Chronic Fatigue Syndrome Advisory Committee
Fall 2011 Meeting

November 9, 2011

Washington, D.C.

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Chronic Fatigue Syndrome (Myalgic Encephalomyelitis)

- HHS/NIH Blood XMRV Study Unable To Identify The Virus In Blood Samples

- NIH Clinical Study Looking For Retroviruses In Large Cohort Of CFS Patients

- All ME/CFS applications now reviewed by a Special Emphasis Panel by CSR

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Examples Of CFS Grants Funded In FY2011 (n = ~20)

- Co-morbid Chronic Pain Conditions (R13) (NIDCR)
- Stress Effects On Viral Reactivation (NIAID)
- Development Of Small Animal Models Of CFS (NIAID)
- Self Management Of Fatigue (NINR)
- Orthostatic Intolerance and Vascular Dysfunctions (NHLBI)
- Comprehensive Molecular Profiling Of CFS (NIAMS)
- Neuropathic Abnormalities (NINDS)
- Brain Mast Cells and CFS (NINDS)

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Trans-NIH ME/CFS Research Working Group Activities

- ORWH Coordinates Working Group Activities
- Composed of representatives from 17 Institutes and Centers and the OD
- Monthly Meetings
- Outreach: Website And Email Listserv
- State of the Knowledge Workshop On ME/CFS – April 2011
    - Thirty two (32) investigators with expertise in basic, clinical and translational sciences
    - Watched live by nearly 900 viewers via NIH VideoCast and 100 in-person attendees
- Grant-Writing Workshop At CFS Conference – Ottawa, Sept 2011
- NIH is preparing to reissue ME/CFS Program Announcements (R01 and R21)

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State of the Knowledge Workshop on ME/CFS Research

Purpose: To bring together patients, advocates, and scientists to review and discuss the opportunities and gaps in ME/CFS

Workshop Report posted on Working Group website:

- Went online mid-August, 2011
- Has been downloaded nearly 4,000 times

http://orwh.od.nih.gov/CSF%202011/ORWH_SKW_Report.pdf

(Or Google “NIH ME CFS”, go to first link, and look under “News and Events”)

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State of the Knowledge Workshop on ME/CFS Research- Gaps

The workshop identified gaps in the ME/CFS field, including:

- Study Designs Weak
- Etiology Unknown
- Validated Biomarkers
- Case Definition and Diagnosis
- More Genetics Needed
- Symptomatic Treatment
- Paucity of Investigators

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State of the Knowledge Workshop on ME/CFS Research- Opportunities

Opportunities for ME/CFS Research include:

- Advances in Neurology
- Improved Bioimaging
- Communication and Outreach
- Increased Overall Awareness
- Repositories, Databases and Standardized Data
- New Biomarkers
- Systems Biology

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Thank You!

Office of Research on Women's Health

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Related Chronic Pain Conditions Research Activities

The 6th Scientific Meeting of The TMJ Association, June 5-7, 2011
"Comorbid Chronic Pain Conditions - Mechanisms, Diagnosis and Treatments"

• The purpose was to review what is currently known about persistent generalized pain conditions and explore ways to advance research in this field.

• There was participation by seven NIH Institute, Office, and Center Directors (including ORWH), the leaders of four patient advocacy groups comprising the Chronic Pain Research Alliance (including the Chronic Fatigue and Immune Dysfunction Syndrome Association of America).

• Main recommendation was for a major paradigm shift in the way chronic pain conditions are studied; field will likely be transformed from isolated, disease silo- and symptom-based research into a broader, mechanism-based multiple-disease, or "new disease"-based research endeavor.

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Comorbid Chronic Pain Conditions: Mechanisms, Diagnosis, and Treatment (NIDCR)

• Conference funding (R13) for the Sixth Scientific Meeting of The TMJ Association, "Comorbid **Chronic Pain Conditions** - Mechanisms, Diagnosis and Treatments", June 5-7, 2011 at the Federation of American Societies for Experimental Biology Conference Center in Bethesda, Maryland.

• Co-morbid Chronic Pain Conditions (CCPC) which often co-exist with TMD conditions are Chronic fatigue syndrome, chronic headaches, endometriosis, fibromyalgia, interstitial cystitis, irritable bowel syndrome, and vulvodynia.

• The meeting engaged key leaders and representatives from funding and patient advocacy organizations who will develop recommendations to advance research in this field. The specific aims of the meeting were to determine:

1. What is currently known about underlying mechanisms of CCPC;
2. What we need to know about CCPC (e.g., case definition, diagnostics);
3. What research areas are most promising to pursue (best approaches, resources);
4. How best to foster the development of treatment modalities for CCPC;
5. What approaches are necessary to encourage, train, and sustain a CCPC research community; and
6. What high-risk research areas have the potential to substantially advance our understanding of CCPC.

