from the **Centers for Disease Control and Prevention (CDC)** reiterated the previous recommendation for a reverse translational research approach—using information from the bedside to inform research happening at the bench--as a prudent way to study ME/CFS. An infectious diseases etiology must be considered in which the pathogen persists in the host or causes an acute infection whereby the host is damaged and the pathogen is eliminated. The dysregulation of multiple different parts of the body adds to the complexity of ME/CFS pathophysiology and complicates clinical phenotyping of the patient. Biomarkers, quantifiable outcomes or end points, and a deeper understanding of patient genomics are critical needs for developing diagnostics and effective interventions. A consensus of the best technology currently available to study ME/CFS is needed, as well as ways to synthesize and aggregate large amounts of data.

## Moving Forward

Throughout the Workshop, participants discussed opportunities for improvements in the current research paradigm for ME/CFS, beginning with a need to define and standardize the terminology and case definitions. This need applies to simple definitions of "fatigue," as well as how to use the words "diagnostic" and "screening tests." Workshop participants also suggested more interdisciplinary research, as seen in a systems biology approach. Creating coordinated and collaborative systems for sharing research was an important topic that included creating standard operating procedures for the field, within and across labs, as well as common data elements. The Workshop pointed to gaps in the ME/CFS field, including gaps in study design and types of studies. There is a lack of longitudinal, natural history, early detection, pediatric-versus-adult-onset, and animal model studies. In addition, few studies look at comorbid conditions, biomarkers, or genetics. Moreover, study designs needed for clinical trials require further refinement. Improved and more extensive data from patient-derived and reported outcomes will better define the successes or failures of treatment interventions. To capture the extensive information from such studies, a centralized interactive database, using common data elements and accessible to everyone, is sorely needed to collect, aggregate, store, and analyze results.

The study of ME/CFS can benefit from an interdisciplinary collaborative approach using well-connected clinical and research networks. Moreover, additional highly qualified investigators must be attracted to study ME/CFS. Keeping in mind that these are lean budgetary times, the panel called for more coordination and leadership by NIH and commended the Office of Research on Women's Health as a driving force behind the transparency used in planning and execution of the Workshop and providing a home for ME/CFS research. Scientists, health care providers, patients, and advocates are encouraged to continue this Workshop dialogue. The Trans-NIH ME/CFS Research Working Group will use the information from the Workshop to help NIH understand the complexity of this illness, and look for ways to further research on this devastating illness.

## References

1. Ramsay AM: *Myalgic Encephalomyelitis and Postviral Fatigue States: The Sage of Royal Free Disease*. Second Edition. Gower Medical Publishing: London, 1988.

2. Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE, Jones JF, Dubois RE, Cunningham-Rundles C, Pahwa S: Chronic fatigue syndrome: a working case definition. *Annals of Internal Medicine* 1988; 108(3): 387-389.

3. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A: The chronic fatigue syndrome: A comprehensive approach to its definition and study. *Annals of Internal Medicine* 1994; 121(12): 953-959.

4. Reeves WC, Wagner D, Nisenbaum R, Jones JF, Gurbaxani B, Solomon L, Papanicolaou DA, Unger ER, Vernon SD, Heim C: Chronic fatigue syndrome—a clinically empirical approach to its definition and study. *BMC Medicine* 2005 Dec 15; 3: 19.

5. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, Bested AC, Flor-Henry P, Joshi P, Powles ACP, Sherkey JA, van de Sande MI: Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition, diagnostic and treatment protocols. *Journal of Chronic Fatigue Syndrome* 2003, 11(1): 7-115.

6. Lombardi VC, Ruscetti FW, Das Gupta J, Pfost MA, Hagen KS, Peterson DL, Ruscetti SK, Bagni RK, Petrow-Sadowski C, Gold B, Dean M, Silverman RH, Mikovits JA. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science* 2009; 326(5952): 585-589.

7. Lo SC, Pripuzova N, Li B, Komaroff AL, Hung GC, Wang R, Alter HJ. Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors. *Proceedings of the National Academy of Sciences*, United States 2010; (107(36): 15874-15879.

# APPENDIX 1
## AGENDA

# State of the Knowledge Workshop Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research

April 7–8, 2011

Building 31C, Conference Room 10
National Institutes of Health
Bethesda, Maryland

## AGENDA

**THURSDAY, APRIL 7, 2011**

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| 7:00 – 8:00 a.m. | **REGISTRATION** |
| 8:00 – 8:05 a.m. | **WELCOME**<br>**James M. Anderson, M.D., Ph.D.**, Division of Program Coordination, Planning and Strategic Initiatives, National Institutes of Health (NIH) |
| 8:05 – 8:15 a.m. | **OPENING REMARKS**<br>**Dennis Mangan, Ph.D.**, Office of Research on Women's Health, NIH |
| **PLENARY OVERVIEW** | |
| 8:15 – 8:45 a.m. | Anthony L. Komaroff, M.D., Harvard Medical School<br>The Clinical Presentation of Chronic Fatigue Syndrome |
| 8:45 – 9:15 a.m. | Leonard A. Jason, Ph.D., DePaul University<br>A Focus on Diagnostic Criteria and Case Definitions |
| **INFECTIOUS DISEASES** | |
| | **NIH Moderator: Catherine Laughlin, Ph.D.,** National Institute of Allergy and Infectious Diseases, NIH<br>**Co-Moderator: Harvey J. Alter, M.D.,** Department of Transfusion Medicine, Clinical Center, NIH |
| 9:15 – 9:20 a.m. | **Session Overview** |
| 9:20 – 9:40 a.m. | **Ronald Glaser, Ph.D.,** The Ohio State University<br>*Chronic Fatigue Syndrome and the Pathophysiology of EBV Infection: Trying to Connect the Dots to Make Sense* |

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| 9:40 – 10:00 a.m. | **John Chia, M.D.,** EVMED Research<br>*The Pathogenic Role of Enteroviruses in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome* |
| 10:00 – 10:15 a.m. | **MORNING BREAK** |
| 10:15 – 10:35 a.m. | **Judy A. Mikovits, Ph.D.,** Whittemore Peterson Institute<br>*XMRV and MLV-Related Viruses in Chronic Fatigue Syndrome* |
| 10:35 – 10:55 a.m. | **John M. Coffin, Ph.D.,** National Cancer Institute, NIH<br>*Endogenous Retroviral Origin of XMRV and MLV-like Sequences* |
| 10:55 – 11:15 a.m. | **Summary and Panel Discussion** |

**SYSTEMS BIOLOGY**

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|---|---|
| | **NIH Moderator: Basil Eldadah, M.D., Ph.D.,** National Institute on Aging, NIH<br>**Co-Moderator: Massimo Gadina, Ph.D.,** National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH |
| 11:15 – 11:20 a.m. | **Session Overview** |
| 11:20 – 11:40 a.m. | **Gordon Broderick, Ph.D.,** University of Alberta<br>*Regulatory Imbalance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Network Biology Perspective* |
| 11:40 – 12:00 p.m. | **Mangalathu Rajeevan, Ph.D.,** Centers for Disease Control and Prevention<br>*Genomic Studies of Chronic Fatigue Syndrome* |
| 12:00 – 12:20 p.m. | **Keith W. Kelley, Ph.D.,** University of Illinois at Urbana-Champaign<br>*From Systemic Infection to Brain Inflammation* |
| 12:20 – 12:35 p.m. | **Summary and Panel Discussion** |
| 12:35 – 1:30 p.m. | **LUNCH** |

