

We have been honored to share the stories of 25 Catalysts over the winter and spring through our website, Facebook and Twitter. We hope you'll take time to read about their remarkable lives and the courage and persistence they demonstrate every day. As unique as each one is, they are united in their hope that research led by the CFIDS Association of America will lead to better treatment and healthier futures.



Honoring Catalysts in Action

Throughout this issue of *SolveCFS* we pay tribute to the collective action that has led up to the launch of the Association's latest research initiative: the **research institute without walls (RIWW)**. Two individuals warrant special attention for their immensely important contributions.



James York, adrift and at work on the award-winning film "Ocean Men: Extreme Dive" with an IMAX Mark II camera housing in Stargate Cave on Andros Island in the Bahamas. The picture explored the beauty and science of breath-hold diving and won a prize at the International Large Format Film Festival in Paris in 2001.

First, **James York**, the first person consented and enrolled to participate in the SolveCFS BioBank. James was working as an underwater camera man and marine coordinator in the film industry when pneumonia turned into CFS in 2004. He has turned to writing when cognitive impairment can be kept at bay, as a form of expression and, occasionally, compensation. James enrolled in the BioBank as soon as it was announced. He returned his signed consent form promptly; completed the extensive medical history questionnaire thoroughly and expeditiously and even recruited his own matched control to participate. He gave blood samples and tissue swabs. He did so as part of an odyssey to learn about CFS and cope with it. He also donates to the Catalyst Fund.

"The CFIDS Association has been, and continues to be, a beacon of steadfast reason amid the sea-changes of politics and medical misinformation. The research you fund and the information you aggregate and then organize and share with us provides valid hope for a desperately underserved patient population. It also helps inform otherwise less-than-knowledgeable medical professionals. Your ongoing advocacy efforts are heroic in scope. I, like many others, am so grateful for your hard work to legitimize, ultimately understand and reverse this challenging disease. Frankly, I am stunned that I was the first to provide written consent. I certainly wish I could do more for you all — financially, physically and intellectually. I firmly believe your hard work and diligence and adherence to the scientific method, will prevail in the ongoing challenge to understand this debilitating disease."

James is a true Catalyst in every sense of the word. We honor and thank him for paving the way.



Laura Hillenbrand

Second, author **Laura Hillenbrand**. Laura's writing has earned her many honors, including two long runs on the *New York Times* bestseller list with *Seabiscuit* and *Unbroken*. Her gripping essay about CFS, "A Sudden Illness," won the National Magazine Award for *The New Yorker* in 2003. It remains one of the magazine's most-requested articles. The critical acclaim and popularity of her books has given her an unparalleled platform to raise awareness and deepen understanding about CFS, a disease that has held her in its grip for 25 years. We are humbled to share news of her exemplary commitment to the cause — a \$250,000 gift to the Catalyst Fund.

"I'm thrilled to be able to make a major commitment to the CFIDS Association of America. This is a pivotal and enormously promising time for ME/CFS patients, and I'm tremendously excited about the organization's innovative, inspired, dynamic, research-focused approach. Guided by a scientific advisory board comprised of the leading luminaries in the field, they're funding cutting-edge research that holds the promise of unraveling the ME/CFS mystery and unearthing treatment and a cure. And through their SolveCFS tissue and blood BioBank, as well as their comprehensive research literature database, they're greatly facilitating and accelerating the study of the disease and bringing the research community together in a coordinated effort to solve it. I believe in the work they're doing, and I believe in the people who are making it happen."

"I've had ME/CFS for 25 years, my entire adult life. The suffering it has caused me, and the losses it has cost me, are beyond my ability to articulate. But I've never been more hopeful than I am now. I believe a breakthrough is imminent, and the CFIDS Association is helping lead the way to it. I want to do everything in my power to help, so I'm delighted to be making this commitment now. I hope others will join me in supporting the CFIDS Association, so everyone who suffers from this disease can finally be set free."

To every one of the James Yorks and Laura Hillenbrands who have made this paradigm shift, the launch of the RIWW and this kind of active partnership possible, we express our deepest, most sincere thanks. ■



SOLVE CFS

The Chronicle of the CFIDS Association of America

Spring 2012

Breaking Ground

On Feb. 23, 2012, we broke new ground by announcing our latest research initiative: the **research institute without walls (RIWW)**. For this ground breaking, there was no dirt to shovel, no ribbon to cut. While we're not literally breaking ground, we believe our approach merits use of the term "groundbreaking." Why?

The eight projects that launch the RIWW will advance effective treatment, including better ways to diagnose and subtype CFS. We know of no other set of projects launched simultaneously with this goal in mind. Read more about these projects on pages 2–6 and on our Research1st.com website.

All of the RIWW projects will be linked through us and to the SolveCFS BioBank, created by the Association in 2010 using the cost-sharing structure of the Genetic Alliance BioBank. The SolveCFS BioBank has already enrolled 470 participants and three projects will offer new study participants the opportunity to enroll in the BioBank. Two of the projects will test BioBank samples already in inventory. One of the projects utilizes the extensive clinical data collected from BioBank participants. Several projects utilize powerful "big data" computational tools to mine the medical literature and other sources, including the BioBank. Never before has one CFS resource been maximized so fully. And it will become more valuable as these studies progress and add data to what we've already collected.



