Solve ME/CFS Initiative

FORMERLY KNOWN AS THE CFIDS ASSOCIATION OF AMERICA

The SolveCFS Chronicle Winter 2014

Spreading the Word About ME/CFS to Family and Friends

by Jennifer Williams

This September, my husband Mark and I attended our fourth Solve ME/CFS Initiative (SMCI) Research Roundtable and brought some family and friends with us. While Mark and I have followed the work of SMCI for years, I believe that getting "outsiders" like family and friends engaged is just as important, if not more, in order to spread the knowledge and increase awareness of myalgic encephalomyelitis/Chronic Fatigue Syndrome or ME/CFS.

We first shared Mark's story in 2003, several months after his diagnosis and 12 years after he first became acutely ill while overseas during his collegiate military training with the Navy. While we finished college and Mark began his naval career, we occasionally dealt with his illness "spells". It wasn't until 2002, after he was no longer able to work, that we learned it was in fact ME/CFS. These spells made it difficult for Mark to maintain any semblance of a consistent schedule and often required large periods of rest before or after any planned event. We had to think about every activity in which Mark engaged. We learned to be flexible with timetables and plans. Just because we scheduled something two weeks out, didn't mean Mark would feel up to it when the day arrived. So I learned to be prepared to not go at all, go by myself, or find someone else to go with me. Hopefully, family/friends would understand. Or maybe they wouldn't… not fully…especially if you hadn't really explained any of this to them. But then, how do you really explain chronic flu-like symptoms, difficulty concentrating, post-exertional malaise, sensory overload, and complications with the hormonal/nervous/cardiac systems in a way that is meaningful? Especially when we were trying to comprehend it all ourselves.

We chose to host a dinner for some of our closest friends and have an open conversation with them. We started the evening asking them to share their relationship to and first memory of Mark. He shared his medical history. I provided an overview of ME/CFS using the ME/CFS

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Mark Williams, living with ME/CFS, and his wife, Jennifer.

Mark and Jennifer after her first NYC Marathon, where she ran for ME/CFS.

From our CEO

Carol Head
President & CEO

Friends,

As we approach the holiday season, our hearts and minds often turn to what we are most thankful for—surely loved ones who have faithfully stood with us top the list. Featured in our cover story, I so appreciate Jennifer Williams' willingness to share the story of how she and her husband Mark have maneuvered the difficult waters of educating and empowering family and friends in their walk with ME/CFS. Our hope is that their story may be helpful to you and yours.

While many in our ME/CFS community are able to gather with family and friends at this time of year, we know it comes at a cost, all too often leading to a crash. For others, an additional heartbreaking consequence of the disease is the inability to be with loved ones, either because the physical toll is too hard or because family and friends have drifted away. Either way, the holiday season can be a difficult one for many.

It is because of this that we remain steadfast and deeply committed to our goal of a world free of myalgic encephalomyelitis/Chronic Fatigue Syndrome. In this issue we bring you in-depth and hopeful news about the progress and promise of our Research Institute Without Walls and our SolveCFS BioBank. As we expand our efforts to **make ME/CFS widely understood, diagnosable, and treatable**, this work is paramount to our vision of a day when all those with ME/CFS can enjoy a warm holiday season, and the richly blessed lives they were meant to lead.

I know it will take all of us working together to defeat this awful illness. Our principal aim is to activate and engage you—our community—in research that will accelerate discovery of safe and effective treatments, while expanding funding for treatments and a cure. We cannot do it alone, but together we can Solve ME/CFS.

I wish you a warm and hopeful holiday season,

President & CEO, Solve ME/CFS Initiative
CEO@SolveCFS.org

P.S. If I could, I'd sit down and talk one-on-one with each of you. But since that isn't possible, I hope you'll take a few minutes to watch this—*http://bit.ly/CarolHeadMessage*

Restructuring Medical Research

By Russell "Rusty" Bromley, Translational Research Acceleration Consulting, member of the SMCI Research Advisory Council

At the Solve ME/CFS Initiative, we are often asked "why is it taking so long for research to come up with something that is going to help me?"

According to a recent article in MedicineNet.com, in the US, it takes an average of 12 years for an experimental drug to travel from the laboratory to your medicine cabinet. Only 5 in 5,000 drugs that enter preclinical testing progress to human trials. And only 1 of these 5 drugs that are tested in people is approved. The chance for a new drug to actually make it to market is only 1 in 5,000. *http://bit.ly/DrugApprovals*

Though it has been 20 years since the Fukuda case definition for ME/CFS was created and 11 years since the more popular Canadian Consensus Criteria was developed, diagnosis still takes far too long and treatment options for people with ME/CFS have not improved much. **So how can the status quo be changed?**

First, we have to understand why the current system for medical research doesn't work for patients.

- Scientists and doctors are not incentivized to cooperate and work together to understand diseases and find treatments and cures more rapidly. Instead, they compete for limited resources and funding, a process that pits them against one another. In the struggle for competitive advantage they often protect new ideas and their scarce resources; access to patients, data and bio samples because being the first to publish a new discovery is vital for career promotion and future funding.
- Rigorous peer review originally designed to ensure only the best science funding can result in scientific incrementalism—i.e. Reviewers want to ensure competitors don't get too far ahead of the herd, making the peer reviewer's future proposals less attractive. Historically, government funding mechanisms have rewarded this behavior in the name of scientific excellence.
- Most research is hypothesis-driven, meaning that the experiments are designed to prove or disprove a specific theory. This hypothesis-driven approach rewards scientists for studies that are very narrowly focused, typically only looking at one or two experimental variables, which can be measured in laboratory animals or a small group of carefully selected patients, under closely controlled conditions.

