STANFORD
SCHOOL OF MEDICINE
Stanford University Medical Center

DIVISION OF INFECTIOUS DISEASES AND GEOGRAPHIC MEDICINE
DEPARTMENT OF MEDICINE
300 PASTEUR DRIVE, S-101
STANFORD CA 94305

Dear Friends,

I want to thank you all for the continued support that we have received from you. Your encouragement and generous financial support has allowed us, the Division of Infectious Diseases at Stanford University Medical Center, to progress in the area of infection-associated Chronic Fatigue Syndrome (CFS).

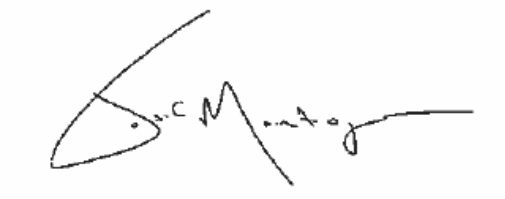
My team and I are committed to keeping our supporters well-informed about our work. We hope that our research will lead to findings to improve the health and quality of life for many people the world over. Our goals, dreams and research projects are explained in the enclosed documents. Much has been accomplished in the past 3 years, and more exciting projects are planned for 2013 and beyond.

It is exciting to partner with you to explore one of the most baffling medical mysteries of the 21st century, Chronic Fatigue Syndrome. We want you to know that YOU are part of our team and you are helping us solve the problem of infection-associated chronic diseases. Your advocacy, letters of encouragement, and financial support make what we are doing possible.

Our work and initial success has been possible through the dedication and persistence of the Stanford team including: Manisha Desai PhD (Statistics), Marcie Zinn PhD (Neurophysiology), Jane Norris PA (Clinical Care and Research Coordinator), Amity Hall PA (Clinical Care), Aimee Jadav (Clinical Care), Amber Ruiz (Research Coordinator), Ian Valencia (Research Coordinator), Diana Dobbs (Research Assistant), Steven Smallberg (Stanford Undergrad), Scott Livingston (Stanford Undergrad), Julian Sanchez (High School Volunteer), Tristan Verguese (High School Volunteer), Cornelia Weyand MD (Immunology), Francois Haddad MD (Cardiology), Holden Maecker PhD (Immunology), James Kang MD (Radiology), Mark Davis PhD (Immunology), Mehdi Skhiri MD (Cardiology), Michael Dake MD (Neuroradiology), and Michael Zeineh (Neuroradiology).

Please take a moment to read the enclosed newsletter. I hope you enjoy learning what we have accomplished with your support and what dreams we have for the future. We would also love to hear from you. Please contact us about any of the items listed in our newsletter or any thoughts that you might have. I send my very best wishes to you and your loved ones for the rest of 2013.

Sincerely,



Jose G. Montoya, MD, FACP, FIDSA
Professor of Medicine
Division of Infectious Diseases and Geographic Medicine
Stanford University School of Medicine
Director, Toxoplasma Serology Laboratory, Palo Alto Medical Foundation
National Reference Center for the Study and Diagnosis of Toxoplasmosis

NEWS FROM THE STANFORD INITIATIVE FOR THE STUDY OF INFECTION-ASSOCIATED CHRONIC DISEASES

SUMMER 2013

Stanford University is taking the lead in a critical area where research is lacking: the study of patients with unexplained chronic illnesses. Myalgic Encephalomielitis/Chronic fatigue syndrome (ME/CFS), chronic Lyme disease (CLD), and multiple sclerosis (MS) for example, can significantly impair the lives of our patients and result in substantial reductions in their previous levels of occupational, educational, social, or personal activities.

Our group has taken a broad and innovative approach to discovery surrounding these debilitating diseases. Seven years ago our team postulated that infection, or the body's immune response to it, can play an etiologic role in chronic unexplained illnesses. We also hypothesized that prolonged and specific antimicrobial interventions coupled with immune modulation could result in partial or complete reversal of a patient's symptoms. Since then, we have been able to successfully identify several subgroups of patients whose lives have been dramatically changed with our approach [Kogelnik, 2006].

Our initiative for infection-associated chronic diseases is now focusing on chronic fatigue syndrome. We are interested in learning more about the infectious agents that may play an etiologic role in CFS, including the human herpesviruses, parasites such as *Toxoplasma gondii*, fungi such as *Coccidiodes immitis*, and bacterial infections such as *Borrelia burgdoferi (Lyme).* We hope that our work will help improve the lives of patients suffering from CLD and CFS. We are collaborating with other CFS researchers throughout the United States to identify biomarkers and other tests that can guide the diagnosis and treatment of CFS which may ultimately improve the lives of millions of patients. Our goal is for healthcare providers worldwide to acknowledge that CFS and CLD are real diseases; thus, validating patients and fully integrating them back into mainstream medicine.

Though the field of CFS research has been surrounded by controversy, we have faith in our endeavors as well as the sound and promising research being conducted internationally. Several teams of talented physicians and researchers are dedicated to better understanding CFS and developing effective treatments and objective diagnostic tools.