RESEARCH
INSTITUTE
WITHOUT
WALLS

Turning Science Into Treatment for CFS

Five of the RIWW projects were selected from the 26 full applications submitted in response to our 2011 RFA; these five ranked at the top for scientific and strategic merit. They will be coordinated individually and as a group by our scientific director, Dr. Suzanne Vernon. Our first investigators meeting, held Mar. 11–12, 2012, provided the chance to synchronize and synergize these multidisciplinary approaches. As we demonstrated with our 2009–2010 grants, this collaboration and coordination strengthened the individual studies and facilitated

new partnerships. (You can read an update about important outcomes from two of those earlier projects on page 6.) Another of the RIWW projects, a collaboration with start-up LogosOmix, is a product of our 2009–2010 grant to Bud Mishra, Ph.D., at New York University. The other two RIWW projects were approved through a separate review process that governs access to our SolveCFS BioBank resources. We will feature these projects in our next issue.

With your support, we have been able to engage the interest of top experts, working at the leading edge of multiple scientific disciplines. Imaging. Post-exercise biomarkers. Big data analysis. Drug repurposing. Epigenetics. Metagenomics. Couple this with clinical investigators relying on solid physiology and years of experience evaluating CFS patients and it's an earth-shattering, transformative approach.

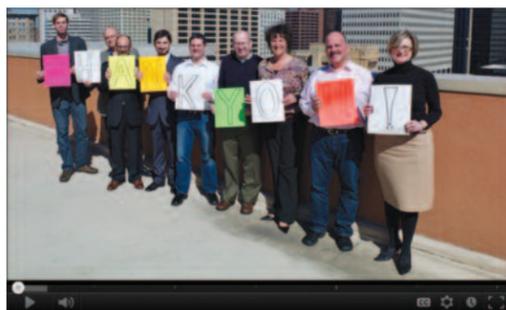
These are just a few reasons why — even without a shovel or a backhoe — we're referring to this set of projects as groundbreaking. We hope you will too! ■

It's About You

Many times over the 25-year history of the CFIDS Association we have shared news about new research grants funded. Before now, those grants were made under a traditional nonprofit model. We raised money from supporters like you, vetted various project proposals and then gave the money to someone else and hoped for the best. Sometimes our hopes were realized, like with the last round of grants made in 2009–2010 that has already yielded more than \$5 million in follow-on funding, seven times the original grant award total. But we're not satisfied with outcomes that don't have more immediate impact on patients' lives.

With the launch of the research institute without walls (RIWW), we break out of that conventional model.

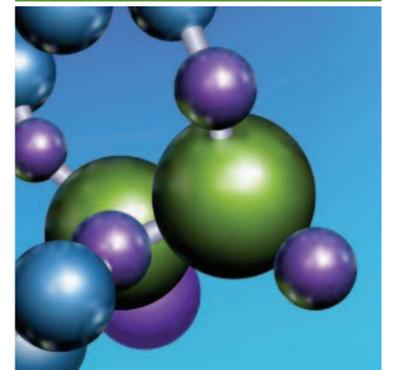
A handful of innovative disease-based organizations are shifting from being passive research sponsors to being active research partners. We join them. Our RIWW positions the Association as the center hub of a multi-spoked wheel of linked research projects led by top talents working in diverse disciplines at leading institutions. We are now active partners with our grantees. YOU are now an active partner in citizen-powered research.



The faculty of the research institute without walls thanks YOU in this 4-minute video posted to our YouTube channel: <http://bit.ly/ty-catalysts>.

Your participation is what fuels the Association's transformative research program. Four hundred seventy eight consented participants in the SolveCFS BioBank. 2,102 donors to The Catalyst Fund. All the people who have shared links to our [Research1st](http://Research1st.com) website or Facebook posts, retweeted our messages and invited a friend to support the cause we share. YOU have inspired our action and made the RIWW possible.

We celebrate and honor your generosity and the hope and optimism you inspire. Thank you. ■



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Web home for this issue of SolveCFS:

www.cfids.org/SolveCFS/Spring-2012.asp

Validate. Innovate. Eliminate.

Transforming Research: The Research Institute Without Walls



Suzanne D. Vernon, Ph.D.
Scientific Director
The CFIDS Association
of America

The five grants and grantees you will read about here were all selected based on their strong scientific merit and their strategic fit with our research program. In 2011, our Board made the important strategic decision to focus our research program on advancing the search for disease-modifying treatments. Now, all of our activities will prioritize studies and collaborations that identify biomarkers that delineate disease subtypes, both of which are critical for identifying effective therapies that may change the course of CFS itself in addition to providing better symptom relief.

I am thrilled with the quality of the proposals we funded and I am particularly excited about the younger investigators and those who are new to CFS and who very quickly became intrigued with the complexity and challenge of CFS. They provide an important opportunity to grow the field while bringing fresh perspectives to the research.

At our launch meeting in March, it was very rewarding to witness the enthusiasm these researchers expressed for our research-institute-without-walls approach, and the opportunity it affords them to work across institutions and disciplines as a coordinated team. It crystallized the promise of our new approach.

I couldn't be more proud to be leading this initiative and look forward to sharing our progress with you as these projects get under way.