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  - » These research design conditions generally do not replicate the human disease or the general patient population. Access to research data is limited to what appears in the publication and supports their hypothesis.

- Even the most important studies frequently suffer from too few animals or people being tested to ensure the results are reliable, reproducible and broadly applicable.
- Scientific journals will not publish negative results so the same failed experiment may be conducted repeatedly by different labs.
- Human studies are limited by regulatory requirements, difficulty in finding enough patients and the time required to recruit them. All this adds substantial, often prohibitive, cost.
- There is virtually no funding to repeat even the most important experiments. Subsequently it is now estimated that up to 90% of the experimental results published in scientific and medical journals cannot be reproduced. Experiments that cannot be repeated, and results that cannot be replicated, have limited value for patients.

Solve ME/CFS Initiative is working to change these fundamental, unproductive structural problems in our work. Through the SolveCFS BioBank, we ask patient and controls to contribute their health data and biosamples for research studies. Our goal is to bring together enough patients to be representative of the entire ME/CFS community. We are catalyzing research by providing access to patient samples and data for any qualified researcher who wants to help us solve ME/CFS better, faster and cheaper.

Through our funding program, SMCI supports researchers who want to test patient samples to understand what ME/CFS is and how it works at a molecular level. We can and have supported studies to replicate research findings that help define ME/CFS and confirm that the findings are accurate and reproducible. And our Research Institute Without Walls creates a collaborative environment where one researchers efforts can be informed by and learn from another. Collaborations are being built and innovative approaches are coming to fruition.

In the future, with additional funds, we can expand this work and do more. We envision a day when we will build a platform for collecting, storing and sharing data from the ME/CFS community and ALL ME/CFS research (including research not funded by our organization) so that the best minds in computer science and bioinformatics, using the most advanced software, can add to our definition of ME/CFS and its sub-types. Today, no comprehensive ME/CFS research database exists. We envision generating this data in the lab and in clinic, demonstrating to diagnostic and pharmaceutical companies that we have the data they need to invest in developing new diagnostic tests and treatments for ME/CFS. It is the for-profit diagnostic and pharmaceutical companies that have the very substantial R&D resources to run the final lap toward approved FDA drugs for ME/CFS.

Our work is to fund and organize rigorous, expansive, early research to deliver results that lead to the development of new diagnostics, therapies and cures as quickly as possible. This is not an easy task. Even with a team of the best scientists and clinicians, using the best available technology it will take years. **But the millions of people suffering from ME/CFS know *we cannot afford to wait!*** The Solve ME/CFS Initiative is targeting our work in order to one day understand ME/CFS at an unprecedented molecular level and be able to guide research and development of new diagnostic tests and better treatments. Your support and participation has gotten us this far and it is critical to the path forward. ■

Funding Research to Inform the Path Forward

SMCI began funding research into myalgic encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) as soon as it was founded in 1987. But the first *competitive* funding opportunity occurred in 2008. That funding cycle solicited research proposals that would advance the discovery of biomarkers and methods for early detection, objective diagnosis and effective treatment of ME/CFS, and included a rigorous review process. That year, SMCI awarded 6 grants, engaging 3 researchers who were ***new to the field of ME/CFS research***. All agreed to use similar measures, share data and collaborate with one another—breaking down the silos in which researchers typically work.

In 2010, SMCI launched our Research Institute Without Walls, offering a stronger 'virtual' infrastructure to support collaboration and data-capture. This was also the year SMCI launched the SolveCFS BioBank—an important resource for researchers, lowering barriers, reducing costs and attracting new investigators into the field.

2011 brought our second competitive funding opportunity. SMCI solicited research proposals that would bridge the gap between bench discoveries and clinical implementation by funding research aimed at discovery and replication of diagnostic and treatment biomarkers and exploring new drug targets and treatments for ME/CFS. Knowledge acquired would be used to attract pharmaceutical and biotech study as well as augment the evidence base for clinical practice and health policy. That year, we funded 5 investigators, ***bringing 2 additional new researchers*** into the field of ME/CFS. Through the virtual structure of the Research Institute Without Walls, every investigator now has a means to archive all of their results in a central place called RedCap—the Research Electronic Data Capture system.

This innovative, collaborative approach, along with Dr. Vernon's knack for recruiting leaders into the field, has allowed SMCI to begin to change the paradigm while bringing important discoveries to light. We brought you a brief overview of our funded research projects in the last issue of the SolveCFS Chronicle; below we explore them in more depth.

For the many of our readers who have donated to our organization, you can take pride in having supported this important work to advance ME/CFS understanding.

2008 Funded Investigators Progress Report

Six awards totaling $647,940 were made to investigators in the US and Canada. The important seed money that our 2008 funding cycle provided led to more than $7 million in follow-on funding from federal agencies for many of these investigators.