**IMMUNOLOGY**

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|---|---|
| | **NIH Moderator: Tim A. Gondre-Lewis, Ph.D.,** National Institute of Allergy and Infectious Diseases, NIH<br>**Co-Moderator: David M. Mosser, Ph.D.,** University of Maryland |
| 1:30 – 1:35 p.m. | **Session Overview** |
| 1:35 – 1:55 p.m. | **Mary Ann Fletcher, Ph.D.,** University of Miami, Miller School of Medicine<br>*Immunology of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and GWI* |
| 1:55 – 2:15 p.m. | **Benjamin Natelson, M.D.,** Albert Einstein College of Medicine<br>*Chronic Fatigue Syndrome and Fibromyalgia Are Not Always the Same* |
| 2:15 – 2:30 p.m. | **Summary and Panel Discussion** |
| 2:30 – 2:40 p.m. | **Francis S. Collins, M.D., Ph.D.** Director, National Institutes of Health |

## NEUROLOGY

**NIH Moderator: John Kusiak, Ph.D.,** National Institute of Dental and Craniofacial Research, NIH
**Co-Moderator: Shaheen Lakhan, M.D., Ph.D., M.S., M.Ed.,** Global Neuroscience Initiative Foundation

2:40 – 2:45 p.m. **Session Overview**

2:45 – 3:05 p.m. Kathleen C. Light, Ph.D., University of Utah
*Greater Post-Exercise Gene Expression of Adrenergic and Sensory Receptors and Cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome versus Multiple Sclerosis, Fibromyalgia, and Healthy Controls*

3:05 – 3:20 p.m. **AFTERNOON BREAK**

3:20 – 3:40 p.m. **Roy Freeman, M.D.,** Beth Israel Deaconess Medical Center, Harvard Medical School
*Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and the Autonomic Nervous System*

3:40 – 4:00 p.m. **James Baraniuk, M.D.,** Georgetown University
*Neuroimmunology of Chronic Fatigue Syndrome*

4:00 – 4:15 p.m. **Summary and Panel Discussion**

## EXERCISE PHYSIOLOGY AND ENERGY METABOLISM

**NIH Moderator: Cheryl L. McDonald, M.D.,** National Heart, Lung, and Blood Institute, NIH
**Co-Moderator: Kevin P. Davy, Ph.D.,** Virginia Polytechnic Institute and State University

4:15 – 4:20 p.m. **Session Overview**

4:20 – 4:40 p.m. **Jane Kent-Braun, Ph.D.,** University of Massachusetts, Amherst
*Muscle Function and Fatigue in Chronic Fatigue Syndrome*

4:40 – 5:00 p.m. **Christopher R. Snell, Ph.D.,** University of the Pacific/Pacific Fatigue Lab, Stockton, CA
*Cardiopulmonary Exercise Testing and the Assessment of Fatigue in CFS/ME*

5:00 – 5:20 p.m. **Peter C. Rowe, M.D.,** Johns Hopkins University School of Medicine
*Orthostatic Intolerance in Chronic Fatigue Syndrome*

5:20 – 5:45 p.m. **Summary and Panel Discussion**

## FRIDAY, APRIL 8, 2011

7:00 – 8:00 a.m. **REGISTRATION**

8:00 – 8:10 a.m. **RECONVENE**

## DIAGNOSIS AND BIOMARKERS

**NIH Moderator: Donald G. Blair, Ph.D.,** National Cancer Institute, NIH
**Co-Moderator: Samir Khleif, M.D.,** National Cancer Institute, NIH

8:10 – 8:15 a.m. **Session Overview**

8:15 – 8:35 a.m. **Nancy Klimas, M.D.,** University of Miami Miller School of Medicine
*Immune-Based Biomarkers in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*

8:35 – 8:55 a.m. **Dane B. Cook, Ph.D.,** University of Wisconsin - Madison
*Can Functional Neuroimaging Data Serve as a Biomarker for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome?*

8:55 – 9:15 a.m. **Michael Dean, Ph.D.,** National Cancer Institute, NIH
*Identifying Genes and Genetic Risk Factors for Complex Diseases*

9:15 – 9:35 a.m. **Summary and Panel Discussion**

## TREATMENT

**NIH Moderator: Christopher Mullins, Ph.D.,** National Institute of Diabetes and Digestive and Kidney Diseases, NIH
**Co-Moderator: Susan Keay, M.D., Ph.D.,** University of Maryland School of Medicine and Veterans Administration Maryland Health Care System

9:35 – 9:40 a.m. **Session Overview**

9:40 – 10:00 a.m. **Fred Friedberg, Ph.D.,** State University of New York, Stony Brook
*Self-Management in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and the Meaning of "Improvement"*

10:00 – 10:20 a.m. **Italo Biaggioni, M.D.,** Vanderbilt University
*Chronic Fatigue and Postural Tachycardia Syndromes*

10:20 – 10:35 a.m. **MORNING BREAK**

10:35 – 10:55 a.m. **Theoharis C. Theoharides, M.D., Ph.D., M.S., F.A.A.A.A.I.,** Tufts University School of Medicine
*Substance P-Stimulated TNF Secretion from Human Mast Cells Involves Fission and Translocation of Mitochondria with Extracellular DNA Release That Induces Auto-Inflammation Processes Blocked by the Natural Flavonoid Luteolin*

10:55 – 11:15 a.m. **Lucinda Bateman, M.D.,** Fatigue Consultation Clinic, Salt Lake City
*Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome at the Fatigue Consultation Clinic: The Art of Supportive Care Medicine*

11:15 – 11:45 a.m. **Summary and Panel Discussion**

11:45 – 1:00 p.m. **LUNCH**

**OPPORTUNITIES FOR COMMUNICATION (A Panel Discussion)**

**NIH Moderators: John T. Burklow and Marin P. Allen, Ph.D.,**
Office of Communications and Public Liaison, NIH

1:00 – 1:05 p.m. **Session Overview**

1:05 – 1:15 p.m. **K. Kim McCleary,** CFIDS Association of America
*Communicating With Research Stakeholders*

1:15 – 1:25 p.m. **Kenneth J. Friedman, Ph.D.,** Castleton State College
*Elephants in the Room: Acknowledging Impediments to Chronic Fatigue Syndrome Research and Education*

1:25 – 1:40 p.m. **Patricia Fero, M.E.P.D.,** Wisconsin ME/CFS Association, Inc.
*3 Generations: A View from Wisconsin*
**Mary M. Schweitzer, Ph.D.,** MCEAS, University of Pennsylvania
*The Role for Internet in Communication*

1:40 – 1:50 p.m. **John T. Burklow**, Office of Communications and Public Liaison, NIH

1:50 – 2:15 p.m. **Summary and Panel Discussion**

2:15 – 2:30 p.m. **AFTERNOON BREAK**

**SUMMARY**

**NIH Moderator: Dennis Mangan, Ph.D.,** Office of Research on Women's Health, NIH
**Co-Moderator: Suzanne D. Vernon, Ph.D.,** CFIDS Association of America

2:30 – 4:45 p.m. **All Speakers and Co-Moderators**
- Summary of Each Session
- Responses by Department of Health and Human Services Federal Agencies
- Full Workshop Panel Discussion

4:45 – 5:00 p.m. **CLOSING COMMENTS**
**Vivian W. Pinn, M.D.,** Office of Research on Women's Health, NIH

# APPENDIX 2
## SPEAKERS AND MODERATORS

### MARIN P. ALLEN, Ph.D.
*Deputy Associate Director, Communications and Public Liaison*
National Institutes of Health
Bethesda, MD

Marin P. Allen, Ph.D., is the deputy associate director for communications, Office of Communications and Public Liaison (OCPL) in the Office of the Director of NIH. OCPL is responsible for all phases of internal and external NIH communications. Prior to 2004, Dr. Allen was the communication director and public liaison officer for the National Institute on Deafness and Other Communication Disorders (NIDCD). Marin has 30 years of communications, public health education, outreach, and media relations experience. Before joining NIH, she directed public relations for Gallaudet University (GU) from 1988 to 1990. She was also a tenured full professor and chair of the Department of Television, Film, and Photography in the School of Communication at GU. Dr. Allen was a media specialist with the White House Conference on Aging, and before that, she was a faculty member in communications at the University of Maryland, College Park. Currently, Dr. Allen has been involved in transagency efforts in health literacy, cultural competency, and health communication. Dr. Allen is the NIH representative to the HHS Working Group on Health Literacy and the Health Communications and Health Literacy working groups for Healthy People. Additionally, she serves on the NIH Nanotechnology Task Force, the subcommittee on communication for the Behavioral Health Coordinating Committee at HHS, and the MedLine Plus Advisory Board. Dr. Allen won two Emmy awards for programs she produced that aired on the Discovery Channel and PBS. She is a two-time CINE award winner.