Brain Fog in CFS: What's Going On?



Marvin S. Medow, Ph.D.
Assistant Professor of
New York Medical College

Many of us experience some slight dizziness when we quickly stand from a sitting or lying position. Now multiply that feeling by 10, add "brain fog" and, possibly, vision loss or fainting to the symptoms, and picture it lasting for minutes or longer. Now you can begin to understand what many people with chronic fatigue syndrome (CFS) experience.

Marvin S. Medow, Ph.D., professor of pediatrics and physiology and associate director for the Center for Hypotension at New York Medical College (NYMC) in Valhalla, has devoted the past several years to studying postural tachycardia syndrome (POTS), a condition that, among other things, can result in reduced blood flow to the brain (cerebral blood flow).

Reduced brain blood flow can lead to dizziness, lightheadedness, and, sometimes, loss of consciousness. It can occur when getting up rapidly because blood pools in the abdomen and legs due to gravity if something interrupts the normal mechanisms that help return blood back up to the heart and brain. This can cause dizziness, forcing you to lie down, which enables blood to return to the brain.

A few years ago, Dr. Medow and Center director Julian M. Stewart, M.D., Ph.D., realized that many of the people they saw with POTS also had CFS. Today, we know that the conditions co-exist in up to 80 percent of those with CFS. Thus, much of the Center's research focuses on studying these two entities. To date, Dr. Stewart has received more than \$5 million in National Institutes of Health grants to support this work.

With a previous CFIDS grant, Dr. Medow showed that subjecting someone with CFS to an orthostatic challenge (placing them on a "tilt table" and tilting the table from a horizontal to a vertical position), led to problems with memory, concentration and information processing, as well as reduced cerebral blood flow. This grant takes that research a step further — testing interventions to see if they can improve the tilt-induced brain fog in people with CFS and using the results to identify CFS subtypes.

Cerebral Blood Flow, Carbon Dioxide, and Orthostasis

One of the most troublesome symptoms in people with CFS is "brain fog," which manifests as impaired working memory and concentration accompanied by difficulty processing complex information. As Dr. Medow showed in his previous work, the greater the orthostatic stress and the harder the mental challenges during neurocognitive testing, the worse the results of cognitive testing.

In addition, some of those with CFS and orthostasis also experience very rapid, deep breathing during an orthostatic challenge, like trying to catch your breath after strenuous exercise. This hyperventilation, in turn, leads to reduced carbon dioxide (CO₂) levels, or hyperpnea, affecting the pH of the body. And, guess what? "One of the most powerful modulators of brain blood flow happens to be CO₂," Dr. Medow said. "The lower the CO₂, the lower the cerebral blood flow."

Dr. Medow's hypothesis: that the reduced cerebral blood flow and brain fog occurs, at least in part, because of impaired control mechanisms for regulating CO₂ and/or blood pressure.

In the study he will "tweak" the physiologic system to see if changing blood pressure during the orthostatic challenge, adding CO₂ to room air, or increasing blood flow to the brain can improve symptoms and neurocognitive ability.

These interventions "may not be therapeutic," Dr. Medow said, "but they may suggest mechanisms leading to the dysfunction that could be addressed by some form of therapy." One other goal: identify CFS subtypes, an important objective of the CFIDS Association. Using objective biomarkers like low blood CO₂ levels to identify CFS subtypes may help clarify some of the confusion around disease given the heterogeneity seen among patients. More clearly defined subtypes helps target new therapies and may make existing therapeutic approaches more effective. ■

Just the Facts

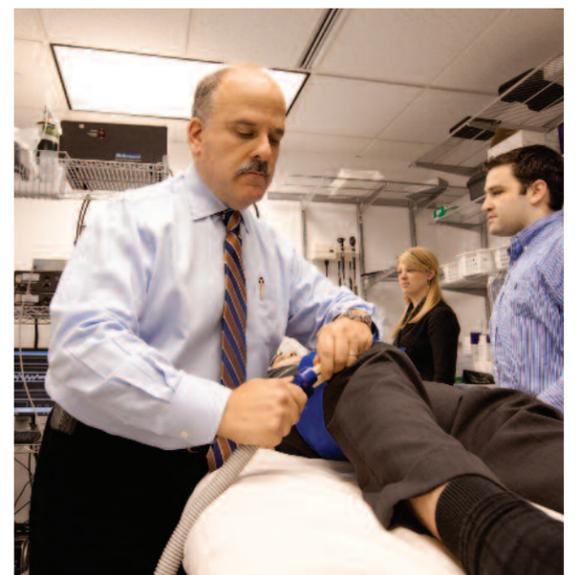
This study involves 15 people with CFS and orthostasis, 15 people with CFS but no orthostasis and 15 healthy controls, all ages 15–29.

The researchers will obtain baseline measures with a tilt table challenge during which they measure cerebral blood flow and cognitive abilities.

Then they will test three interventions during three follow-up visits:

- Breathing supplemental carbon dioxide to prevent the tilt-induced rapid breathing/reduced CO₂
- Administering intravenous phenylephrine, a drug used to increase blood pressure, to prevent the rapid breathing/reduced CO₂
- Administering intravenous acetazolamide, a drug that increases blood flow to the brain, to assess its potential for improving cognitive abilities

During each challenge, the researchers will collect a variety of data, including cerebral blood flow, blood pressure, heart rate and rhythm, breathing rate and volume and amount of CO₂ in each participant's breath. They will also test cognitive function using the "N-back tests," which evaluates working memory, concentration, attention, and information processing with progressively increasing levels of mental stress.