Eric Aslakson, MS and Bud Mishra PhD, Professor of Computer Science & Mathematics New York University are accustomed to dealing with massive amounts of data. Their 2008 award was to create a relational database of the 20 million abstracts in PubMed to begin to translate publicly available biomedical knowledge to further our understanding of ME/CFS. SMCI is now contracting with Eric's company, Poiema, LLC, to utilize large scale natural language processing techniques to analyze hundreds of thousands of ME/CFS-related full text journal articles and all 20 million PubMed abstracts to identify subtypes and associated biomarkers. When complete, we aim to identify partners to further explore and validate the subtypes and biomarkers we identify.

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Funding Research to Inform the Path Forward (continued from page 5)

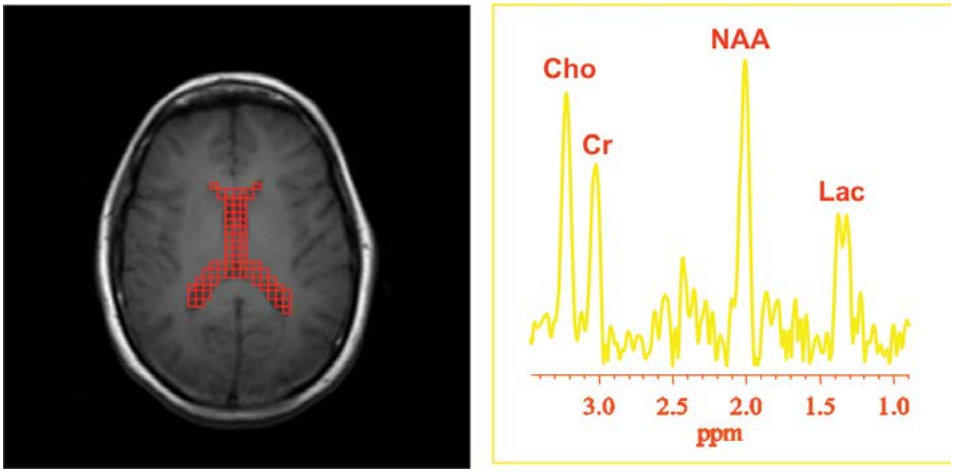
Gordon Broderick PhD, professor at NOVA Southeastern University and Ben Katz, MD professor of pediatrics at Northwestern University Feinberg School of Medicine teamed up to identify predictive markers of post-infection fatigue. Their 2008 funding was used to study samples that Katz had collected from an NIH-funded study. Broderick applied his computational skills to create a model of how the molecules worked and communicated with each other. (He spent years as a chemical engineer before Dr. Vernon recruited him into the field of ME/CFS research.) The Broderick team showed that five specific cytokines might be useful in diagnosing ME/CFS that occurs as a result of infection. Our 2008 award to Broderick has helped him receive funding from the Department of Defense to extend these findings in both ME/CFS and Gulf War Illness. He is also co-investigator on grants made by the National Institutes of Health to Mary Ann Fletcher and Nancy Klimas.

Alan R. Light PhD and Kathleen C. Light PhD are both research professors at the University of Utah. The Light team generated intriguing preliminary data of receptors on blood cells that detect metabolites that could be biomarkers for fatigue and pain. SMCI awarded the Lights a grant to increase the sample size and test the markers in other diseases. Subjects in their study provided blood samples before and several times after riding a stationary bicycle to induce fatigue and the post-exertion crash. The Lights confirmed that the metabolite detection sensory gene expression increased following exercise in ME/CFS patients but not in the other disease groups or in healthy controls. They have received more than $2 million from the National Institutes of Health to learn more about these sensory receptors and how they can be used as biomarkers for ME/CFS. Even more important, the Light team continues to collaborate with our funded investigator Dane Cook to examine these biomarkers in Cook's study.

Marvin Medow PhD, Associate Director of the Center for Hypotension at NY Medical College and Julian Stewart MD, PhD, Director of the Center for Hypotension at NY Medical College received an award from SMCI in 2008 to investigate how blood flow and orthostatic intolerance affect the flow of blood to the brain in ME/CFS patients. Medow and his team have been one of the most prolific scientific teams we've funded, publishing more than 10 papers in the biomedical literature. These results describe altered blood flow to the brain and how this altered flow affects ME/CFS symptoms, particularly brain fog. SMCI funded Medow again in 2011 to study how various treatments could be used to increase the blood flow to the brain. The Medow team has just published a paper showing that phenylephrine (a drug that increases blood pressure) improved blood flow to the brain when ME/CFS patients were on a tilt table and this improved blood flow correlated with improved cognitive testing.

Dikoma Shungu PhD, Professor of Physics in Radiology at Weill Cornell Medical College and Sanjay Mathew MD now Associate Professor of Psychiatry at Baylor College of Medicine were awarded seed funding by SMCI to use a powerful imaging technology known as *proton magnetic resonance spectroscopic imaging* to measure brain metabolism and oxidative stress in ME/CFS compared to other diseases and healthy controls. They published several papers and showed conclusively that there was oxidative stress (increased levels of reactive oxygen species) in the brain of ME/CFS patients. Shungu and his team went on to receive more than $1.4 million from the National Institutes of Health to continue studying the role of oxidative stress in ME/CFS and how it may be treated.