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### HARVEY J. ALTER, M.D.
*Distinguished NIH Investigator, Associate Director for Research*
Department of Transfusion Medicine, Clinical Center
National Institutes of Health
Bethesda, MD

Dr. Harvey Alter has spent most of his research career at the National Institutes of Health. He is currently designated Distinguished NIH Investigator and serves as Chief of Clinical Studies and Associate Director for Research in the Department of Transfusion Medicine. Dr. Alter was co-discoverer of the Australia antigen that later proved to be the hepatitis B virus and was principal investigator in studies that identified non-A, non-B hepatitis, defined its chronic sequel, and later showed its link to HCV. His prospective studies of transfusion-associated hepatitis demonstrated how different donor interventions reduced hepatitis incidence from 30percent in 1970 to near zero in 1997. In recognition of his research accomplishments, Dr. Alter was awarded the Landsteiner Prize, the highest award of the American Association of Blood Banks; the Inserm Medal from France; and the Clinical Lasker Award. He has been elected to both the National Academy of Sciences and the Institute of Medicine and is a Master of the American College of Physicians.

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### JAMES M. ANDERSON, M.D., Ph.D.
*Director, Division of Program Coordination, Planning and Strategic Initiatives*
National Institutes of Health
Bethesda, MD

Dr. James Anderson was appointed as the deputy director for program coordination, planning, and strategic initiatives, and director of the Division of Program Coordination, Planning, and Strategic Initiatives on September 27, 2010. Prior to joining NIH, Dr. Anderson was professor and chair of the Department of Cell and Molecular

Physiology in the School of Medicine at the University of North Carolina at Chapel Hill, a position he held since 2002. Before his appointment at Chapel Hill, he was professor of medicine and cell biology and chief, Section of Digestive Diseases, at the Yale School of Medicine. Dr. Anderson has extensive clinical experience in both internal medicine and hepatology, and he is considered among the top authorities in the world in his primary research field of tight junctions and paracellular transport. Dr. Anderson continues his research of the paracellular barrier in a laboratory located in the intramural research program of the National Heart, Lung, and Blood Institute. He was a principal investigator on NIH grants for almost 20 years. With experience in clinical medicine, academic research, and administration, Dr. Anderson has a broad understanding of the biomedical research spectrum that informs his work with the NIH community in evaluating, prioritizing, and coordinating a wide range of trans-NIH research opportunities. Dr. Anderson graduated from Yale University in 1974, received his Ph.D. in Biology from Harvard University in 1979, and earned his M.D. from Harvard Medical School in 1983.

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## JAMES BARANIUK, M.D.

*Associate Professor, Pain and Fatigue Research Alliance*
Georgetown University
Washington, DC

Dr. James Baraniuk began investigating neuropeptides and how nerves regulate mucosal function while at the National Institute of Arthritis and Infectious Diseases. His division chief, Daniel Clauw, M.D., began referring fibromyalgia patients for allergic rhinitis evaluations. The surprising finding that was investigated through an OR1 was that these subjects had CFS and a neurologic non-allergic rhinopathy. Dr. Baranjuk is following these dysfunctional nerves into the brain by investigating cerebral fluid proteomics. The aim is to phenotype CFS subjects based on pathophysiologic mechanisms.

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## LUCINDA BATEMAN, M.D.

Fatigue Consultation Clinic
Salt Lake City, UT

Dr. Lucinda Bateman completed medical school at the Johns Hopkins School of Medicine, internal medicine residency at the University of Utah, and certification by the American Board of Internal Medicine. She practiced general internal medicine until 2000, when she changed her focus to the diagnosis and management of chronic fatigue, chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS). Dr. Bateman's goal in establishing her Fatigue Consultation Clinic and the nonprofit OFFER (Organization for Fatigue and Fibromyalgia Education and Research) is to encourage a thoughtful evaluation process, better sharing of information, and more research efforts aimed at understanding the cause(s) and treatment of CFS and FMS. In addition to the co-founder, Executive Director, and board chair of the Utah-based nonprofit, OFFER, she has been on the boards of the Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) Association of America and the International Association for Chronic Fatigue Syndrome/Myalgic encephalomyelitis (IACFS/ME) and was the board chair of Easter Seals of Utah.

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## ITALO BIAGGIONI, M.D.

*Professor, Medicine and Pharmacology*
Vanderbilt University

Dr. Biaggioni is professor of medicine and pharmacology, Division of Clinical Pharmacology, Vanderbilt University, and associate director of the Clinical Research Center. His clinical practice is focused on the Vanderbilt Autonomic Dysfunction Center, one of a handful in the country dedicated to the evaluation and care of patients with autonomic disorders. New diseases have been discovered and characterized in this Center, such as dopamine beta-hydroxylase deficiency, norepinephrine transporter deficiency, and baroreflex failure. Dr. Biaggioni's clinical research focuses on the interaction between neural (autonomic) and metabolic (nitric oxide, adenosine) mechanisms regulating blood pressure. He has 25 years of continuous NIH support and has published more than 200 papers in peer reviewed journals.

## DONALD G. BLAIR, Ph.D.

*Chief, Cancer Etiology Branch, Division of Cancer Biology*
National Cancer Institute
National Institutes of Health
Bethesda, MD

Dr. Donald Blair is chief of the Cancer Etiology Branch, Division of Cancer Biology, NCI. He was a member of the NCI Intramural Program from 1978 to 2002. He received his B.S. in chemistry from the California Institute of Technology and his Ph.D. in cChemistry) from the University of California, San Diego.

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## GORDON BRODERICK, Ph.D.

*Associate Professor, Medicine*
University of Alberta
Alberta, ON, Canada

Trained at McGill and the University of Montreal in engineering and applied mathematics, Dr. Gordon Broderick received postdoctoral training in computer science (cancer genomics; McGill) and cellular biochemistry (University of Alberta). An associate professor with the Department of Medicine at the University of Alberta, his current research efforts are focused on understanding immune dysfunction and autoimmunity from an integrated systems perspective. In particular, his group is investigating how subtle imbalances in the interplay between the immune system's multiple components as well as its interactions with the endocrine and nervous systems may lead to complex disorders such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Gulf War illness (GWI). Illnesses such as these continue to defy a conventional one-piece-at-a-time approach. Focusing on the systems biology of these illnesses, Dr. Broderick's group has so far published more than a dozen peer-reviewed papers in this specific field and currently receives research funding from NIH, DoD, and the CFIDS Association of America. An associate editor for the journal BMC Systems Biology (impact factor 5), Dr. Broderick also serves on review and advisory panels for NIH, Veterans Affairs, Scottish Health Directorate, Research Board of Ireland, Microsoft Research (Cambridge), and others. Recently he has accepted an invitation to join the Scientific Advisory Board of the CFIDS Association. Working at the crossroads of several disciplines, he continues to collaborate closely with clinical and basic life scientists in the United States (Chicago, Miami), the United Kingdom,and Israel.