Dr. Medow and staff prepare a volunteer for orthostatic challenge testing.

Exercise, Fatigue, Genes and Brain Function: Identifying the Linkages in People with CFS



Dane B. Cook, Ph.D.
Assistant Professor of
Kinesiology, University of
Wisconsin, Madison

Most experts agree that avoiding physical activity can compound CFS symptoms, yet exercise is also the very thing that can make symptoms worse! This catch-22 situation even has a name: “post-exertion malaise” (PEM), or post-exertion relapse, and it is considered one of the most debilitating aspects of CFS.

It occurs not just with physical activity; mental exertion and any kind of stress can provoke a relapse of the classic flu-like symptoms of CFS, negatively impacting thinking and memory, and sleep for days or even weeks.

Yet no single research group has ever evaluated the effects of mental and/or physical stress on PEM in a multi-systemic manner, notes Dane B. Cook, Ph.D., an assistant professor of kinesiology at the University of Wisconsin in Madison. Now, thanks to a grant from the CFIDS Association, he and his team plan to do just that.

“The overarching theme is to understand the pathophysiology (or underlying processes) of PEM in CFS,” he says, including connections between the immune system, the brain, and behavioral outcomes such as fatigue. “This is a first step towards a more comprehensive understanding of PEM.”

Research Confusion on PEM

Current research on PEM is inconsistent and confusing, says Dr. Cook. It’s not even clear how much activity leads to PEM, or how long after the stressor PEM occurs. For instance, his group has performed maximum exercise tests in people with CFS and didn’t see any changes in symptoms until five days later, which may or may not have been related to the stressor. However, others have worked with participants in whom moderate exercise for 30 minutes increased symptoms 30 minutes to two days afterwards. Studies also use varying definitions and intensities of exercise, leading to significant variability in our understanding of PEM, he said.

Dr. Cook takes a psychobiological approach to the study of PEM, looking for objective markers that could trigger symptoms. He then uses exercise as a model to identify the effects of physical activity and other stressors on people with CFS. “That’s important, he notes, because

you can’t begin to fix a problem like PEM until you can understand its underlying cause.

Comprehensive, Interdisciplinary Approach

Dr. Cook’s grant is unique in that it is designed to bring disparate research into a comprehensive whole.

The first piece of the puzzle comes from his own work using a special MRI that tracks oxygen uptake throughout the brain to identify brain function changes in CFS patients after they complete a fatiguing cognitive task such as repeatedly subtracting 7 from a starting number. He’s found significant differences in brain function of those with CFS and those without after such stressors, although there are no differences in brain function between the two groups without inducing mental fatigue.

The second piece of the puzzle comes from previous CFIDS Association grantee Kathleen Light, Ph.D., her husband Alan Light, Ph.D., and their team at the University of Utah. They identified unique post-exercise gene expression markers that can be used to differentiate people with CFS from those without and from those with multiple sclerosis and fibromyalgia. They also discovered increased expression of sensory and immune system genes after exercise.

The third piece of the puzzle is provided by another past CFIDS Association grantee, Gordon Broderick, Ph.D., of the University of Alberta in Canada. He used his previous grant to advance his work in identifying evidence of persistent immune activation after Epstein-Barr virus infection, which is thought to trigger CFS.

Together, the three groups will hopefully be able to begin to piece together the puzzle and create a



Dr. Cook monitors a volunteer as she performs the exercise challenge.

clear picture of PEM, says Dr. Cook. “This grant is the outcome of many years of talking to other scientists about CFS and merging that information with other important findings,” he said. “It is really and truly an interdisciplinary project.”

The study has three principle components:

- 1) Collect blood before and after a moderate exercise challenge on a stationary bicycle to evaluate and validate the expression of genes identified in the Light’s research.
- 2) Use brain-imaging techniques to evaluate the structure and function of the brain during fatiguing and non-fatiguing cognitive tasks, focusing on areas of the brain associated with fatigue.
- 3) Integrate gene expression and symptom data with the brain imaging results.

Just the Facts

This study involves 15 women with CFS who will be evaluated over three days.

- On the first day, they will provide baseline blood samples, complete questionnaires about their symptoms and undergo a baseline MRI.
- On the second day, they will complete a 25-minute moderate exercise challenge, with blood samples, as well as symptom descriptions, taken prior to and 30 minutes post exercise.
- Twenty-four hours after the second day, participants will provide blood samples, undergo MRI, and again complete questionnaires about their symptoms.

Their blood will be analyzed for evidence of genetic biomarkers already discovered the two Drs. Light and Dr. Broderick will conduct sophisticated data analysis using cutting-edge bioinformatics techniques to identify patterns between symptoms, brain function, exercise response, cognitive tasks and blood markers of enhanced genetic expression.

An important component of the study is the use of sophisticated mathematical modeling to integrate the disparate information that comes in from the different biologic systems (nervous system, blood, genes) to identify patterns and connections. The result, says Dr. Cook, is that “we can see systems ‘communicate’ (in the statistical sense) with one another and how that ‘communication’ changes when you introduce a stressor such as exercise.”