Sanjay Shukla PhD and Steve Yale MD of Marshfield Medical Research Foundation in Marshfield Wisconsin received a grant from SMCI to determine whether the gut microbiome was



An example from Dikoma Shungu's research using proton magnetic resonance spectroscopic imaging.

affecting post-exertion relapse. Shukla and Yale teamed up with Dane Cook at University of Wisconsin to conduct the exercise challenge testing and the Light team in Utah to test the blood biomarkers (described above). ME/CFS patients and controls provided blood and stool samples before and after the exercise challenge and reported their symptoms before and after the exercise challenge to determine the extent of their post-exertion relapse. The Shukla team identified another gene that was expressed in ME/CFS patients that correlated with their post-exertion symptoms. They also found increased microbe DNA in the blood (that likely came from the gut microbes) in both patients and healthy people following exercise. These results are being prepared for publication and put an interesting new twist on possible causes of the cardinal feature of ME/CFS—post-exertion crash.

2011 Funded Investigators Progress Report

Six grants were awarded totaling $470,487 to investigators in the US and Canada. To date this funding has led to more than $1.6 million in additional funding for our grantees.

The Solve ME/CFS Initiative awarded Biovista, a small biotech company, to find new uses for approved drugs—a process known as drug repurposing. **Spyros Deftereos, MD, PhD**, **vice president for drug discovery**, was excited to research ME/CFS because of the neurological impairment and neurology-related mechanisms, an area Biovista specializes in. They used their proprietary software to explore the biomedical literature, pharmaceutical databases and the SolveCFS BioBank for all of the symptoms of ME/CFS then matched these with underlying mechanisms of these symptoms and drugs known to target these mechanisms. In less than a year, Biovista identified two drugs that, when used in combination, could potentially target fatigue and pain—two major ME/CFS symptoms. A proof of concept clinical trial needs to be conducted to determine the efficacy of this drug combination in ME/CFS. Biovista is currently seeking partners and raising funds to conduct this trial.

Dane B. Cook, PhD is associate professor of Kinesiology at University of Wisconsin, Madison. SMCI provided funding to Cook to study the relationships between the post-exertion crash, gene expression and brain function in ME/CFS patients and controls. Post-exertion malaise (PEM) can be induced by physical and mental exertion and has been described by patients as a "crash" because of the relapse that occurs within 24 hours. This "crash" presents in a worsening of all symptoms affecting thinking and memory, heart function, and sleep for days or even weeks. Despite being a cardinal feature of ME/CFS, no single research group had ever evaluated the effects of mental and/or physical stress on PEM in a comprehensive manner. Cook's team is using both an exercise challenge and mathematical mental challenge to define PEM. He has completed testing on most of the

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Funding Research to Inform the Path Forward (continued from page 7)

ME/CFS patients and all the healthy controls and is deep into analyzing this amazing dataset. He has teamed up with Alan Light and Gordon Broderick for an integrated, systems biology approach to defining PEM. Because of the work he was able to do under our award, Cook recently received a $750,000 award from the Department of Veterans Affairs to conduct the same study in Gulf War Veterans. (Go to *http://bit.ly/PostExertionalMalaise* to watch Dane Cook's webinar on this.)

Patrick O. McGowan, PhD, is an assistant professor of neuroscience and epigenetics at the University of Toronto. McGowan's award allowed him and his team to study epigenetics—a first of its kind study for ME/CFS. Epigenetics refers to patterns of change in gene expression—not the gene itself—that occur in response to such things as nutrition, infection and physical and mental trauma, *not* genetic factors. These outside influences trigger a process called methylation that affects gene function but doesn't change the underlying DNA structure. McGowan and his team used the SolveCFS BioBank for this innovative study; they've already published results in PLOS One, an open-access high-impact journal and are preparing the next set of results for publication. SMCI has provided McGowan with additional funding because his research shows promise for delineating ME/CFS subtypes and identifying biomarkers. Further, because of the results achieved through our seed funding, McGowan has received $845,000 from the Department of Defense to establish an animal model to further study how these epigenetic changes effect the immune and endocrine response. (Go to *http://bit.ly/EpigeneticsMECFS* to watch Patrick McGowan's webinar on this.)

Peter C. Rowe, MD is the Sunshine Natural Wellbeing Foundation Professor of Chronic Fatigue and Related Disorders at Johns Hopkins University School of Medicine. Rowe was the first to describe the connection between orthostatic intolerance and ME/CFS. SMCI has funded Rowe to determine if neuromuscular strain increases the cardinal symptoms, contributes to post-exertional malaise and increases central sensitization. Central sensitization is the process of the brain and nervous system becoming more sensitive and reactive. In Fibromyalgia for example, central sensitization helps explain why light pressure is felt as intense and widespread pain. So far Rowe's research indicates that ME/CFS patients have more body areas with impaired range of motion and are more likely to have abnormal responses like increased heart rate variability to simple physical examination maneuvers. He's published these results and is now analyzing how central sensitization might help explain post-exertion malaise. (Go to *http://bit.ly/NeuromuscularStrain* to watch Peter Rowe's webinar on this.)