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Small Animal Model for XMRV Infection (NIAID)

• A novel human gammaretrovirus, entropic murine leukemia virus-related virus (XMRV), has been identified in association with familial cases of prostate carcinoma and in patients with chronic fatigue syndrome (**CFS**).

• However, the etiological link and the mode of transmission of XMRV remain to be determined. If the roles of XMRV in development of prostate cancer or **CFS** are established, detection and prevention of XMRV would provide novel intervention strategies for early diagnosis and treatment of both diseases.

• The overall goal of this proposal is to develop a small animal model for XMRV infection. Although laboratory mice have provided important small animal model systems for the study of many human diseases, studies of XMRV infection in laboratory mice have been hampered by their lack of a functional XMRV receptor.

• In our preliminary studies, we have demonstrated that Mus pahari can support XMRV replication in vitro and in vivo. Based on these observations, our central hypothesis is that Mus pahari can serve as a small animal model for XMRV infection. This small animal model for XMRV infection would allow in vivo evaluation of anti-XMRV strategies, including small molecules and vaccines.

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Efficacy of Home-Based Self-management for Chronic Fatigue(NINR)

The long-term objective of this proposal is to establish a commercially viable program of illness Self-Management in people with Unexplained Chronic Fatigue (UCF) and Chronic Fatigue Syndrome (CFS) that will potentially offer:

(1) improved access to treatment for patients who may be unable or unwilling to travel to regular appointments;
(2) a minimal time commitment and lower cost for higher credibility 'Self- Management' in comparison to face-to-face counseling and longer-term mental health care;
(3) a substantially reduced illness burden and improved quality of life; and .
(4) reduced medical and behavioral utilization for these patients.

This Phase II study is a randomized trial of feasibility-tested fatigue self-management programs that compares three conditions:

(a) the Phase I Self-Management product utilizing web diaries and activity monitors
(b) the Phase I Self-Management product utilizing inexpensive paper forms and step counters
(c) a wait list control condition.

It is hypothesized that both self-management conditions condition will be more efficacious than the wait list condition in lessening fatigue, improving functioning, and reducing depression, and outcomes will not be significantly different between the two self-management programs.

Phase III Commercialization: The Self-Management product will be promoted to (a) health plan decision makers (e.g., managed care companies and large employers),and (b) retail end users via targeted internet sites that offer products and support services to UCF/CFS patients.

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Orthostatic Intolerance in CFS (NHLBI)

Orthostatic intolerance (the postural tachycardia syndrome; POTS) is the most common autonomic manifestation in chronic fatigue syndrome (**CFS**). There is evidence that some patients with POTS have a restricted autonomic neuropathy (neuropathic POTS), while others have POTS unassociated with an autonomic neuropathy. It is proposed that nitric oxide availability may differ in these two subtypes. It is not known whether nitric oxide abnormalities are merely a biological marker, whether the abnormalities have hemodynamic and pathophysiological significance, or whether these differences underlie the unsatisfactory response to therapeutic intervention in POTS patients.

The long-term objectives of the project are

1. To delineate the pathophysiology and pathogenesis of orthostatic intolerance in patients with chronic fatigue;
2. To investigate the role of orthostatic intolerance in producing the symptoms of fatigue;
3. To use this information to institute physiologically appropriate therapeutic interventions;
4. To thereby decrease the symptoms of fatigue.

The specific aims of the application are:

A. In two separate experiments, we will increase and decrease nitric oxide availability, and examine the autonomic cardiovascular effects of this intervention in neuropathic and non- neuropathic POTS.
B. In two separate therapeutic interventions, increase and decrease sympathetic tone and examine the autonomic cardiovascular effects, fatigue scores, and quality of life in response to these interventions.

We anticipate that the responses to changes in nitric oxide availability and the therapeutic interventions will be different in the two POTS subtypes.

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Vascular dysfunction in CFS (NHLBI)

Blood flow abnormalities associated with the postural tachycardia syndrome (POTS) produce major disability in younger **CFS** patients. These may be due to defects in a fundamental signaling molecule called nitric oxide (NO). Data suggest the involvement of nitric oxide (NO) and angiotensin in producing decreases in blood volume and excitation of the sympathetic nervous system.

The overall objective of the application is to define mechanisms of **CFS**/POTS related to bioavailable NO, and to explore the subclinical microvascular abnormalities in **CFS** without POTS (**CFS**/~POTS).

We will subset **CFS** patients (16-29 years) by POTS, and subgroup POTS based on peripheral blood flow. We will compare low flow POTS (N=30) and normal flow POTS (N=30), to **CFS**/~POTS (N=30) and control (N=30) with and without POTS to explore the following hypotheses:

1) Low flow **CFS**/POTS is due to decreased bioavailable NO
2) Oral losartan (an angiotensin receptor blocker) increases regional circulation and cutaneous microvascular NO dependent responses in low flow **CFS**/POTS.
3) NO is increased in normal flow **CFS**/POTS producing nitrosative stress. Cutaneous somatostatin administration can reduce skin NO excess.
4) Subcutaneous octreotide, a somatostatin analog, reduces orthostatic splanchnic pooling and cutaneous microvascular NO dependent responses in normal flow **CFS**/POTS..