If successful, he notes, the study will provide preliminary data to guide future large-scale studies targeting specific subtypes of CFS, determining the impact of PEM and identify potential targets for treatment. ■

Repurposing Old Drugs for CFS



Spyros Deftereos,
M.D., Ph.D.
Senior Vice President for
Drug Discovery, Biovista

With approximately 6,000 approved drugs on the market here and in Europe for thousands of diseases, you’d think at least a handful would prove effective for chronic fatigue syndrome (CFS). Well, that’s exactly what the CFIDS Association’s grantee Biovista hopes to find by identifying existing drugs ripe for “repurposing.”

The concept of repurposing drugs is not new. Existing drugs are used “off label” all the time, particularly for cancer. That’s because once drugs are approved for one use, doctors are free to use them for other conditions. For instance, antidepressants, narcotics and amphetamines are often used off label to manage CFS symptoms such as fatigue, “brain fog” and unrefreshing sleep. None, however, address the disease holistically, leaving patients still suffering and still searching for relief.

Another example is rituximab, a drug approved to treat cancer and rheumatoid arthritis that is being studied in CFS after a research team in Norway noted its benefits in patients who had cancer and CFS. (See page 6.)

Repurposing, however, goes a step further than the hit-and-miss approach of off-label use: systematically assessing every known aspect of a compound, whether approved or failed, for its potential to treat other diseases.

For instance, the erectile dysfunction drug Viagra began life as a possible treatment for hypertension, while thalidomide, a morning-sickness drug banned in the early 1960s after it was found to cause horrible birth defects, was reborn in 2006 as an effective treatment for the bone cancer multiple myeloma.

The process of drug repurposing, also called “drug repositioning,” can slash the time and cost

(continued on page 4)

Repurposing Old Drugs for CFS (continued from page 3)

to bring new therapies to the patients who need them most, says Biovista vice president for drug discovery Spyros Deftereos, M.D., Ph.D.

Biovista is one of the leaders in the drug repurposing field. The Charlottesville, VA-based company has a systematic process that identifies the potential of existing, approved drugs for other medical conditions. As Biovista co-founder Aris Persidis, Ph.D., says, “A drug that is well seasoned is an excellent starting point for innovation.”

The grant request to the Association came after several discussions with Association staff, said Dr. Deftereos. “We thought it would be interesting for both parties,” he said. In addition, the neurological impairment and neurology-related mechanisms thought to be involved in CFS, particularly dysfunction of cellular mitochondria (the so-called “power house” of the cell), are right in line with other Biovista research. The company already has two drug candidates for another neurological condition, progressive



Dr. Deftereos and the Biovista team

multiple sclerosis, as well as candidate drugs for brain cancer, thyroid cancer and melanoma.

With its grant, Biovista will identify drugs that target what is known so far about the underlying biological dysfunction, or pathophysiology, associated with CFS. Investigators will also search for drugs that could resolve the symptoms of the syndrome, particularly CFS-related cognitive impairment and unrefreshing sleep. However, they will also explore potential therapies against other CFS-related symptoms, ideally finding drugs that can treat more than one symptom.

Three-Step Process

The repurposing process begins with the company’s proprietary software, the Biovista Clinical Outcome Search Space (COSS) drug repurposing platform. The software conducts a comprehensive search of numerous biomedical databases to identify potential compounds for further assessment, searching for linkages between genes and proteins implicated in the biological pathways of a disease. If diseases share such molecular pathways, then a drug that works in one might be effective in another. Dr. Persidis once likened the process to “eHarmony for medicine.”

“That’s why we can navigate all 23,000 diseases and all 6,000 adverse events against all 20,000 human targets and 95,000 drugs and pharmacologically active compounds with reasonable data in the public domain,” he told a reporter from *The Scientist* magazine.

Then, using a proprietary algorithm that assesses 25 different components to identify every known gene, pathway, disease, anatomical location, cell

structure and other component of potential drugs, including why and how they succeeded or failed, as well as potential side effects and drug/drug interactions, researchers develop a list of relevant drugs that should be further investigated.

The next step is to rank the identified drugs and make predictions about their potential benefit for CFS. The predictions are based not only on potential benefits, but also on safety profiles, potential interactions with other drugs already used to treat CFS, pharmacological characteristics (such as how long the drug remains in your system, any potential liver or kidney concerns) and their overall relevance to the underlying disease processes.

So far, the company has a 70 percent success rate in matching its predictions of drug activity against a given disease to actual efficacy. Its success is so good, in fact, that pharmaceutical giants such as Pfizer, Novartis and others have hired it to repurpose several of their existing drugs.

Finally, Biovista will use the Association’s SolveCFS BioBank to identify sets of biomarkers and clinical characteristics that can be used to validate the potential of the identified drugs to treat the syndrome and/or its symptoms.

The entire project should span 11 months. Ideally it will be followed by the design and launch of follow-up research and development work, either by Biovista, pharmaceutical companies, or research support organizations like the Association.