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## JOHN T. BURKLOW

*Associate Director, Communications and Public Liaison*
National Institutes of Health

John Burklow is the associate director for communications and public liaison at the National Institutes of Health (NIH), the primary medical research agency in the Federal government. NIH receives several thousand press inquiries a year and is often in the news. John serves as the chief advisor to the NIH director, principal deputy director, and senior staff on communications and public liaison issues. He also serves as the NIH spokesman for the agency (on nonscience issues). John is the director of the NIH Office of Communications and Public Liaison, overseeing news media (and new media), editorial operations, online communications, special projects, NIH visitor center functions, and NIH Freedom of Information Act Office and is the acting director of the NIH Office of Community Liaison. John and his staff work closely with each of NIH's 27 Institutes and Centers communications offices and the Department of Health and Human Services Office of Public Affairs.

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## JOHN CHIA, M.D.

*President*
EVMED Research
Torrance, CA

Dr. John Chia graduated from UCLA School of Medicine and completed an internship and residency in internal medicine at Cedars-Sinai Medical Center in Los Angeles. After completing an infectious diseases fellowship at Bethesda Naval Hospital, he did research on the immunopathogenesis of gram-negative sepsis for 3 years with Dr. Matthew Pollack at the Uniformed Services University of the Health Sciences. After returning to Los Angeles, he spent 2 years working with Dr. David Ho on the immunopathogenesis of HIV infection at the AIDS research unit of Cedars-Sinai Medical Center. Since 1990, he has been a practicing infectious disease specialist in Torrance, CA. In 1998, his son, Andrew, developed ME/CFS after a severe viral respiratory infection, and Dr. Chia devoted his time to understanding this illness. A number of papers have been published recently on the role of enteroviruses as the etiology of ME/CFS—an area that has been implicated as one of the causes by a number of British studies. He and his son confirmed the finding of enterovirus RNA in the blood of ME/CFS patients. By analyzing samples of stomach tissue from 165 patients with CFS, they found that 82 percent of patients had high levels of enteroviruses in their digestive systems and demonstrated viral RNA and limited growth of noncytopathic viruses in cell cultures. He first published a paper on the development of chronic enterovirus infections and ME/CFS in patients following acute infections. Viral persistence has been demonstrated in the stomach biopsies of ME/CFS patients. It is hoped that Dr. Chia's research will result in the development of drugs against enteroviruses to treat the debilitating symptoms of ME/CFS.

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## JOHN M. COFFIN, Ph.D.

*American Cancer Society Research Professor*, Tufts University, Boston, MA
NCI-Frederick, Frederick, MD

Dr. John M. Coffin is American Cancer Society Professor and Distinguished Professor of molecular biology and microbiology atTufts University, Boston MA. He also serves as advisor on HIV and AIDS to the National Cancer Institute (NCI) and to the HIV Drug Resistance Program (DRP), which he founded in 1997. He received his Ph.D. in molecular biology from the University of Wisconsin, Madison, in 1972, where he worked on retroviruses in the laboratory of Howard Temin. He joined the Tufts faculty after 3 years with Charles Weissmann at the University of Zürich, Switzerland. In 1997, he was recruited to organize the HIV DRP within NCI, where he served as director until 2005 and remains as senior advisor. He is well known for his work on retrovirus genetics, genome structure, evolution, and pathogenesis and is author of more than 150 peer-reviewed publications and senior editor of Retroviruses, the definitive text on the subject. In 1999, he was elected to the National Academy of Sciences in recognition of his contributions to the field of retrovirology.

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## DANE B. COOK, Ph.D.

*Assistant Professor*
University of Wisconsin - Madison
Madison, WI

Dr. Dane Cook's research focuses on the psychobiological mechanisms of pain, fatigue, and effort. His lab has employed several experimental approaches to gain a better understanding of the effects of physical activity and exercise on subjective experiences and brain responses, including the phenomenon of postexertion malaise. These studies have characterized pain intensity during exercise, tested the effects of pharmacologic manipulations on muscle pain perception, and determined the influences of disease on pain and fatigue during and following an exercise challenge. His recent work has focused on using functional magnetic resonance imaging (fMRI) to understand central nervous system mechanisms of pain and fatigue in patients with fibromyalgia (FM) and chronic fatigue syndrome (CFS) and veterans with Gulf War illness (GWI)—combining exercise science and brain imaging methods to further

understand the psychobiological mechanisms of pain and fatigue. His laboratory also has begun to examine genetic and immune system influences pre-and postexercise in chronic fatigue syndrome, using standardized exercise challenges to perturb these systems and test for potential mechanisms of postexertion malaise.

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## KEVIN P. DAVY, Ph.D.

*Professor*
Virginia Tech University, Department of Human Nutrition, Foods and Exercise
Blacksburg, VA

Dr. Kevin Davy is currently a professor in the Department of Human Nutrition, Foods and Exercise at Virginia Tech. He received his Ph.D. in applied physiology at Virginia Tech and postdoctoral training at the University of Colorado at Boulder. Dr. Davy is a clinical physiologist with expertise in exercise physiology. Dr. Davy's NIH- and industry-funded work has focused on understanding and treating obesity and age-related cardiovascular and metabolic dysfunction.

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## MICHAEL DEAN, Ph.D.

*Chief, Human Genetics*
National Cancer Institute
National Institutes of Health
Bethesda, MD

Dr. Michael Dean obtained his Ph.D. from the Biochemistry Department at the Boston University School of Medicine. He performed his postdoctoral studies at the National Cancer Institute on the MET oncogene and cystic fibrosis gene. His laboratory has been involved in the cloning of the genes for cystic fibrosis and several inherited cancers, and the identification of genes involved in response to HIV, age-related macular degeneration and adult cancers. He is a member of the American Society of Human Genetics, American Association of Cancer Research, Centre Etude du Polymorphisme Humaine (CEPH), and Human Genome Organization (HUGO) and is an adjunct faculty member at Hood College.

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## BASIL ELDADAH, M.D., Ph.D.

*Program Officer*
National Insititue on Aging
National Institutes of Health
Bethesda, MD

Dr. Basil Eldadah is in the Division of Geriatrics and Clinical Gerontology at NIA. He received an M.D./Ph.D. from Georgetown University, completed residency in internal medicine at Georgetown, and completed a fellowship in clinical pharmacology at NIH. He came to NIA in 2006.

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## PATRICIA FERO, MEPD.

*Executive Director*
Wisconsin ME/CFS Association, Inc.
Sun Prairie, WI

Ms. Patricia Fero is a founding member of the Wisconsin ME/CFS Association, Inc. (1987). She became ill in 1980 and left teaching in 1988. From 1992 to 1998, Ms. Fero set up a Wisconsin network with 27 groups including a 50-member family group with 66 children. Since 2003, Ms. Fero has focused on the NIH grantmaking process and increased efforts to collaborate with other national groups.

## MARY ANN FLETCHER, Ph.D.

*Professor*
University of Miami, Miller School of Medicine
Miami, FL

Dr. Mary Ann Fletcher started her independent NIH-supported work on the immunochemistry of heterophile antibodies associated with infectious mononucleosis (IM). These antibodies are found only in the acute phase of IM resulting from acute Epstein-Barr virus (EBV) infection. She isolated highly purified sialoglycoproteins from animal erythrocyte membranes that were recognized by these antibodies. This work was the basis for the mono-spot test that replaced the animal erythrocyte-based test as a standard diagnostic test for IM.

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## ROY FREEMAN, M.D.

*Professor, Neurology*
Harvard Medical School
Cambridge, MA

Dr. Roy Freeman is professor of neurology at Harvard Medical School and director of the Center for Autonomic and Peripheral Nerve Disorders in the Department of Neurology at Beth Israel Deaconess Medical Center in Boston. Dr. Freeman's research and clinical interest and expertise are in the physiology and pathophysiology of the small nerve fibers and the autonomic nervous system. He is also an expert on the neurologic complications of diabetes,,neuropathic pain, the autonomic complications of Parkinson's disease and multiple system atrophy, and diagnosis and treatment of autonomic and peripheral nervous system disorders.
Dr. Freeman received his MB ChB at the University of Cape Town Medical School in South Africa. Subsequently, he completed his neurology residency and served as chief resident in neurology at Brigham and Women's Hospital and at Beth Israel Hospital in Boston. A frequent invited lecturer, Dr. Freeman has presented his work at national and international scientific forums on topics including diabetic peripheral neuropathy, neuropathic pain, and the diagnosis and treatment of autonomic nervous system disorders. He has authored more than 160 original reports, chapters, and reviews.