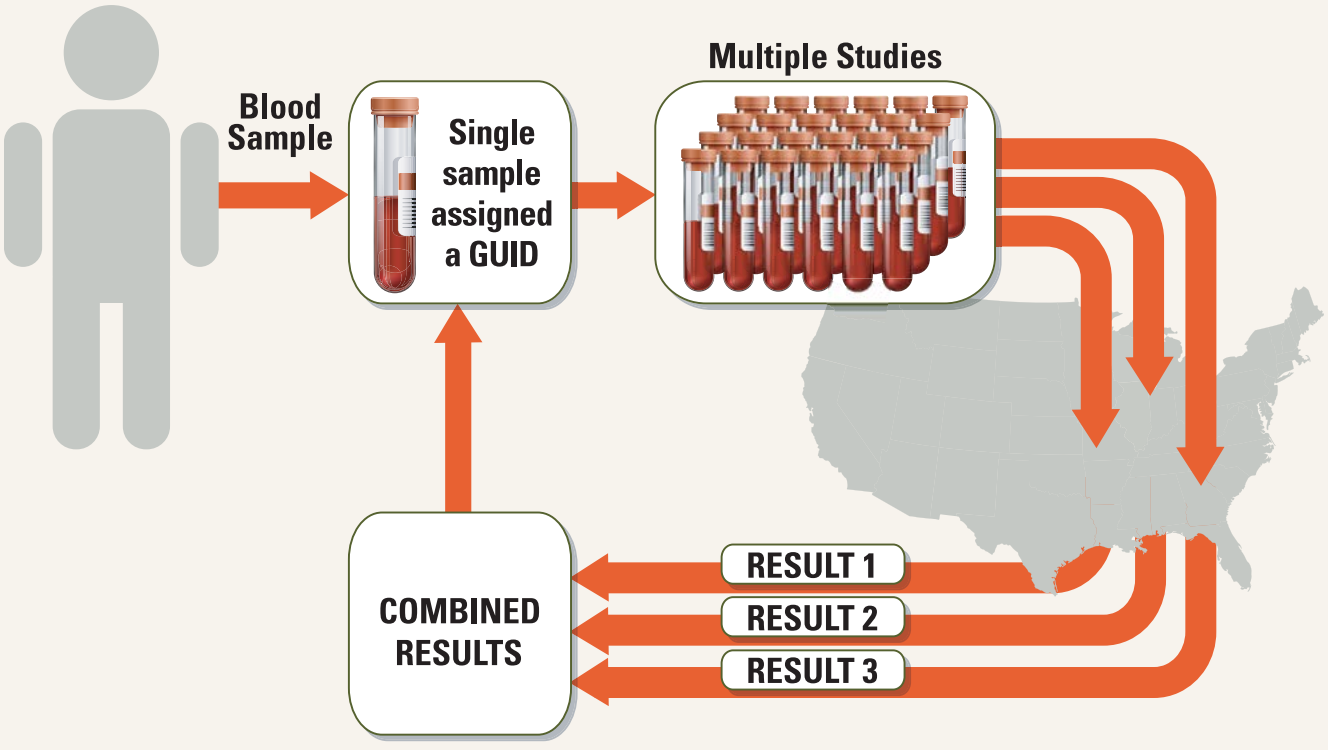
The road to real discovery and life-changing progress is long, arduous and costly. The Solve ME/CFS Initiative is taking strategic steps to shorten the road and speed up progress. Despite our modest budget, SMCI has made great strides and was the first organization to fund research into epidemiology, viral causes, immunology, neuroimaging, exercise physiology and the autonomic nervous system.

All of this research work is only possible because of the support of the many who fund it. The investments made by those suffering with ME/CFS and their loved ones have fueled the Solve ME/CFS Initiative's work. With that support, we have become one of the largest and most successful private funders of ME/CFS research…paving the road to objective diagnosis, treatment and a cure. ■

Being Patient Centric

As our logo depicts, patients are central to a solution for ME/CFS. We have designed our SolveCFS BioBank to collect and manage data so that the individual is the central organizing principle. A patient-centric design allows for patterns to emerge from the group of biobank participants, while capturing unique individual information. In the future, our SolveCFS BioBank will collect experiential, health and genomic information as well as health history and genetic profiles from a large number of individuals, allowing us to identify disease determinants.

The patient-centric design of our SolveCFS BioBank allows individuals to participate in many different types of research studies—through online surveys and by providing a genetic sample (i.e. blood)—all without ever entering a research lab. A single carefully collected and processed blood sample can be used to detect antibodies, quantify cytokines, measure gene expression, sequence genes, and examine chemical modification, measure metabolites and more. Importantly, all of the data generated on each individual stays connected to that individual through their assigned global unique identifier (GUID), creating a biological explanation specific to the individual while maintaining the individual's anonymity and privacy.



Being Patient Centric (continued from page 9)

The SolveCFS BioBank was the first to use a patient-centric design specifically for ME/CFS. Here are some of the researchers that are generating patient-centric data on samples currently in the SolveCFS BioBank inventory:

Michael Cooperstock, M.D., MPH, University of Missouri Health System
Cooperstock partnered with Madeleine Cunningham, PhD and David Kem, MD of the University of Oklahoma and Armin Alaedini, PhD of Columbia University to test blood samples for autoantibodies to a number of different human **proteins.** Alaedini has made a finding that may help describe an ME/CFS subtype. Results are being prepared for publication.