The ultimate goal: New drugs that target not only the symptoms of CFS, but the underlying disease process, possibly leading to the holy grail of effective treatment and, ultimately, a cure. ■

Neuromuscular Strain in CFS



Peter C. Rowe, MD
Professor of Pediatrics
and Director of the
Chronic Fatigue Clinic,
Johns Hopkins Children’s
Center, Baltimore, MD

It’s been more than 70 years since the first research appeared linking rapid heartbeat (tachycardia) and low blood pressure (hypotension) with neurasthenia, or abnormally sensitive nerves. Yet for decades, the research sat forgotten, in part because of the medical field’s insistence that the lower the blood pressure, the better.

“But what they forgot

is that problems can be present in those who lie at the bottom of any bell-shaped curve in biology, just as they are at the top,” says Peter C. Rowe, M.D., professor of pediatrics and director of the Chronic Fatigue Clinic at Johns Hopkins Children’s Center in Baltimore, MD. So people with chronic fatigue syndrome (CFS), who often exhibit hypotension along with tachycardia “were patted on the head and told how lucky they were that they wouldn’t have a stroke.”

Now, though, that old research is getting more attention, as are the circulatory problems that often accompany CFS. For, based on the work of Dr. Rowe and others, it appears that the three conditions — rapid heartbeat, low blood pressure, and abnormal nerve sensitivity — may hold a critical clue to CFS.

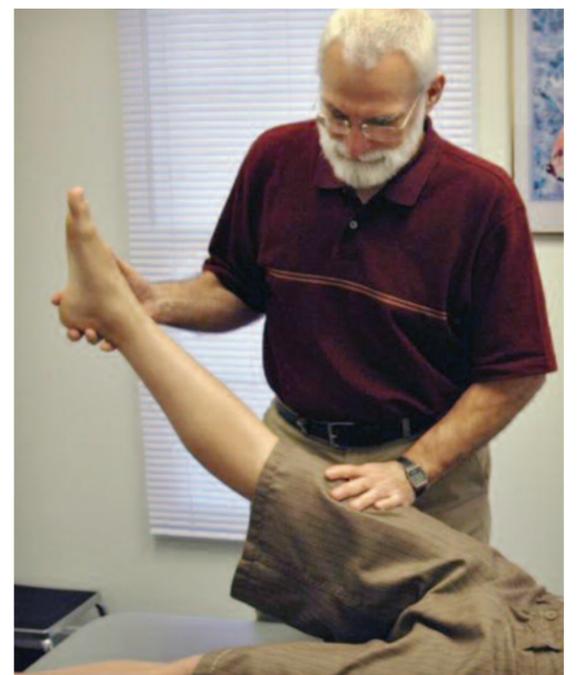
It’s a hypothesis that Dr. Rowe and his team plan to explore in depth with their recently awarded CFIDS Association grant. The results, he says, could lead to better ways of diagnosing, categorizing and treating the condition.

One Patient’s Story

Dr. Rowe’s current research began, in part, several years ago when he treated young girl with CFS and recurrent fainting. She didn’t want to try any medications, he recalls, although she agreed to increase her fluid and salt intake to increase her blood pressure. Her mother asked Dr. Rowe if he thought physical therapy might help. “Go ahead and see if it works,” he told her.

Within two months, the girl’s fainting episodes had significantly improved and she felt 90 percent better. “I was quite astonished, because I thought she would almost certainly need medication,” he remembers. After meeting the girl’s physical therapist, he realized the approaches the physical therapist used might provide helpful insights into CFS symptoms.

Today, that physical therapist, Rich Violand, is part of the grant Dr. Rowe has received from the CFIDS Association. The goal: examine scientifically what he saw in that young patient and others since: that some form of neuromuscular dysfunction may underlie CFS, an understanding that might also help us understand the connections between hypotension, tachycardia and nerve sensitivity.



Physical therapist Rich Violand demonstrates the straight leg raise that provokes CFS symptoms in some individuals.

When Nerves Get “Stuck”

The research stems from the observation that some people with CFS have restrictions in their normal range of movement, i.e., they can’t lift or stretch their legs and arms as well as those without the condition. In addition, the classic CFS symptoms (fatigue, cognitive foginess, light-headedness, etc.) often seemed to get worse after a physical therapy evaluation that strains muscles and nerves. Even raising the leg of someone who has this subtype of CFS can make symptoms worse, sometimes for up to 24 hours.

Genetic Changes and CFS: Identifying the Culprit



Patrick O. McGowan, Ph.D.
Assistant Professor,
Department of Biological
Sciences, University of
Toronto, Scarborough

Contrary to what some might think, our fate is not set upon conception when the genome is created, nor is our fate determined entirely upon the environment into which we are born and live. Instead, everything we are and everything we will be stems from a complex interaction between our genes and our environment, with

the environment influencing which genes turn on and off and when, and our genes influence how we react to the environment.

For decades, scientists believed that while the genome was very plastic and could adapt to the environment in very early life, that window closed as we developed in utero. They also believed that genetic changes could only occur through changes to the underlying DNA. Today, however, an exciting new field called epigenetics has set that thinking on its head and created new possibilities for understanding how diseases develop — and how to prevent and treatment them.

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.

“Epigenetics is really a funnel by which the outside environment interacts with the genome,” explains CFIDS Association grantee Patrick O. McGowan, Ph.D., assistant professor in the Department of Biological Sciences at the University of Toronto in Canada. This, in turn, influences how cells work (or don't work). Already, research shows that epigenetic changes are implicated in numerous diseases, including cancer, asthma and heart disease.