TO DATE WE HAVE MADE PROGRESS IN THE FOLLOWING AREAS:

Establishment of the Stanford ME/CFS Advisory Committee

- With the participation of Mrs. Margarett Raffin, President Ishiyama Foundation, Mark Davis PhD, Dennis Mangan, PhD, Lily Chu, MD, MPH, Thomas Raffin MD, Abraham Verghese MD, and the support of a development team, Natalie Fleishman and Elizabeth Burke, we have founded this Board on March 2013. The group meets quarterly and discusses alternatives to decipher possible etiologies, diagnostic methods and treatments associated with this illness, and ways to address the main needs of our patient population.

Completed Research:

- We published a paper on the analysis of a randomized, double-blind, placebo-controlled trial on the use of Valganciclovir in patients with chronic fatigue syndrome (CFS) and elevated Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV) antibodies.

- We published a paper using observational data on the response to Valganciclovir treatment in Chronic Fatigue Syndrome patients with positive Human Herpesvirus 6 and Epstein-Barr virus IgG titers.
- We published a manuscript on antiviral therapy inducing viral and clinical response in patients with central nervous system dysfunction and chromosomally integrated Human Herpesvirus 6
- A manuscript depicting sex differences in response to antiviral therapy is in the process of being submitted for publication.
- In a collaboration headed by Ian Lipkin, MD, at Columbia University, we were involved in a multi-site study funded by the National Institutes of Health (NIH). Through this research effort, we hoped to learn the prevalence of XMRV and MLV in CFS patients compared to healthy controls. This work has been published in *mBio,* an online scientific journal associated with the American Society of Microbiology. Please visit our CFS website for more information.

Updates to the Stanford ME/CFS Initiative Website: In early 2011 our research group launched the Stanford ME/CFS Initiative website. This website was created to inform patients, physicians, and the general population about infection associated chronic illnesses. We frequently update our website to provide up-to-date findings in the field of CFS research. We created a page specifically designed for patients. This page provides step by step instructions on how to navigate our website and offers additional information and resources pertaining to health management. If you wish to visit our website go to: http://mecfs.stanford.edu

Addition of a Physician's Assistant to our Clinical Team: In an effort to better serve our CFS patients, we welcomed three physician's assistants to our team: Amity Hall, Jane Norris and Aimee Jadav. Our physician's assistants assist Dr. Montoya in the Stanford infectious disease clinic. The addition of a physician's assistant to our clinic was made possible by the generosity of our supporters.

WE ARE CONTINUING OUR IMPORTANT WORK IN THE FOLLOWING AREAS:

Detection of infectious pathogens that may contribute to chronic diseases: We are looking for pathogens such as herpes viruses, *Borrelia burgdorferi (*the Lyme disease etiologic agent) , *Toxoplasma gondii*, or any unknown pathogen that may be a trigger for chronic diseases such as CFS (chronic fatigue syndrome). We are looking for such pathogens in a broad population of CFS patients at Stanford and compare the findings to age- and sex-matched controls.

Towards this end we are collaborating at Stanford with: Manisha Desai, Ph.D, Clinical Associate Professor of Medicine and Holden Maecker, Ph.D, Director, Human Immune Monitoring Center, and my colleagues at Columbia University Medical Center in New York City: W. Ian Lipkin, MD, Director, Center for Infection & Immunity, and the John Snow Professor of Epidemiology, and Professor of Neurology and Pathology and Mady Hornig, MA, MD, Associate Professor of Epidemiology. We have met our recruitment goal for this effort and are in the process of testing our blood samples. This work was made possible by the generous support of our donors.

Investigation of gene expression and immune system dynamics of infection in acute and chronic diseases: Our team is currently working on new studies to understand the immune response and possible immune dysfunction observed in our patients. We are looking at gene expression, cytokine profiles, and phospho immunoflow to learn whether our patients' immune response correlates with the presence of pathogens and other infectious agents. We have embarked on the task to identify new

biomarkers that may help predict changes in disease over time and response to changes in medication. Towards these goals we are collaborating closely with the Human Immune Monitoring Center facility at Stanford, including Mark Davis, Ph.D, Professor of Medicine in the Division of Microbiology and Immunology, and Holden Maecker, Ph.D. We have met our recruitment goal for this effort and are in the process of testing our blood samples.

Assessment of neuronal and neurovascular changes in infection-associated CFS patients: We are collaborating with the Neuroradiology department at Stanford to investigate the role of novel magnetic resonance imaging (MRI) techniques in the hope of discovering structural changes in the brain for infection-associated CFS. These MRI tests are not available for routine clinical use at this time. Michael Zeineh, MD, Professor of Medicine in the Division of Radiology, and his neuroradiology fellow, James Kang, MD, are helping us analyze preliminary imaging data to apply for an NIH grant to begin a larger study on neuroimaging in CFS patients.

