

June 1st, 2015

Dear ME/CFS Community, Family, Fellow Physicians and Researchers,

We would like to take this opportunity to thank you for all of your invaluable support, instrumental for our progress and continued research in the area of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The Stanford ME/CFS Initiative at the Stanford University Medical Center is committed to the tasks of understanding the causes of this disease and of improving treatment for all patients.

As in years past, our yearly Newsletter is intended to share our current and future projects with all of our supporters, as we fervently believe that your participation fuels our dreams to conquering this disease once and for all.

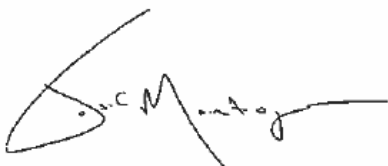
In the past year, we have opened and completed clinical trials, submitted and published research papers to respected peer-reviewed journals, and hosted conferences, but none of this would have been possible without your involvement and your support, *you*, our esteemed team member. We would also like to give special thanks to those that have participated in our studies.

Other team members whose participation has been key to our success at Stanford include Diana Dobbs, Amity Hall PA, Aimee Jadav, PA Luciana Mendiola MA, Jane Norris PA, Amber Ruiz, Ian Valencia, Marcie Zinn PhD, Mark Zinn MM; collaborators such as Lily Chu MD, Mark Davis PhD, Ron Davis PhD, Manisha Desai PhD, Rosemary Fernandez, Francois Haddad MD, Mady Hornig MA, MD, Safwan Jaradeh MD, Xuhuai Ji, James Kang MD, Kristopher Kapphahn PhD, Amit Kaushal MD, PhD, Michael Kertesz PhD, W. Ian Lipkin MD, Holden Maecker PhD, Jose R. Maldonado MD, Michael Mindrinos PhD, Aya Mitani, Linda Nguyen MD, Stephen Quake PhD, William Robinson MD, Yael Rosenberg-Hasson, Mehdi Skhiri MD, Cristina Tato MPH, PhD, Janine Sung, Wenzhong Xiao PhD, Weihong Xu PhD, Jared Younger PhD, Michael Zeineh MD, PhD; summer interns Stanford Undergrads Steven Smallberg and Tristan Verghese, and high school students Scott Livingston and Julian Sanchez.

Please find enclosed our 2014 Newsletter, which includes a summary of our completed research, our ongoing research and those research projects we will excitingly embark on in 2015. As always, we would love to hear from you. Write to us at The Stanford ME/CFS Initiative, 1000 Welch Road, Suite 202, Palo Alto, CA 94304.

On behalf of the Stanford ME/CFS Initiative, we wish you all the best in 2015!

Yours truly,



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***NEWS FROM THE STANFORD MYALGIC ENCEPHALOMYELITIS/
CHRONIC FATIGUE SYNDROME (ME/CFS) INITIATIVE***

SPRING 2015

In the last four years, the Stanford ME/CFS Initiative has collaborated with experts in a wide number of fields with the purpose of understanding the causes of ME/CFS and the end goal of improving treatment. At the ME/CFS Initiative, we believe that a multidisciplinary clinical and research approach combined with patient-centered care might provide a foundation for future improvements in diagnosis and treatments of these patients.

We are pleased to welcome two new members to our ME/CFS Advisory Board, gastroenterologist Linda Nguyen MD and neurologist Safwan Jaradeh MD. They join the distinguished group of Board members, Margaret Raffin, Abraham Verghese MD, Mark Davis PhD, Thomas Raffin MD, Dennis Mangan PhD, and Lily Chu MD.

In December of last year, the National Institutes of Health (NIH) held the Pathways to Prevention (P2P) Workshop where a multidisciplinary group of experts discussed the clinical and research evidence to identify research gaps and future research priorities. Among their recommendations, NIH P2P made a call for increased funding for advancing research in the field in order to fill the gaps in current knowledge of ME/CFS, and accelerating the progress for adequate patient treatment.

More recently in February of 2015, the Institute of Medicine (IOM) was convened to conduct an extensive literature review to develop evidence-based diagnosis criteria for ME/CFS, as well as a new terminology and an outreach strategy to disseminate these findings to health professionals. The final recommendations by the Expert Committee, which included Dr. Montoya's participation, proposed new diagnostic criteria, a new name, Systemic Exertion Intolerance Disease (SEID), and an increase in research funding.