And, if Dr. McGowan is right, they may also play a role in the development of chronic fatigue syndrome (CFS).

Disrupted Signaling in Body's “Conductor”

To understand where Dr. McGowan and his team hope to go with their research, you first need to understand the hypothalamic-pituitary-adrenal (HPA) axis, often referred to as the “conductor” of our body and its responses.

The HPA is one of the most important communication pathways in the brain. The signals it produces (from hypothalamus to pituitary gland to the adrenal glands and back again) help maintain balance in the neuroendocrine system, which enables communication between various hormones throughout your body and your brain; and the sympathetic nervous system, which regulates the infamous “fight-or-flight” system and determines how the immune system responds to environmental stressors.

This latter component involves cortisol, a glucocorticoid hormone that helps dampen immune system inflammation and keep the body in balance. It also “turns on,” or activates, glucocorticoid receptors that then act on hundreds of genes that

control development, metabolism, cognition and inflammation. Think of these receptors as a lock, and cortisol as the “key” that unlocks them to allow the hormone to enter the cell and tell it what to do. Yet one of the most consistent findings in CFS is that patients don't produce enough cortisol. Without that cortisol, immune system cells called lymphocytes continue to release pro-inflammatory cytokines, keeping the system activated and wreaking all sorts of havoc throughout the body. The whole process likely contributes to many of the symptoms of CFS.

If Dr. McGowan is correct, epigenetic changes may be at the heart of this cortisol/cytokine imbalance.

Tracking the Epigenetic Changes and the Environmental Causes

Dr. McGowan's research has three main goals:

- Confirm that there is, indeed, altered sensitivity to glucocorticoids and increased inflammatory cytokine production in immune system cells of people with CFS.
- Identify patterns of DNA methylation and the specific epigenetic locations in the genome in people with CFS.
- Analyze the epigenomic and genetic changes in CFS patients in conjunction with symptoms, their severity and medication response — all areas associated with the HPA axis.

To do this, Dr. McGowan and his team will use immune system cells from the SolveCFS BioBank. They will first stimulate the cells with a synthetic glucocorticoid hormone to assess their

(continued on page 6)

Conversely, treating that restricted range of motion using the manual physical therapy techniques that Mr. Violand and other physical therapists used on Dr. Rowe's patients not only seemed to improve daily function but also increased exercise tolerance.

Dr. Rowe and his team suspect that these movement restrictions are related to problems with abnormal tension or tightness within the nerves and soft tissues. Nerves need to be free to slide over and between the muscles and other soft tissues they branch through. But sometimes they lose this mobility and come under increased mechanical tension, leading to abnormal pulling that makes the nerve hypersensitive. In response to that sensitivity, muscles along the nerve highway tighten to “protect” the nerve from further irritation. The tight muscles, in turn, further restrict movement.

This persistent muscle tightness in response to the tightness and lack of glide in the nerves may contribute to the fatigue that is so prevalent in CFS, Dr. Rowe explains. It may also explain why certain movements and postures can place increased strain on nerves and muscles, worsening symptoms. It may also affect the autonomic nervous system which, in turn, controls blood pressure and heart rate.

“Our study is an attempt to see if that kind of nerve and muscle strain loads the nervous system in such a way as to increase its sensitivity so it then ‘over-responds’ to various stresses,” he said.

If the group can firmly establish that physical problems in range of motion and nerve glide interact to increase CFS symptoms, “that would

suggest new ways to treat people with physical therapy techniques that haven't been emphasized in the past,” he said. These include gentle manual techniques to reduce muscle spasm and tightness, improve soft tissue range of motion, reduce tension in the nerves and surrounding soft tissues, and, using a technique called neural mobilization, improve the ability of nerves to “glide” through muscles and soft tissue.

It seems to work in many patients, he says. Once their peripheral nervous system strain is

reduced with physical therapy, often they report less dizziness and lightheadedness. Even the adolescents he treats, who “are almost never willing to wear compression stockings,” almost always stick with physical therapy because it makes them feel so much better.

“I feel like we're further ahead clinically than we are from a research perspective,” he admits. But then, he notes, trying to figure out why something works in the real world is often what drives the research. ■

Just the Facts

Dr. Rowe's study will enroll 60 people with CFS and 20 healthy people as controls. Each group will be randomly assigned to either a 15-minute passive straight leg raise or a “sham” neuromuscular strain. Then the researchers will assess whether the CFS group experiences any change in symptoms, pain sensitivity or sympathetic nervous system tone after the straight leg raise and 24 hours later.



Kristi Mizelle, M.D., Ph.D.



Kevin R. Fontaine, Ph.D.

Three collaborators will assist with the study: Kevin R. Fontaine, Ph.D., associate professor of medicine at Johns Hopkins Bloomberg School of Public Health; Kristi Mizelle, M.D., Ph.D., who directs the Rheumatology Holistic Care Clinic at The Johns Hopkins Hospital; and Richard L. Violand, Jr., of Violand and McNerney Physical Therapists, in Ellicott, MD.