Stephen J. Elledge, **PhD**, **Howard Hughes Medical Institute**, **Harvard University**
Elledge developed a technology that reveals all the viruses targeted by the antibodies in the blood, detecting the interactions between antibodies and the millions of virus proteins, thereby generating millions of data points for each sample. Elledge and his team have completed the testing and are now analyzing the data to determine whether antibodies against viruses are different in ME/CFS patients compared to other diseases and against healthy controls. We will report on these important findings in 2015.

Michael Houghton, PhD, Lasker Laureate, Canada Excellence Research Chair in Virology, Professor in the Department of Medical Microbiology & Immunology, University of Alberta
Houghton is using samples to validate a possible diagnostic biomarker he has identified for ME/CFS. Analysis of this potential biomarker validation is underway and we hope to describe it in 2015.

Leonard Jason, PhD, Professor, Center for Community Research, DePaul University
Jason focuses his research on case definition for ME/CFS. For the past 2 years he has used the clinical information in the SolveCFS BioBank to understand how best to classify and define ME/CFS patients. So far Jason and his team have published 2 papers and another is under consideration describing their work using the SolveCFS BioBank data.

Derya Unutmaz, MD, Professor of Microbiology and Pathology, NYU Medical Center
His laboratory has developed highly sophisticated and detailed profiling technology of the functional subsets of immune cells isolated from human blood. Unutmaz has completed immune profiling on 25 ME/CFS patient samples from the SolveCFS BioBank and is now in the process of analyzing the data, comparing it to immune profiles from other diseases as well as from healthy controls. (Please go to *http://bit.ly/HumanImmuneResponse* to watch a recent webinar led by Unutmaz on his work.) ■

Federal ME/CFS News & Notes

NIH Pathway to Prevention Workshop—Evidence Review Report

Solve ME/CFS Initiative understands the impact a program like the Pathway to Prevention workshop can have on the research landscape. Because of its importance, we utilized the collective brainpower of our Research Advisory Council, led by our scientific director, Suzanne D Vernon, PhD, to perform a careful review and response to the Evidence-Based Practice Centers' draft evidence-based review for ME/CFS that was released on September 22. Comments to the report were due by October 20.

Read our full-length analysis here: *solvecfs.org/p2p-draft-evidence-review*

Through that review, we concluded that the Pathway to Prevention (P2P) process, though not entirely appropriate for ME/CFS, has produced an evidence report that clearly illustrates the lack of rigor in crucial research design elements and the absence of high quality clinical trial data. The evidence review shines a bright light on the need for well-designed, adequately powered studies to identify diagnostic gold standards and safe and effective treatments. This review substantiates the negative cycle currently in play with ME/CFS research—Because there is little funding, there is little research. And because there is little research, there is little evidence to prompt additional funding. **But this process may be what is needed to break through that negative cycle and move us to a day when ME/CFS is appropriately funded.**

The systematic review clearly implies that more resources must be focused on well designed, adequately powered studies. NIH set out to identify gaps in the research and they found more gaps than substance. **We believe that it is NIH's responsibility to address their own finding of research inadequacy.**

What Happens Next?

The P2P panel will review this evidence-based report, including the comments and feedback submitted, in advance of the meeting that will take place on December 9 & 10, 2014. At that two-day workshop in Washington DC, the P2P panel will hear from expert speakers and be able to ask clarifying questions in a town-hall-like Q&A that will take place after each session.

Anyone who is interested can register to attend live or participate via web-cast. It is our hope that many stake-holders will participate in this process in order to ensure that patients have a strong presence and a voice.

Register to attend the NIH Pathway to Prevention Workshop:

http://bit.ly/P2Pregistration

We are pleased to announce that Suzanne D. Vernon, PhD, SMCI Scientific Director, will be among the expert presenters. She will address the panel on day 2, as the final speaker.

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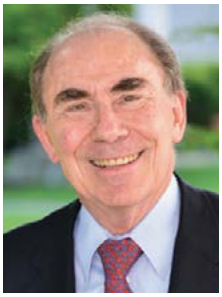
To stay up to date on all of this activity and more:

Sign up for updates from our Research 1st blog at SolveCFS.org/category/blog and join our e-newsletter list at SolveCFS.org/ get-involved/newsletters

Important Advances in ME/CFS

Suzanne D. Vernon, PhD
Solve ME/CFS Initiative Director of Research



Anthony Komaroff
Simcox-Clifford-Higby Professor of Medicine, Harvard Medical School

Senior Physician, Brigham & Women's Hospital, Boston MA

We asked Dr. Vernon and Dr. Komaroff to summarize what they regard as the most important recent advances in our field. They are not listed in a specific order. If starred, SMCI played a role in the discovery.

ONE*

There is ample evidence that ME/CFS is a heterogeneous illness. As is true with many illnesses, not every person with the illness has all of the same features. Now we are able to delineate ME/CFS subtypes using tools that measure phenotype (the ensemble of a patient's observable and measureable signs and symptoms) and genotype (the inherited genetic code and gene expression). By objectively identifying subtypes, researchers are able to study groups of patients that are similar: this increases the likelihood of identifying biomarkers and of targeting treatment.