At the ME/CFS initiative, we echo the messages set forth by the NIH P2P and the IOM: ME/CFS is a complex, multisystemic and crippling illness in much need of multidisciplinary research approach that must always take heed of patients' concerns in order to improve diagnosis and treatment once and for all. These recommendations provide the ME/CFS community with a step forward into changing the narrative of the disease and significant progress in ensuring that patients will be properly recognized and supported by their health care providers.

We are excited to share with you what the ME/CFS Initiative has been up to in the past year and first half of 2015, and we anticipate further successes in the coming year.

2014 and FIRST HALF OF 2015 ACTIVITIES AND PUBLISHED RESEARCH

Neuroradiology applied to studying ME/CFS: Our collaboration with Michael Zeineh MD, PhD at the Neuroradiology Department at Stanford, yielded the first ever study to use a novel magnetic resonance imaging (MRI) technique, diffusion tensor imaging (DTI) in visualizing ME/CFS brain function. Our preliminary data suggests that an abnormality in right arcuate fasciculus in ME/CFS patients might be a biomarker for this disease. We are in the process of submitting a grant proposal that will validate these findings in a larger group of ME/CFS patients and hopefully uncover the connection between ME/CFS and brain abnormality.

Right arcuate fasciculus abnormality in chronic fatigue syndrome. Zeineh MM, Kang J, Atlas SW, Raman MM, Reiss AL, Norris JL, Valencia I, Montoya JG. *Radiology*. 2015 Feb;274(2):517-26

Immunology in ME/CFS: With the leadership of Mady Hornig MA, MD and W. Ian Lipkin at the Center for Infection and Immunity at Columbia University, an in-depth analysis of the immune system of ME/CFS patients objectively confirmed that ME/CFS is a biological illness, and not a psychological disorder. This was observed by detecting elevated levels of cytokines in ME/CFS patients, proteins released by the immune system for fighting infections and other immune responses. These data indicate that ME/CFS is indeed an inflammatory disease. We will also be publishing a paper on cytokines that further supports ME/CFS as an inflammatory disease in the coming months.

Distinct plasma immune signatures in ME/CFS are present early in the course of illness. Hornig M, Montoya JG, Klimas N, Levine S, Felsenstein D, Bateman L, Peterson DL, Gottschalk CG, Schultz AF, Che X, Eddy ML, Komaroff AL, Lipkin WI. *Science Advances*. 2015 Feb; 1(1) ePub.

Chronic Fatigue Syndrome (CFS) Patient-Centered Outreach and Communication Activity (PCOCA): On February 23rd, 2015, Dr. Montoya presented on the “Stanford ME/CFS Initiative: Collaboration, Innovation and Discovery” for the Center for Disease Control (CDC) Chronic Fatigue Syndrome (CFS) Patient-Centered Outreach and Communication Activity (PCOCA). During this Conference Call, Dr. Montoya talked about the Initiative’s accomplishments, past and current collaborations and future research projects. We have included a summary of his presentation.

2014 Stanford Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Symposium: Advances in Clinical Care and Translation Research: On March 20th, 2014, the Stanford University ME/CFS Initiative hosted a ME/CFS Symposium, sponsored by the Stanford University School of Medicine. Attendance at the Symposium included researchers and physician experts in ME/CFS, as well as patients, their families, journalists and the general public. Among Stanford faculty presenters, Dr. Montoya presented on circulating cytokines in ME/CFS patients, Amit Kaushal MD, PhD summarized gene expression findings in ME/CFS, Mehdi Skhiri MD talked about cardiovascular aging in CFS, Michael Zeineh MD, PhD shared about his MRI findings in ME/CFS patients. Elizabeth Unger MD, PhD from the Centers for Disease Control and Prevention summarized the current knowledge of the epidemiology of ME/CFS, W. Ian Lipkin from Columbia University presented on microbial diagnostics and discovery in ME/CFS and Jarred Younger MD from the University of Alabama at Birmingham, and previously at Stanford University, shared his studies on the daily fluctuations of cytokines in ME/CFS patients. The Symposium also included a discussion session, in which journalists, ME/CFS activists, patients and caretakers reviewed the media portrayal of ME/CFS.