In the current application we will determine how NO produces POTS in **CFS** patients and whether drugs that alter NO can improve patient health.

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Study of CFS Using Comprehensive Molecular Profiling (NIAMS)

Research has shown that immune, endocrine and nervous systems are all affected in CFS. Though these systems function in close collaboration , **CFS** continues to be studied using a traditional piece-by-piece approach focusing on the failure of individual neuroendocrine and immune components.

We hypothesize that **CFS** results not only from component failure but perhaps more importantly from a significant deterioration of regulatory function linking these components.

We will test regulatory fitness by using an exercise challenge to stimulate stress response and its modulation of the nervous, endocrine and immune systems.

Objectives: The objective of this study is to improve our understanding of **CFS** pathogenesis in three ways:

(i) by using broad-scale molecular profiling to create a comprehensive assessment of status in several of the body's regulatory systems,

(ii) by using information theory to integrate this disparate data into a single interpretable map describing the interactions between these physiologic systems and

(iii) by using novel elements of network theory to study the structure of these signaling networks and isolate alterations in the "wiring" that might be specific to **CFS**.

These maps will show how the entire body responds to exercise stress. This quantitative knowledge of the rates and directions with which biological information is spread through the neuroendocrine immune networks will be used as a basis for simulating response to treatment. Indeed computer simulations of neuroendocrineimmune response will be used to perform computer-aided design of candidate clinical trials in much the same way simulations have been used to train flight crews.

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Neuropathologic Abnormalities Define a Subgroup of Patients with CFS (NINDS)

A major step forward in understanding the pathophysiology of CFS would involve reducing the heterogeneity of CFS patients included in clinical studies by identifying one or more subgroups of patients with different pathophysiological causes of their illness, and then selecting one of these subgroups for inclusion into research studies.

Over the past few years, we and others have provided substantial data supporting the existence of a subgroup of patients with a neurobiological cause for their illness, based on stratifying the sample according to the absence or presence of comorbid Axis I psychopathology (CFS-no psych or CFS-NP and CFS-psych or CFS-P, respectively). Compared to CFS-P patients, the CFS-NP patients had more cognitive dysfunction, a higher rate of abnormal cerebrospinal fluid (CSF) findings, lower regional cerebral blood flow (rCBF), and higher ventricular CSF lactate values.

The purpose of this proposal is to rigorously assess and confirm whether patients in the CFS- NP group have consistent abnormalities across several different neuropathological variables and to use these results to classify the CFS subjects into subtypes, and then compare the resulting subgroups based on membership into CFS-NP or CFS-P groups

Specifically, in the same subjects, we will

(a) assess cognitive function using objective neuropsychological testing;
(b) conduct biochemical analysis of spinal fluid samples obtained by lumbar puncture; and
(c) measure rCBF and ventricular lactate using magnetic resonance imaging and spectroscopy, respectively, in CFS-P and CFS-NP patients.

If successfully completed, this study could validate an approach for selecting more homogeneous CFS patient populations in future research studies to enable them to focus better on understanding the exact cause of CFS and developing effective treatments for the illness.

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Brain Mast Cells and CFS (NINDS)

Neuroimmune interactions in CFS are still unknown, creating a vacuum in diagnosis and treatment. Central and peripheral cytokines produced in response to viral infections or other inflammatory stimuli may be implicated, but there is no distinct pattern. Mast cells and their mediators have been implicated in all diseases that are comorbid with CFS. Brain mast cells are abundant in areas close to corticotropin-releasing hormone (CRH)-positive neurons; CRH is secreted under stress and can activate mast cells. This activation of mast cells could disrupt gut-blood-brain barrier and lead to brain inflammation and release of fatigue causing molecules.

Tricyclic antidepressants have been reported to be beneficial in treating CFS, and our preliminary results indicate that only the tricyclic amitriptyline, and certain natural flavonoids can inhibit mast cell secretions.

Our hypothesis is that external triggers, along with CRH secreted by stress, activate diencephalic centers and mast cells, leading to release of proinflammatory and fatigue producing molecules, and these can be inhibited by select flavonoids.

We will investigate:

(1) the effect of CRH, other neural signaling molecules, or restraint stress using female C57BL/6 mice on:
- (a) Fatigue using the forced water immersion test,
- (b) Blood brain barrier disruption (by measuring brain levels of the fluorescent marker AngioSense)
- (c) Brain expression of mast cell cytokines and other activation products

(2) The requirement for mast cells in the endpoints studied in Aim 1 by using C57BL-derived WW mast cell deficient mice,

(3) Inhibitory effect of a flavonoid formulation on endurance and brain biomarkers.

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