In collaboration with another faculty member of Stanford University School of Medicine, Michael Dake, MD, Professor of Medicine in the Division of Cardiothoracic Surgery, we are investigating the correlation between the symptoms associated with Chronic Fatigue Syndrome and abnormal cerebral venous drainage through magnetic resonance venography (MRV). We have begun recruitment of a limited number of participants and may expand recruitment in the near future.

Examination of cardiovascular health in patients with CFS: Francois Haddad, MD, Clinical Assistant Professor of Medicine in the Division of Cardiovascular Medicine, is heading a collaboration with Mehdi Skhiri, MD, working with our CFS patients to evaluate their cardiovascular aging. In this project, Dr. Haddad and his team use a sub-maximal effort exercise testing machine. Additionally, Dr. Haddad utilizes a device which evaluates endothelial dysfunction. Ultimately, we hope the findings from this study will help to improve our diagnostic capability as well as better evaluate the effects of CFS on cardiovascular health. We have currently met our recruitment goals and have embarked on analyzing blood samples and other study data.

Use of qEEG to assess the neurological changes in CFS patients: Marcie Zinn, Ph.D, an accomplished neuropsychologist, focuses her research on the objective measures of cognitive dysfunction in our patients. Through this project, we are using electroencephalography, or EEG, to evaluate peak alpha frequency measurements of CFS patients and healthy controls. We hope that our efforts will result in objective assessments of cognitive impairment as well as inform future research on the treatment of cognitive impairment in CFS. We have reached our recruitment goal of 50 CFS patients and 50 healthy controls and have analyzed our results. A manuscript is currently being written and will be submitted for publication.

Dissemination of CFS research: Our team frequently presents research findings at national and international meetings. Dr. Montoya has presented his research at 10th Annual International Association for CFS/ME Research and Clinical Conference, in Ottawa, Canada, September 2011. Sharing Stanford's perspective on pathogens in chronic illness and talking with other physicians who share our interest is important in advancing knowledge and treatment in the entire field of infectious disease.

Subgrouping chronic fatigue syndrome patients by genetic and immune profiling: We have been awarded a grant by the Department of Defense (DoD) office of the Congressionally Directed Medical Research Programs (CDMRP). With these funds we are exploring the immune responses of CFS patients as well as analyzing human leukocyte antigen (HLA) type of CFS patients compared to healthy controls.

Using Cytof-phosphoflow technologies under the direction of Holden Maecker (PhD), we are also conducting detailed phenotypic and functional analysis of stimulated cell populations. Blood sample testing has begun.

ME/CFS Biobank

In coordination with Stanford's Human Immune Monitoring Center (HIMC), our ME/CFS Research team has collected multiple samples to conduct a variety of Pathogenic, Genetic, and Immunological tests to help learn more about ME/CFS and contribute to the elucidation of the pathogenesis of ME/CFS. These samples include DNA Paxgene, RNA Paxgene, Heparin Plasma, Serum, and PBMCs. We are in the process of testing blood samples and look forward to continue to work hard and learn more about ME/CFS.

UPCOMING PROJECTS

Gene Expression and Immune System Dynamics in Acute and Chronic Disease- Lyme Disease Cohort:

In an effort to expand our knowledge in the realm of chronic disease, our team is working on a new study aimed at understanding the immune profile and gene expression of patients suffering from chronic Lyme disease. Specifically, we will look at gene expression, cytokine profiles, and phospho immunoflow which may help us to identify new biomarkers specific to chronic Lyme disease. Towards these goals, we are collaborating with the Human Immune Monitoring Center facility at Stanford, including Mark Davis, Ph.D, Professor of Medicine in the Division of Microbiology and Immunology, and Holden Maecker, Ph.D. Additionally, we are collaborating with physicians outside of Stanford Hospital and Clinics who have extensive clinical experience with patients suffering from Lyme disease. We hope to begin participant recruitment in the Fall of 2013.

DREAM PROJECTS:

Educational outreach: We plan to host a major research meeting at Stanford University with the participation of international investigators to increase the understanding and the exchange of information in the field of chronic inflammatory disease. A biennial educational meeting aimed at practicing physicians, fellows, residents, and medical students will be initiated as well. We believe that we can significantly impact the field by re-educating the nascent and established medical community about the major and complex issues faced by our patients.

Formation of a Center for Infection Associated Chronic Diseases at Stanford: We hope, with your support, to establish an inpatient center separate from a hospital environment where patients with chronic diseases can benefit from a holistic approach to their treatment. Patients will receive treatment for the specific infectious agents likely to be playing a role in their disease over the course of weeks to months. In addition, they will receive complementary treatments to promote recovery and healing.

MOVING FORWARD:

During the next five years we will continue to mobilize and integrate many of Stanford's best faculty and resources toward our mission and goals. The director of the Institute for Immunity, Transplantation and Infection, Dr. Mark Davis, has also committed to support our mission and has been integral in the development of this initiative. The task ahead of us is monumental and requires the participation of faculty and researchers from many areas. We have assembled a world-class team of researchers, post-doctoral fellows, statisticians, bioinformatics faculty, graduate students, laboratory personnel, and a neuropsychologist.