Dr. Freeman is the principal investigator on NIH-funded studies on the pathophysiology of orthostatic intolerance, autoimmune autonomic ganglionopathy, and hypoglycemia and the autonomic nervous system. Dr. Freeman is the chairman of the World Federation of Neurology research group on the autonomic nervous system. He is the former president of the American Autonomic Society and former chairman of the Autonomic Nervous System Section of the American Academy of Neurology. Dr. Freeman has served as chair of scientific sessions at the American Academy of Neurology and other national and international meetings. He has been a member of the scientific program committee of the American Academy of Neurology and American *Autonomic Society. Dr. Freeman is co-editor of Autonomic Neuroscience—Basic and Clinical and, associate editor of the Clinical Journal of Pain* and is on the editorial board of Clinical Autonomic Research.

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## FRED FRIEDBERG, Ph.D.

*Research Associate Professor, Psychiatry*
Stony Brook University
Stony Brook, NY

Dr. Fred Friedberg is a psychologist and research associate professor in the Department of Psychiatry and Pehavioral Sciences at Stony Brook University. As a practicing psychologist for 25 years, Dr. Friedberg has authored six books on ME/CFS, fibromyalgia, and eye movement desensitization and reprocessing (EMDR). Over the past decade, he has conducted NIH-funded research that began with a career development K award. His research on ME/CFS and fibromyalgia has focused on the areas of self-management, home-based assessment of symptoms and functioning, and long-term outcomes. Dr. Friedberg has authored or co-authored more than 35 peer review publications. He also has conducted numerous invited professional workshops on ME/CFS and fibromyalgia. Dr. Friedberg is currently the president of the International Association for Chronic Fatigue Syndrome/ME (IACFS/ME).

## KENNETH J. FRIEDMAN, Ph.D.

*Adjunct Instructor*
Castleton State College
Wells, VT

Dr. Kenneth J. Friedman is a recently retired medical school professor whose interest in chronic fatigue syndrome was prompted by his daughter contracting the illness in 1991. Dr. Friedman wrote the lead chapter of the *Consensus Manual for the Primary Care and Management of Chronic Fatigue Syndrome* and co-wrote several other chapters. He is the author of several articles on CFS and is currently part of the writing team for the International Association for Chronic Fatigue Syndrome/ME's (IACFS/ME's) *ME-CFS Primer*. A member of the Master Educator Guild of the University of Medicine and Dentistry of New Jersey, where he taught both basic sciences and clinical courses for 34 years, and the winner of numerous teaching awards, Dr. Friedman has taught the CDC's *CFS Diagnosis and Treatment* Course, as well other CFS continuing education courses to physicians and health care providers with accreditation coming from other organizations and societies. Dr. Friedman was a member of the first Chronic Fatigue Syndrome Advisory Committee panel and served on both the research and education subcommittees. He currently serves on the boards of the Vermont CFIDS Association and the New Jersey Chronic Fatigue Syndrome Association. He is vice president and director of public policy of the Patient Alliance for NeuroEndrocrine Disorders Organization for Research and Advocacy (P.A.N.D.O.R.A.), and is treasurer of the IACFS/ME. Dr. Friedman currently holds adjunct appointments at Green Mountain College and Castleton State College.

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## MASSIMO GADINA, Ph.D.

*Director, Office of Science and Technology*
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
Bethesda, MD

Dr. Massimo Gadina is currently the director of the Office of Science and Technology at NIAMS, National Institutes of Health. Prior to this appointment, he was senior lecturer at the Division of Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University of Belfast, Northern Ireland, UK. Dr. Gadina gained his doctoral degree in medicinal chemistry and technology at the Universitá di Milano, Italy, and his Ph.D. at the Université de Dijon, Dijon, France. Dr. Gadina's research and interest are focused on immune diseases, specifically on the biology of cytokines and the signaling pathways activated by these molecules.

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## RONALD GLASER, Ph.D.

*Director, Institute for Behavioral Medicine Research*
The Ohio State University Medical Center
Columbus, OH

Dr. Ronald Glaseris a professor of molecular virology, immunology, and medical genetics at the Ohio State University College of Medicine, and Director of The Ohio State University Behavioral Medicine Research Institute. He is past chair of the Department of Medical Microbiology and Immunology, past associate dean for research and graduate education in the College of Medicine, and is past associate vice president for Research at the Ohio State University. He has published 318 articles and book chapters in the area of viral oncology, and stress and immune function. His research has been supported by several grants from the National Institutes of Health, including a MERIT award from the National Institute of Mental Health (on which he was a co-principal investigator; Janice Kiecolt-Glaser, PI). He was selected by the Institute for Scientific Information as one of the most highly cited authors. He was a recipient of a Leukemia Society Scholar Award, twice fellow of the Franco-American Exchange Program, Fogarty International Center, NIH, and INSERM. He was a member of the AIDS policy subcommittee, National Advisory Mental Health Council, NIMH. He is presently a member of the Chronic Fatigue Syndrome Advisory Committee to the Secretary of HHS. He currently holds the Gilbert and Kathryn Mitchell Endowed Chair in Medicine. He is past president of the, Psychoneuroimmunology Research Society and past president of the Academy for Behavioral Medicine Research. He is also an AAAS fellow.

## TIMOTHY A. GONDRÉ-LEWIS, Ph.D.

*Program Officer, Immunoregulation Section*
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Dr. Tim Gondré-Lewis joined the Division of Allergy, Immunology, and Transplantation in September 2002 as a program officer in the Basic Immunology Branch. As a program officer and contracting officer technical representative, Dr. Gondré-Lewis is responsible for a large portfolio of grants, program projects, and contracts. His portfolio covers antigen processing and presentation pathways, computational modeling of immunity, technology development, signal transduction, and chronic fatigue syndrome. Specific areas of focus include the T cell antigen epitope identification and immune modeling of host response to influenza and other pathogens. Dr. Gondré-Lewis received an A.B. in Biology and African-American studies from Oberlin College in 1989 and continued his education at the Medical College of Virginia–Virginia Commonwealth University where he received a Ph.D. in microbiology and immunology. He completed his postdoctoral training at the Trudeau Institute in Saranac Lake, NY. His graduate and postdoctoral research focused on antigen processing and presentation in B cells and macrophages with emphasis on protease activities within those cells. Prior to coming to NIH, Dr. Gondré-Lewis was an assistant professor at York College of the City University of New York, where he taught and had an active research laboratory.

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## LEONARD A. JASON, Ph.D.

*Director, Center for Community Research*
DePaul University
Chicago, IL

Dr. Leonard Jason is a professor of psychology at DePaul University and director of the Center for Community Research. He is a former president of the Division of Community Psychology of the American Psychological Association. He received the 1997 Distinguished Contributions to Theory and Research Award and the 2007 Special Contribution to Public Policy Award from the Society for Community Research and Action. Dr. Jason has edited or written 23 books, and has published more than 540 articles and 77 book chapters. He has served on 83 thesis committees (of which he chaired 57) and 70 dissertation committees (of which he chaired 36). He has served on the editorial boards of 10 psychological journals. He was presented the 1997 CSN ACTION Champion Award by the Chronic Fatigue Immune Dysfunction Syndrome Association of America in appreciation of his research and educational efforts on behalf of persons with CFS. He was presented with the Dutch ME-Foundation International ME-Award for 2003 for outstanding work in the past 10 years in the field of CFS. Dr. Jason was the vice president and a member of the Board of Directors of the International American Association of CFS/ME, the scientific organization in this field. He is currently a member of the Chronic Fatigue Syndrome Advisory Committee, which makes recommendations to the Secretary of Health and Human Services.