TWO*

Many studies now have demonstrated that **people with ME/CFS suffer from oxidative stress.** Oxidative stress occurs when the damaging effects of reactive oxygen species (free radicals) are not taken care of by antioxidant defense mechanisms. In other words, oxidative stress occurs when too many free radicals are produced, or not enough antioxidants are produced, or both. Prolonged oxidative stress can damage cells and the structures inside cells that affect energy production and cell signaling. Evidence for oxidative stress in ME/CFS has been found in the brain, as reflected by increased levels of lactate. Oxidative stress more generally throughout the body is reflected by increased lipid peroxidation—which is caused when free radicals attack the lipids in cell membranes. Oxidative stress is not specific to ME/CFS but it does help us understand the biological processes that are going awry.

THREE

Scientists at RIKEN, Japan's renowned research institution have shown that **the ME/CFS brain is inflamed.** They used a specific kind of brain imaging to show that immune system cells in the brain were highly activated (inflammation) in people with ME/CFS, compared to healthy individuals. They further showed that the greater the inflammation, the greater a person's symptoms. The inflammation was a chronic, continuing state. Investigators from other countries including the U.S. are now collaborating with the Japanese team to develop possible diagnostic markers and effective treatments.

FOUR*

Central sensitization is state in which the pain-sensing mechanism in the

central nervous system gets "stuck" in a highly reactive state. When this happens, a simple bump or light pressure causes greater and more widespread pain than it otherwise would. Central sensitization has been best demonstrated in people with fibromyalgia, an illness similar in many respects to ME/CFS. **New research on restrictions in range of motion in ME/CFS patients indicates that central sensitization may also explain the fatigue, brain fog and post-exertion malaise.**

FIVE*

The immune system is built to attack "foreign" things (like germs) and substances (like plant pollen). In autoimmune diseases, instead of attacking something foreign, the immune system attacks healthy cells and organs. Since women experience higher rates of many autoimmune diseases, and since women appear to develop ME/CFS more often than men, **autoimmunity has been suspected as a possible cause of ME/CFS.** A clinical trial of rituximab, a drug that destroys B cells (these are the antibody producing cells of our immune system), showed benefit in a number of ME/CFS patients. This result has suggested that autoimmunity may be present in at least a subset of ME/CFS patients. There are also several studies that show elevated antibodies to various "self" proteins in ME/CFS patients. Understanding the role of autoimmunity in ME/CFS will help identify biomarkers and target treatments.

SIX

Patient-centered outcomes research seeks to determine if a treatment is leading to an improved outcome: reduced symptoms and suffering. One problem with outcomes research has been that the "outcomes" that doctors measure do not always reflect the outcomes that are important to patients. For example, during a 2012 FDA patient-focused drug development teleconference, an ME/CFS patient told the audience that she knew she was doing better when she could stand in the kitchen and make a salad. Another problem with outcomes research until recent years has been that it was very difficult for patients to report, and therefore for doctors to study, how well the patient was doing every day. Now **web-based, smart phone or personal device tracking and monitoring technology is making it possible for patients to participate in patient-centered outcomes research from anywhere including the comfort of their home.**

SEVEN

Risk factors are behaviors or conditions that raise the risk of developing a particular disease. Identifying risk factors can help us understand how to control and prevent disease. Smoking is a classic example of a factor that increases your risk of lung cancer. Epidemiological research has suggested a few risk factors for developing ME/CFS such as a history of viral infection. Research has shown that **ME/CFS patients have a 2-fold increased instance of high allostatic load, a quantitative index of hormones, inflammatory and cardiovascular measures of the body's physiological balance.** It is not yet clear if the high allostatic load caused the ME/CFS or the ME/CFS caused the high allostatic load, but additional research may show that allostatic load can be used to screen patients to assess ME/CFS risk.

EIGHT

Abnormalities in the white matter of the brain (white matter contains the nerve bundles) have been found in ME/CFS patients using a variety of magnetic resonance imaging (MRI) scanning techniques. The abnormalities have been found throughout the brain (likely due to the heterogeneous nature of ME/CFS). A team at Stanford University found that a specific area of white matter on the right side of the brain was altered, adding to the increasing evidence that the neurocircuitry is affected in ME/CFS patients.

NINE*

Abnormalities of the autonomic nervous system have been found by numerous independent researchers. These include a failure of the body to maintain blood pressure after a person stands up, abnormal responses of the heart rate to standing and unusual pooling of blood in the veins of the legs. These heart rate abnormalities

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We Can Solve ME/CFS Together

Throughout this issue of the SolveCFS Chronicle, we have shared important information on how the status quo in ME/CFS research must change. We've also shared some of the very important work we are doing to do just that—to enact massive, determined action and progress. Despite our modest budgets, our Research Institute Without Walls allows us to fund the brightest researchers from the best institutions, without the cost of a bricks-and-mortar institute, while fostering an innovative and collaborative environment. Our SolveCFS BioBank provides the means for patients to participate in research without leaving their homes, broadening the base of patients studied.

But we cannot do this alone. We count on the gifts of individuals just like you to make a difference in this fight for a cure. Your donation, no matter the size, will fuel progress toward making ME/CFS widely understood, diagnosable and treatable for millions of people worldwide.

People like Marie, who misses her vibrant career and that feeling of satisfaction and self-worth her work used to bring her.