The 11th Biennial International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (IACFS/ME): On March 20th to the 23rd of 2014, the Stanford University ME/CFS Initiative helped support the International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (IACFS/ME) 11th Biennial Conference. The meeting featured expert physicians and researchers from around the country and the world. Dr. Montoya presented on virology research and antiviral treatments during the conference.

Synergy Trial: In 2014, we participated in a multi-site study to evaluate the safety and efficacy of a combined medication to treat ME/CFS during a 12-week intervention. Enrollment is now complete, at 134 subjects from four research sites throughout the United States. We anticipate to complete analyses of results in the upcoming weeks, and manuscript publication in the following month. Additionally, we are looking at conducting mitochondrial testing for the samples collected during the trial to understand how mitochondria function is affected among ME/CFS patients. Please visit <http://thesynergytrial.org> to learn more about this trial.

GENERAL UPDATES

The Stanford ME/CFS Initiative Website: In the last few months, we have been adding updates to our “Recent News” and will continue to do so on a periodic basis. We have also added a “News Archive”, where you may find older posts. Our website has now transitioned to a more user-friendly and streamlined version. We invite you to visit our webpage to access information regarding ME/CFS, general patient information, and to learn more about upcoming events at <http://med.stanford.edu/chronicfatiguesyndrome/>

Addition of a Research and Grant Writer Assistant: Thanks to the philanthropic support from a patient's family, we welcomed Luciana Mendiola, MA, Research and Grant Writer Assistant to our team. She will assist in preparing grant submissions for both government and private institutions to build on the current knowledge of ME/CFS and improve care and treatment. Additionally, we are currently reviewing exceptional candidates for Biostatistician and Clinical Research Coordinator positions to further expand our team.

ONGOING RESEARCH

High Throughput Sequencing/Pathogen Discovery: Through our continued partnership with Holden Maecker PhD at Stanford and W. Ian Lipkin MD and Mady Hornig MA, MD at Columbia University, our effort of looking for pathogens present or abundant in ME/CFS patients has yielded exciting results. We are in the process of preparing a manuscript for submission to a peer-reviewed journal.

Gene Expression and Immune System Dynamics-Gene Expression: In order to understand the immune response and possible immune dysfunction observed in our ME/CFS patients, we are collaborating closely with Mark Davis PhD at Human Immune Monitoring Core facility at Stanford, and with Holden Maecker PhD. We are in the process of finalizing analysis of samples and plan on submitting a manuscript shortly.

Cardiovascular Health in ME/CFS patients: Our study in collaboration with Francois Haddad MD and Mehdi Skhiri MD of evaluating cardiovascular aging in ME/CFS patients has concluded with the recruitment and analysis of samples. Even though their work revealed that the heart is highly unlikely to be affected by ME/CFS, Drs. Haddad and Skhiri are now looking at endothelial function and cytokine levels before and after physical exercise. The manuscripts are currently in preparation for publication.

Cognitive Impairment Study in ME/CFS patients: Marcie Zinn PhD, Mark Zinn MM, and José R. Maldonado MD at Stanford University led a study utilizing electroencephalography (EEG) to yield objective measurements for evaluating cognitive impairments in ME/CFS patients. The manuscript is currently in review for publication.

Subgrouping Chronic Fatigue Syndrome Patients by Genetic and Immune Profiling: This is an ongoing Department of Defense (DoD) grant, which aims to explore the immune responses of ME/CFS patients and how they differ to healthy controls. We are also analyzing human leukocyte antigen (HLA) types in ME/CFS patients, responsible for the regulation of the immune system. We are currently finalizing analysis and will start preparing manuscript shortly.

FUTURE ENDEAVORS

Gene Expression and Immune System-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 phosphor-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 Core facility at

Stanford, including Mark Davis PhD, Professor of Medicine in the Division of Microbiology and Immunology, and Holden Maecker PhD. Additionally, we are collaborating with other physicians from the Stanford Healthcare and other institutions, who have extensive clinical experience with patients suffering from Lyme disease. We hope to begin participant recruitment in late spring of 2015.

Universal Pathogen Discovery: Building upon preliminary data we collected from our GEISD-Pathogen Discovery study, we are planning to, in addition to blood, sample cerebrospinal fluid, lymph nodes, bone marrow, and NK cell compartments, in a partnership with bioengineer Stephen Quake DPhil. In collaboration with Linda Nguyen MD, gastroenterologist and motility expert at Stanford, we will also collect gastrointestinal biopsies. This study will be the first comprehensive effort to search for pathogens in sites never attempted before.