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## SUSAN KEAY, M.D., Ph.D.

*Professor of Medicine*
University of Maryland School of Medicine
and Veterans Administration Maryland Health Care System
Baltimore, MD

Dr. Susan Keay received her M.D. and Ph.D. degrees from the Medical College of Wisconsin; she completed internship and residency training in internal medicine at the Mayo Clinic and postdoctoral fellowship training in infectious diseases at Stanford University School of Medicine. Her research focuses on the pathogenesis of interstitial cystitis/painful bladder syndrome, a chronic painful bladder disorder. In studies to determine the possible causes of IC/PBS, Dr. Keay's laboratory has discovered two specific and significant findings: a factor that inhibits bladder epithelial proliferation, and altered levels of certain epithelial cell growth factors in the urine of IC/PBS patients. The

antiproliferative factor (or APF), which is made by bladder epithelial cells from IC/PBS patients, has been completely characterized, its functional receptor determined, and four antagonists of its activity identified. APF and active synthetic derivatives also have been shown to inhibit the growth of certain carcinoma cells. Studies to determine the specific mechanism(s) by which APF inhibits both normal bladder epithelial and carcinoma cell proliferation are in progress.

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KEITH W. KELLEY, Ph.D.
*Professor, Immunophysiology*
University of Illinois at Urbana-Champaign
Champaign, IL

Professor Keith Kelley is involved in defining reciprocal systems of communication between the immune and central nervous systems, including the role of proinflammatory cytokine receptors and downstream mechanisms that are involved in both sickness and depressive-like behaviors. Since 2003, he has served as editor in chief of Brain, Behavior, and Immunity.

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JANE KENT-BRAUN, Ph.D.
*Professor*
Department of Kinesiology
University of Massachusetts, Amherst
Amherst, MA

Dr. Jane Kent-Braun's primary focus is on quantifying age- and physical activity-based changes in human skeletal muscle function. Her research uses a combination of noninvasive techniques to measure the roles of neural activation, intramuscular bioenergetics, and contractile function in the development of muscle fatigue.

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SAMIR N. KHLEIF, M.D.
*Head, Cancer Vaccine Section*
National Cancer Institute
National Institutes of Health
Bethesda, MD

Dr. Khleif completed his fellowship in medical oncology at NCI in Bethesda, Maryland. He is currently the chief of the Cancer Vaccine Section at NCI and a professor of medicine at USUHS. His research program focuses on understanding the interaction between the immune system and tumor cells and utilizing the knowledge for the development of immune biomarkers and novel immune therapeutics and vaccines against cancer. Dr. Khleif served as a special assistant to the FDA Commissioner from 2006 to 2009. During that tenure, he led the Critical Path for Oncology. He currently leads/co-leads many national efforts and committees on biomarkers development and integration of biomarkers in clinical trials including the American Association for Cancer Research National Cancer Institute Food and Drug Administration Cancer Biomarker Collaborative, the ASCO Alternative Clinical Trial Design, International Society for Biologic Therapy Cancer Immune-Biomarkers Working Group, and American Society for Clinical Oncology Small Population Clinical Trials Working Group. Dr. Khleif is the author of many book chapters and scientific articles on tumor immunology and biomarkers process development, and he is the editor of two textbooks on cancer therapeutics and tumor immunology and cancer vaccines. He has been a visiting professor and an invited speaker at many prestigious scientific conferences and academic institutions Dr. Khleif has received numerous awards: He was inducted into the American Society for Clinical Investigation, received the NCI Director Golden Star Award, the National Institutes of Health Award for Merit, and the Commendation Medal of the U.S. Public Health Service.

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## NANCY KLIMAS, M.D.

*Professor, Medicine*
University of Miami Miller School of Medicine
Miami, FL

Dr. Nancy Klimas is a professor of medicine, psychology, microbiology and immunology at the University of Miami Miller School of Medicine. She is a clinical immunologist and directs the UM/VAMC Gulf War Illness and Chronic Fatigue Syndrome Research Center, initiated with an NIH Center Award in 1995. The Center has focused on better understanding of the neuro-immune-endocrine interactions in CFS and GWI and their role in the pathogenesis of these complex disorders. She is also the medical director of the Chronic Fatigue Center, a multidisciplinary clinic for diagnosis and treatment of ME/CFS and related conditions (www.cfsclinic.com). She is immediate past president of the International Association for Chronic Fatigue Syndrome/ME, an organization of researchers and clinicians dedicated to furthering our knowledge of this disabling illness. She continues to work nationally and internationally to bring a better understanding of ME/CFS to clinicians and policymakers.

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## ANTHONY L. KOMAROFF, M.D.

*Simcox-Clifford-Higby Professor of Medicine*
Harvard Medical School
Boston, MA

A senior physician at Brigham & Women's Hospital (BWH), Harvard Medical School, and former director of general internal medicine at BWH, Dr. Anthony Komaroff has cared for CFS patients and conducted research on CFS for 25 years. He has authored more than 230 publications and served on NIH and CDC review committees related to CFS.

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## JOHN KUSIAK, Ph.D.

*Director, Molecular and Cellular Neuroscience Program*
National Institute of Dental and Craniofacial Research
National Institutes of Health
Bethesda, MD

Dr. Kusiak, a graduate of Colby College, received a Ph.D. in biochemistry from George Washington University Medical School and worked at NIH studying Alzheimer's disease. He did postdoctoral fellowships studying inherited diseases that afflict infants and children, including Tay-Sachs and Fabry disease, and drugs for high blood pressure in older adults. He then joined NIH's Gerontology Research Center at the National Institute on Aging in Baltimore as a molecular neurobiologist studying the causes and prevention of Alzheimer's disease. Dr. Kusiak currently heads the extramural neuroscience program at NIDCR and plays a leadership role in the trans-NIH Blueprint for Neurosciences Research initiative.

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## SHAHEEN E. LAKHAN, M.D., Ph.D., M.S., M.ED.

*Medical Scientist*
Global Neuroscience Initiative Foundation
Panorama City, CA

Serving as the executive director of the Global Neuroscience Initiative Foundation, Dr. Shaheen E. Lakhan strives for the advancement of neurologic and mental health patient welfare, education, and research.

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## CATHERINE LAUGHLIN, Ph.D.

*Chief, Virology Branch*
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Dr. Catherine Laughlin is chief of the Virology Branch in the extramural program of NIAID. She received her Ph.D. in microbiology at Rutgers University and did postdoctoral work at the University of Oregon Health Science Center and the intramural NIH program. As an assistant professor at the Uniformed Services University of of the Health Sciences, she taught pathology and managed a research program on human adeno-associated virus genome integration. Since joining NIAID she has had responsibility for the management of basic, translational and clinical extramural research on a variety of viral pathogens. For the past 10 years, her program has emphasized emerging and reemerging viral infections as well as defense against viruses with the potential to be used as agents of bioterror.

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## KATHLEEN C. LIGHT, Ph.D.

*Research Professor, Anesthesiology*
University of Utah
Salt Lake City, UT

Dr. Kathleen Light received her undergraduate education at Vassar and her master's and doctoral degrees at Syracuse University. For many years at the University of North Carolina and now at the University of Utah, Dr. Light has led a successful interdisciplinary research team merging behavioral, physiologic, and medical approaches in the study of health problems as diverse as high blood pressure, depression, the mother-infant relationship, and disorders of chronic pain and fatigue. The linking theme is to understand the physiologic pathways through which stress influences health and disease, particularly health problems affecting women and minorities. Recently, her work has focused on chronic fatigue syndrome and fibromyalgia, two disorders that disproportionately affect women. Working jointly with her husband, well-known neuroscientist and pain researcher Dr. Alan Light, she is currently working on the development of blood-based biomarkers for these disorders, using gene expression of sensory, adrenergic, and immune measures. These gene expression profiles have the potential to be part of an objective diagnostic test for these disorders, which is greatly needed. Another very active topic of her current work is oxytocin (sometimes called the "bonding hormone") and its role in some of the health benefits associated with warm contact and caring support from family and friends. Her CV lists more than 130 original research papers and many book chapters. Dr. Light was elected president of the Academy of Behavioral Medicine Research in 2007–2008. She also was named Distinguished Mentor of the Year in 2001 by the Society of Behavioral Medicine.