People like Joshua, who longs to enjoy a Friday night football game with his college buddies, but they have drifted away since his diagnosis.

People like Joan who just missed another one of her child's class parties because she was in a crash.

People like YOU.

There is no better time than now to give.

To join the vital group of patients and family members fighting ME/CFS through gifts to SMCI, please visit *www.solvecfs.org/donate* or send a tax-deductible donation to: Solve ME/CFS Initiative, P.O. Box 36007; Los Angeles, CA 90036-0007 using the envelope included in this publication.

Want to include SCMI in your own registry or have an idea for a personal fundraising campaign? We'd love to talk to you about it. Contact Erin E. Parsons-Wright, Director of Development, at *eeparsonswright@solvecfs.org* or call 704-364-0016. Check out our official 'friends-asking-friends' fundraising platform, Crowdrise, at *Crowdrise.com/SolveCFS*.

Important Advances in ME/CFS
(continued from page 13)

persist during sleep along with abnormal levels of hormones known to regulate the cardiovascular system. This is further evidence of a physiological imbalance in ME/CFS patients.

TEN

Although many viruses and other infectious agents are completely eliminated by the immune system after an infection, other viruses can remain "latent" in the body for a long time—even for the rest of a person's life. **There's evidence of more frequent latent active infection with various herpesviruses and enteroviruses.** The herpesviruses include Epstein Barr, HHV-6 and cytomegalovirus. Other infectious agents, like bacterium that cause Lyme disease, Ross River virus and Q fever, can also trigger ME/CFS. Whether these chronic infections cause the symptoms of ME/CFS remains unclear. ■

Spreading the Word About ME/CFS to Family and Friends (continued from page 1)

Fact Sheet and other available research. We watched and discussed a documentary about ME/CFS. Mark talked about his current condition and treatment plan. We shared how they could best support us going forward. Throughout, we allowed them to ask questions and share their thoughts. Afterwards, we stopped all ME/CFS-related talk and had a nice dinner.

After the dinner, we knew we wanted to share this information with more family and friends. So, that year we included details about Mark's condition in our annual holiday letter.

We noticed the positive impact these actions had on our family and friends. They were more understanding when we declined/changed/cancelled plans. They called or stopped by more frequently just to check in on us. They offered assistance to help us with chores and errands. They provided a sympathetic ear when we needed to talk.

In 2012, inspired by attending our first SMCI Research Roundtable, I chose to run my first marathon and ask family and friends to cheer me on by making donations to SMCI. Each time we shared Mark's diagnosis with our family and friends, the circle widened. While difficult to do, we recognized that without taking the courageous step to share his story, many would continue to misunderstand his situation and what is needed to cure this life-altering disease.

Yes, sharing intimate health details can be difficult. But we found it to be the best way for our family and friends to truly understand what ME/CFS patients and their immediate families have to deal with every day. Starting small by sharing with our closest friends and family then building out to our wider circle of connections is what was comfortable to us. Now that they are all armed with this information, our family and friends have become part of our personal support network as Mark continues to live with ME/CFS, as well as advocates for organizations like SMCI to make this disease understood, diagnosable and treatable. ■

If you are considering reaching out to your family and friends to educate them about ME/CFS, maybe this fact sheet can help:

http://bit.ly/ForThoseWhoCare

Federal ME/CFS News & Notes (continued)

To read the full workshop agenda visit: *http://bit.ly/P2PWorkshopAgenda*

The day after the P2P meeting, the P2P Panel will write a draft report which will be published and **the public will have 30 days for comment on the final report.** Once the comment period closes, the report will be finalized and NIH will organize a plan to disseminate it widely with a goal of improving the nature of the research being conducted in ME/CFS.

In a separate effort, the **Institute of Medicine (IOM)** study, commissioned by the Department of Health and Human Services to develop and distribute diagnostic criteria for ME/CFS and possibly suggest the need for a new name, will come to fruition in spring 2015.

For far too long, ME/CFS has been underfunded, misunderstood, and even disbelieved. Our community has been pushing a very heavy fly-wheel aimed at increasing understanding, acceptance and progress toward treatments and cure. Now there is federal activity, all aimed at moving the needle for ME/CFS—FDA Voice of the Patient, IOM activity on creating clean diagnostic tools and other much-needed tasks, and this P2P. **What this activity is showing is that the status quo must change. We hope P2P will illuminate the clear need for more funding, increased research activity and faster progress.** ■

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There's Black Friday and Cyber Monday…and now GIVING TUESDAY on December 2, 2014, an international day of doing good—when charities, families, businesses, and retailers come together in a day dedicated to sharing with others. You can join us by:

- Making a direct gift to the Solve ME/CFS Initiative to support our crucial work at **SolveCFS.org/donate**.
- Using social media, email or even writing a personal letter to invite family and friends to support us.
- Making Giving Tuesday the day you sign up to be an SMCI recurring monthly donor to sustain our efforts year-round.
- Using Giving Tuesday as your launch date for a personal fundraising campaign using the personal web options on Crowdrise.com. SMCI's official online fundraising platform. Learn more at **www.crowdrise.com/SolveCFS**.

While it is unacceptable that there are still so many unanswered questions, we are making strides toward a day when ME/CFS is widely understood, diagnosable and treatable. It is only through YOUR support that this is possible!

We've Moved!

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