Neuroendocrine Study: In an effort to understand pathogenesis of ME/CFS, we will study how the Hypothalamic–pituitary–adrenal (HPA) axis functions in ME/CFS patients. With the expertise of Laurence Katznelson MD, endocrinologist at Stanford, we aim to explore how biomarkers for HPA dysfunction might serve as objective markers for the disease. We hope to start recruiting participants by summer of 2015.

Homebound ME/CFS Patient Study: The Stanford University ME/CFS Initiative is committed to improving the lives of all patients with ME/CFS, and especially those patients who are homebound. We consider imperative to conduct studies addressing the problems faced by these severely ill patients to learn more about their treatment needs. Shortly, we will set up a study and plan to start enrolling homebound patients in fall of 2015.

Donations

If you would like to make a gift to Stanford's ME/CFS Initiative, please visit <http://stanford.io/1cw09WP> or call (650) 497-7084.

Centers for Disease Control and Prevention
CFS Patient-Centered Outreach and Communication Activity (PCOCA) Conference Call
February 23, 2015 @ 12 pm Pacific / 3 pm Eastern

“Stanford ME/CFS Initiative: Collaboration, Innovation, and Discovery”

Jose G. Montoya, MD

Professor of Medicine, Stanford University

Our vision at the Stanford Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) team is that ME/CFS will be a scientifically and medically understood, treatable, preventable and curable disease. Our work was born as a response to the suffering experienced by millions of patients waiting for an answer from the medical and scientific communities, and from the possibility that an infection may play a role as a trigger and/or perpetuator of the disease.

Stanford’s ME/CFS team was built on the following guiding principles:

- Integrate several disciplines
- Use novel technology
- Summon the spirit of innovation that permeates the Stanford campus
- Apply the rigor of the scientific method, and
- Have an open mind, and let our results stand on their own merit and guide us on our next steps.

Our involvement began 10 years ago, when we were asked to see a patient with significant and generalized lymphadenopathy and very high levels of IgG and IgM antibodies against cytomegalovirus (CMV), human herpes virus 6 (HHV-6) and Epstein-Barr virus (EBV). It quickly became clear that her entire life had been devastated by ME/CFS. We prescribed the drug valganciclovir since it was, and still is, the only oral drug that is active against these three herpes viruses. Her lymphadenopathy of years quickly disappeared, and to our surprise, her cognitive dysfunction and severe fatigue started to improve as well.

In 2006, we published an open label study, in which 9 out of 12 patients experienced near resolution of their symptoms after taking valganciclovir, allowing them to resume a normal lifestyle. We then carried out a randomized, double-blind, placebo controlled clinical trial which demonstrated that valganciclovir treatment had statistically significant improvements in patients. These results opened the door to the exciting possibility that valganciclovir and/or other antiviral therapies could be helpful in the treatment of ME/CFS patients.

In 2012, we showed that extended valganciclovir treatment correlated with an improved response in patients. This six-month study directly countered skepticism generated by a previous study of similar sample size, but of substantially shorter duration (37 days).

Research suggests that Herpes viruses (and other infectious agents with similar characteristics) may be good candidates for triggers and/or aggravators of chronic unexplained illnesses, including those capable of activating significant inflammation. So, what does this mean for ME/CFS research? (1) We need a more in-depth look at the potential role of herpes viruses, (2) we need to apply novel technology to address their role, and (3) suppressing herpes viruses may be an important component in a holistic approach to treating ME/CFS.

In 2009, our work was galvanized by the generosity of an anonymous donor who provided full support to our program for five years. With this unprecedented support, we launched a case-control, cross-sectional study with arguably the largest sample size to date. We created a biobank with blood samples from around 200 ME/CFS patients, and sex- and age- matched healthy controls. In partnership with Dr. W. Ian Lipkin at Columbia University, and Dr. Holden Maecker and Dr. Mark Davis at the Stanford Human Immune Monitoring Center,

we are currently analyzing this data to provide a comprehensive view of the immune system of ME/CFS patients.

In 2013, Dr. Jarred Younger (former Stanford faculty, currently at University of Alabama) generated a machine-learning algorithm that measured cytokines, then used those measurements to predict high and low fatigue days in ME/CFS patients with nearly 80% accuracy.