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## DENNIS MANGAN, Ph.D.

*Chair, Trans-NIH ME/CFS Research Working Group*
*Senior Research Advisor*
Office of Research on Women's Health
National Institutes of Health
Bethesda, MD

Dr. Dennis Mangan is a senior research advisor responsible for analysis and evaluation of research projects supported by ORWH. Dr. Mangan has a Ph.D. in microbiology from West Virginia University and postdoctoral training in cellular immunology at the University of Michigan. As an assistant professor at the University of Rochester, Dr. Mangan led a program in oral microbiology and immunology prior to engaging in advanced research in molecular biology in the lab of Dr. Sharon Wahl in the NIDCR intramural program studying the role of programmed cell death in monocyte/macrophage homeostasis. Between 1992 and 2006, he worked in the NIDCR extramural program as a program director in various infectious disease research programs. From 2006 to 2009, as the associate dean for research at the University of Southern California School of Dentistry, he helped faculty and students enhance their research programs and increase funding opportunities from government, industry, and foundation sources.

Dr. Mangan returned to NIH in November 2009 to join Dr. Vivian Pinn's ORWH 20th anniversary initiative to advance research on women's health issues and sex/gender factors related to diseases and conditions over the next decade. He assumed the position as chair of the Trans-NIH ME/CFS Research Working Group in October 2010.

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## K. KIMBERLY McCLEARY

*President and CEO*
CFIDS Association of America
Charlotte, NC

Since 1991 Kim McCleary has led the CFIDS Association of America's research, public policy, and communications programs, which seek to make chronic fatigue syndrome (CFS, also known as chronic fatigue and immune dysfunction syndrome, or CFIDS) widely understood, diagnosable, curable, and preventable. She has worked closely with Congress and Federal health agencies to define priorities and provide funding for CFS research, education, and awareness. She also worked closely with the Social Security Administration to develop a policy ruling identifying CFS as a potentially disabling condition, making it easier for disabled CFS patients to gain access to Federal disability benefits. She served on the Department of Health and Human Services CFS Coordinating Committee from 1996 to 2001, has testified before Congress numerous times, has done dozens of media interviews about CFS, and was selected by Redbook magazine as one of its 2001 "Mothers and Shakers" promoting progress in health. Ms. McCleary currently serves as a member of two AABB Interorganizational Task Forces on XMRV, a newly described human retrovirus that has been associated with CFS and is the focus of intense scientific inquiry.

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## CHERYL L. McDONALD, M.D.

*Medical Officer, Division of Cardiovascular Sciences*
National Heart, Lung, and Blood Institute
National Institues of Health
Bethesda, MD

Dr. Cheryl McDonald is a oedical Officer in the Division of Cardiovascular Sciences of the National Heart, Lung, and Blood Institute. She oversees research in cardiovascular diseases, gene therapy, and HIV/AIDS. Dr. McDonald is board certified in internal medicine and infectious diseases of Adults.

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## JUDY A. MIKOVITS, Ph.D.

*Research Director*
Whittemore Peterson Institute
Reno, NV

Dr. Judy Mikovits spent more than 20 years at the National Cancer Institute in Frederick, MD, during which time she received her Ph.D. in biochemistry and molecular biology, from George Washington University investigating mechanisms of HIV latency in monocytes. This work led to the discovery of the role that aberrant DNA methylation plays in the pathogenesis of HIV. Formally trained as a cell biologist, molecular biologist, and virologist, she studied the immune response to retroviruses and herpes viruses including HIV, SIV, HTLVI, HERV, HHV6, and HHV8, with a special emphasis on virus host cell interactions in cells of the hematopoietic system, including hematopoietic stem cells (HSC). Her research has focused primarily on translational research in government, biotechnology, and academic settings. Dr. Mikovits joined the Whittemore Peterson Institute for Neuroimmune Disease (WPI) in November 2006 as its first research director charged with establishing a translational research program aimed at identifying biomarkers and underlying causes of chronic fatigue syndrome (CFS) and other debilitating neuro-immune diseases with overlapping symptoms such as fibromyalgia (FM), atypical multiple sclerosis, and autism spectrum disorder (ASD). She established a collaborative network of world-renowned experts in retrovirology, human genetics, immune cell biology, flow cytometry, bioinformatics, and drug development. This approach resulted in the detection of a new blood-borne human retrovirus, XMRV, in the majority of patients tested and a cytokine signature associated with XMRV infection.

## DAVID M. MOSSER, Ph.D.

*Professor, Cell Biology and Molecular Genetics*
University of Maryland
College Park, MD

Dr. David Mosser is a professor of cell biology and molecular genetics at the University of Maryland, College Park, and the founding director of the Maryland Pathogen Research Institute. He has studied macrophages and their products for more than 20 years. The basic question his laboratory addresses is how leukocytes can efficiently mediate host defense while maintaining the integrity of the host. Dr. Mosser received his Ph.D. from North Carolina State University and did his postdoctoral training at Harvard Medical School. He is a former member of the NIH, NIAID Board of Scientific Counselors and has served on the editorial boards of five prestigious journals dedicated to the study of leukocytes, cytokines, and inflammation. Dr. Mosser has published more than 100 papers pertaining to leukocytes and their products.

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## CHRISTOPHER MULLINS, Ph.D.

*Director, Basic Cell Biology Programs in Urologic and Kidney Disease*
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, MD

Dr. Christopher Mullins is a graduate of the University of Louisville and the Vanderbilt University Graduate School of Medicine, where he completed his graduate training in the Department of Microbiology and Immunology in 1997. As a National Research Council fellow, Dr. Mullins conducted research at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development from 1997 to 2002 and joined the NIDDK Division of Kidney, Urologic, and Hematologic Diseases in his present position in 2002. His responsibilities include serving as the project scientist for the NIDDK's Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network and providing development and oversight for additional NIDDK initiatives, including the NIDDK Prostate Research Strategic Plan.

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## BENJAMIN H. NATELSON, M.D.

Director, Pain and Fatigue Study Center, Beth Israel Medical Center
Professor, Neurology, Albert Einstein College of Medicine
New York, NY

Dr. Benjamin H. Natelson received his bachelor's and medical degrees at the University of Pennsylvania in Philadelphia and then did his neurology residency at the Albert Einstein College of Medicine in New York City. Next he did two postdoctoral fellowships: one in behavioral neurosciences at the Cornell University Medical Center in White Plains, NY, and one in physiologic psychology at the Walter Reed Army Institute of Research in Washington, DC. He then moved to the New Jersey Medical School in Newark and the Veterans Administration Medical Center in East Orange. He rose through the ranks, attaining the position of professor of neurosciences in 1981, leaving in 2008 as an emeritus professor. He had continual funding from the VA through 1999 for his experimental work on stress and chronobiology. With the award of a federally funded research center to explore the causes of chronic fatigue syndrome (CFS) in 1991, he shifted his research to studies of humans with CFS and more recently has extended those studies to include those with fibromyalgia. He served as president of the Pavlovian Society and o the Academy of Behavioral Medicine Research. He has more than 230 papers published in peer review journals and has authored 3 books. Since 2008, Dr. Natelson has moved his activities to the Department of Pain and Palliative Care at the Beth Israel Medical Center in Manhattan where he directs the Pain & Fatigue Study Center (see **www.painandfatigue.com**). In that capacity, he is also a professor of neurology at the Albert Einstein College of Medicine.