In a separate cytokine-related study carried out in partnership with the Human Immune Monitoring Center, we found that several cytokines, chemokines, and cell factors clearly correlated with the severity of ME/CFS. This data contradicts claims that ME/CFS is not an inflammatory disease. Not only does inflammation exist in these patients, but also our study opened the door for using anti-inflammatory drugs or biologics to treat ME/CFS. Further analysis of mRNA gene expression, in a study led by Dr. Lipkin and Dr. Mady Hornig, showed that the disease with the closest resemblance to ME/CFS is Systemic Inflammatory Response Syndrome (SIRS). These two studies provide objective evidence that ME/CFS is indeed an inflammatory disease.

Does ME/CFS have anatomical or functional implications for other organs in the body? We asked Stanford cardiologists and neuroradiologists to help us answer this question.

Drs. Francois Haddad and Mehdi Skhiri carried out an analysis of the correlation between heart activity and ME/CFS. Their work revealed that the heart is highly unlikely to be affected by ME/CFS. In a different study, Drs. Haddad and Skhiri are looking at endothelial function and cytokine levels before and after physical exercise.

Drs. Michael Zeineh, Kang, Atlas, and Reiss, faculty in the Neuroradiology Department, embarked on a thoughtful exploration of how the brains of ME/CFS patients might differ from healthy subjects. This study, which resulted in the recent publication of an article in the journal *Radiology*, employed a novel MRI technology, called diffusion tensor imaging (DTI). Dr. Zeineh and his colleagues found white matter atrophy and a white hemispheric abnormality in the anterior arcuate fasciculus of ME/CFS patients. To our knowledge, this is the first published study that applies DTI technology to ME/CFS patients. We are currently seeking funding to validate these initial results with a larger sample size and hopefully uncover the connection between the cognitive dysfunctions observed in ME/CFS patients, with their brain function and structure.

We are at the tipping point in our scientific pursuit to identify the biomarkers and central abnormalities of ME/CFS. Several treatment interventions will stem from our work and that of other institutions. While one single pharmacological approach will be unlikely to adequately address the multisystemic, chronic, complex, and highly variable nature of the disease, we believe that by applying the appropriate methodology and technology, we will be able to conquer and defeat ME/CFS within our lifetime.

Questions from Patients to Dr. Montoya:

- *Will targeting the cytokine IL-17 represent an option for ME/CFS treatment?*
 - JGM: Good question, but it is too early to tell if targeting one single cytokine will be able to produce the benefit we want. We need to conduct clinical trials, as we are unaware of the risks, such as that of fungal infection.

- *What will it take to completely open our understanding of this illness and bring about meaningful treatment options?*
 - JGM: Having healthy, unrestricted funding. Assembling a multidisciplinary team. Using novel technologies. Get everyone aligned under a single, clear vision. This enables us to give patients treatment they deserve.

- *Research and patient reports show exertion that pushes heartrate up can cause a relapse. Have there been studies that use beta-blockers to prevent relapses of ME/CFS?*
 - JGM: I am not aware of those studies, so I can't say. From the medical standpoint, I would be very careful if studies were to be set up. If we block heartrate levels we could be causing harm. Would be very difficult study to do. That's where exercise physiologists could and should be part of those study designs.
 - JGM: It would be best to understand *what* is triggering high heartrate, rather than trying to control the symptom perhaps in a tenuous way.

- *What are the top three things in the IOM report that stand out to you as the most/least helpful for patients?*
 - JGM: The first is that I loved seeing the IOM report: it comes from a serious institution and clearly states that this is a real disease. This validates the disease and can change the narrative in the US and hopefully outside. The second is that it does not require ME/CFS to have a diagnosis of exclusion and perhaps could aid in the faster diagnosis of ME/CFS. Lastly, the IOM called for more funding, which is a great step in the right direction, and although the IOM didn't specify a dollar amount, I believe it will perhaps get more support from the government and institutions.

- *Is this disease communicable?*
 - JGM: No good evidence that it is, or conclusive evidence that shows that it is inheritable. However, there have been epidemics of reported ME/CFS cases in the past. Anecdotally, seems like it might be transmittable.
 - JGM: Having it be both endemic and epidemic is not unreasonable. We think there still may be a possibility of an infectious agent that has not been found yet, that may activate other infectious agents.
 - JGM: Patients should not worry about having disease transmitted.