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## MANGALATHU RAJEEVAN, Ph.D.

*Research Microbiologist*
Centers for Disease Control and Prevention
Atlanta, GA

Dr. Mangalathu Rajeevan has more than 25 years of experience in biomedical research. He is a CDC senior scientist with expertise in molecular biology, genetics, and genomics. Dr. Rajeevan joined CDC in 1999, and since then he has actively contributed to establishing a molecular epidemiology program to study CFS at CDC. He directed studies that led to the identification of genes and polymorphisms associated with CFS. His recent publications include approaches to integrate genomic studies of CFS. Dr. Rajeevan's research continues to focus on the identification and validation of genetic, epigenetic, and molecular markers of CFS. His long-term goal is to identify the etiology and pathophysiology of CFS. He has mentored graduate and postdoctoral fellows in medical genomics.

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## PETER C. ROWE, M.D.

*Professor, Pediatrics*
Director, Chronic Fatigue Clinic, Johns Hopkins Children's Center
Johns Hopkins University School of Medicine
Baltimore, MD

Dr. Peter Rowe has directed the Chronic Fatigue Clinic at the Johns Hopkins Children's Center since 1996 and is the inaugural recipient of the Sunshine Natural Wellbeing Foundation Chair in Chronic Fatigue and Related Disorders. He graduated from McMaster University Medical School, Hamilton, ON, Canada, in 1981. From 1981 to 1987, he was a resident, general academic pediatrics research fellow, and chief resident in pediatrics at Johns Hopkins Hospital. Between 1987 and 1991, he was a staff member at the Children's Hospital of Eastern Ontario, Ottawa, and an assistant professor of epidemiology and community medicine, and of pediatrics. Dr. Rowe returned to Johns Hopkins University in 1991. His work focuses on conditions characterized by chronic fatigue, most importantly the relationship between chronic fatigue syndrome and treatable orthostatic intolerance syndromes, as well as the association between Ehlers-Danlos syndrome and CFS. His work has been funded by NIH, the Department of Defense, and the CFIDS Association of America, as well as by private donations.

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## MARY M. SCHWEITZER, Ph.D.

*Senior Research Associate*
MCEAS, University of Pennsylvania
Newark, DE

Dr. Mary Schweitzer is a patient advocate and author. She collapsed in 1994 with severe ME/CFS and later improved from 30 to 60 on the Karnovsky scale on experimental immune modulator. Dr. Schweitzer is completing a book "Slightly Alive" on disease experience and analysis of government response.

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## CHRISTOPHER R. SNELL, Ph.D.

*Professor, Exercise Science*
University of the Pacific
Stockton, CA

Dr. Christopher R. Snell is a professor of exercise science and department chair at the University of the Pacific, Stockton, CA. He is co-founder and research director of the Pacific Fatigue Laboratory (PFL), a research, clinical, and teaching facility focused on the functional aspects of chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS) and other fatigue-related disorders. In addition to research and clinical testing, a primary purpose of the PFL is to educate patients in conjunction with health, fitness, and legal professionals on various aspects of ME/CFS. Dr. Snell is currently chair of the Chronic Fatigue Syndrome Advisory Committee to the U.S. Department of Health and Human Services.

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## THEOHARIS C. THEOHARIDES, M.D., Ph.D., M.S., FAAAAI

*Professor, Pharmacology, Internal Medicine, and Biochemistry*
Director, Molecular Immunopharmacology and Drug Discovery Laboratory
Tufts University School of Medicine
Boston, MA

Dr. Theoharis Theoharides received his degrees from Yale University. He has more than 290 publications and is in the top 1 percent of authors most cited in pharmacologic journals. He first showed that mast cells can be stimulated by stress peptides to secrete mediators selectively, thus contributing to neuroinflammation.

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## SUZANNE D. VERNON, Ph.D.

*Scientific Director*
CFIDS Association of America
Charlotte, NC

Dr. Suzanne Vernon has a broad background in infectious disease epidemiology, with specific training and expertise in laboratory diagnostics, genomics, and computational biology. After 17 years at the Centers for Disease Control and Prevention in Atlanta, she had the opportunity to direct the research program for the CFIDS Association of America—an excellent opportunity to identify and fund projects that were important for bridging the gap between the bench and bedside and directing a translational research effort. Beginning in 2008, Dr. Vernon directed an accelerated research campaign for the Association and was one of several staff responsible for successfully raising $1 million from donations to support research. She directed the funded investigators as a coordinated CFS research network. Prior to becoming cientific director, she was a CFS program team leader at the Centers for Disease Control and Prevention. Her team's research included identifying CFS biomarkers, constructing computational models of CFS, and validating these models in the laboratory. In 2005, she coordinated an interdisciplinary computational challenge that included 25 investigators from around the world to analyze a common dataset to identify biomarkers. This challenge resulted in a special issue in April 2006 of the journal Pharmacogenomics. CFS is a chronic, debilitating disorder that is an important public health problem diagnosed by self-report and exclusion of other conditions that can explain the symptoms. Given the knowledge base, technology, and computational capabilities available today, Dr. Vernon's goal is to conduct and direct research that will identify objective biomarkers for diagnosis and treatment of ME/CFS.

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# APPENDIX 3
## TRANS-NIH ME/CFS RESEARCH WORKING GROUP

Donald Blair, Ph.D.
National Cancer Institute

Maureen Boyle, Ph.D.
Office of Behavioral and Social Sciences Research

Janine Clayton, M.D.
Office of Research on Women's Health

Becky Costello, Ph.D.
Office of Dietary Supplements

Basil Eldadah, M.D., Ph.D.
National Institute on Aging

Simone Glynn, M.D., M.P.H.
National Heart, Lung, and Blood Institute

Timothy Gondré-Lewis, Ph.D.
National Institute of Allergy and Infectious Diseases

Jenny Haliski
Office of Communications and Public Liaison

Jack Harding, Ph.D.
National Center for Research Resources

Kathy Jung, Ph.D.
National Institute on Alcohol Abuse and Alcoholism

Annette Kirshner, Ph.D.
National Institute of Environmental Health Sciences

Cheryl Kitt, Ph.D.
Center for Scientific Review

John Kusiak, Ph.D.
National Institute of Dental and Craniofacial Research

Catherine Laughlin, Ph.D.
National Institute of Allergy and Infectious Diseases

Dennis Mangan, Ph.D.
Office of Research on Women's Health

Cheryl L. McDonald, M.D.
National Heart, Lung, and Blood Institute

Christopher Mullins, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Eun Chung Park, M.D.
National Institute of Allergy and Infectious Diseases

Matthew Rudorfer, M.D.
National Institute of Mental Health

Xenia Tigno, Ph.D.
National Institute of Nursing Research

Yan Wang, M.D., Ph.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases

May Tze Wong, Ph.D.
National Institute of Neurological Disorders and Stroke

# APPENDIX 4
# WORKSHOP PLANNING(STEERING) COMMITTEE

Charge: To draft workshop topics, set an agenda, and submit nominations of moderators and speakers.

## Scientific/Clinical Topic Experts

Leonard Jason (DePaul University)
Nancy Klimas (University of Miami)
Suzanne Vernon (CFIDS Association of America)

## Patients and Advocates

Patricia Fero
Kenneth Friedman
Mary Schweitzer

## Chronic Fatigue Syndrome Advisory Committee (CFSAC) ex officio Member

Christine Williams, AHRQ

## NIH ME/CFS Working Group Members

Donald Blair, NCI
Timothy Gondré-Lewis, NIAID
John Kusiak, NIDCR
Catherine Laughlin, NIAID
Dennis Mangan, ORWH/OD
Eun-Chung Park, NIAID
Xenia Tigno, NINR
May Wong, NINDS



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