Ideal outcome: Identifying a new biomarker (neuromuscular strain) that could be used to diagnose and classify CFS patients, as well provide a target for treatment. It would also raise other questions for investigation, such as: “Does the severity of the neuromuscular strain correlate with the severity of CFS and symptoms?” “Are there differences in gene expression in response to the strain?” And, of course, “What is the best way to treat these neuromuscular dysfunctions?”

Genetic Changes and CFS: Identifying the Culprit (continued from page 5)

sensitivity to glucocorticoids and cytokine production. They will also extract DNA from the blood cells to evaluate epigenetic patterns and



Dr. McGowan explains DNA methylation at the first RIWW investigators meeting in March.

compare the results to those of cells from people without CFS. They also want to see if cells from different CFS patients respond differently, which would provide evidence of subtypes of CFS, something many researchers suspect exist.

“The exciting thing is that we’re looking across the entire genome, so we’re not making assumptions about what system is influencing the HPA abnormalities,” he says.

In addition to identifying potential epigenetic changes, Dr. McGowan and his team will also try to understand the environmental triggers that likely set about those changes. To do this, they will use disease-specific family history and current health reports for the patients whose cells they are examining.

Unlike genetic differences, which are fixed from conception and remain relatively stable across

the lifespan, epigenetic differences are stable but respond to environmental factors; thus, Dr. McGowan said, they may be amenable to therapeutic intervention. For instance, some cancer drugs alter gene expression through epigenetic changes. But there are also potential lifestyle interventions that could have similar results, he said.

“I’m really excited about this grant because we are right at the beginning stages of being able to look at very complex diseases like CFS in a holistic way” by targeting the genome, he said. “If we can start to get biomarkers for this disease that correlate with clusters of symptoms, we will have a better idea of how to approach interventions.” Those biomarkers could also make it easier to study CFS, even aiding in early diagnosis of the disease and, possibly, approaches designed to prevent its development in susceptible individuals, as well as targets for treatment. ■

Journal Highlights

You’ll find more detailed information about these studies and summaries of many more recent publications on our Research1st.com website.

XMRV Studies Wrapping Up

In October 2009, CFS was linked to xenotropic murine leukemia virus-related virus, or XMRV, in a paper published by Lombardi et al in *Science*. A second study published in the *Proceedings of the National Academy of Sciences (PNAS)* in August 2010 broadened the search, linking CFS to fragments of viruses from the larger family of murine leukemia-like viruses (MLVs). High-profile studies sustained research interest and media attention in this potential association, the role of infectious agents in CFS and immune system abnormalities.

To date, more than 20 studies have failed to support these initial observations. A pair of retractions issued just before and just after the 2011 Christmas holiday removed from the record the two published reports linking CFS to these viruses. In its Dec. 23, 2011 issue, *Science* editor-in-chief Bruce Alberts retracted the 2009 publication by Lombardi et al. On Dec. 26, 2011, Lo et al., authors of the 2010 *PNAS* study, retracted their study.

The National Institutes of Health (NIH) has provided funding for two multicenter studies to try to resolve the scientific controversy. The first, known as the Blood XMRV Scientific Research Working Group (SRWG) study, was completed in August 2011 and results were published in *Science* on Sept. 22, 2011. None of the 19 assays used by nine participating labs was able to distinguish previously XMRV/MLV-positive CFS cases from healthy blood donors or pedigreed negatives on the basis of results for XMRV or the larger family of murine leukemia viruses.



The Sept. 22, 2011, issue of *Science* included a provocative 8-page article by journalists Jon Cohen and Martin Enserink who followed the XMRV story from its beginnings.

The second large NIH-supported study is being coordinated by Ian Lipkin, M.D., at Columbia University. Six clinical sites have provided samples from well-characterized CFS patients and matched healthy controls. Coded samples are now being tested under blinded conditions by investigators using their own assay methods and Dr. Lipkin will break the code. The laboratory investigators involved in the study include Dr. Judy Mikovits, Dr. Francis Ruscetti (NCI), Dr. Shyh-Ching Lo (FDA) and William Switzer (CDC). The study is due to be completed by mid-2012.



Drs. Øystein Fluge and Olav Mella reported a successful outcome of their phase II study of rituximab and made headlines around the world.

Rituxan Shows Promise

On Oct. 19, 2011, results of a double-blind placebo-controlled phase II clinical trial of rituximab were published in *PLoS ONE*. The study conducted in Norway was small, with just 15 CFS patients in each arm, but it showed promising results. Sixty-seven percent of the patients treated with rituximab (Rituxan), a monoclonal antibody, showed improvement after two infusions given two weeks apart, compared to 12 percent of those who received placebo. Rituximab is approved for use in certain cancers and rheumatoid arthritis and has been tested in a wide range of conditions. It is one of manufacturer Roche/Genentech’s “blockbuster” drugs.

The CFS study attracted attention from media around the world. Two additional open-label phase II studies are now under way and the team at Haukeland Hospital in Bergen (Norway) is working with other centers to design a larger phase III study. So far, there have been no formal studies announced in the U.S., although some physicians are prescribing the drug on an off-label basis for selected patients.

Ampligen Data Disappoints

During the years 1998-2004, 234 individuals with severe CFS at 12 clinical sites took part in

a phase III study of the experimental therapy rintatolimod (Ampligen). After a long wait, the study results were published on Mar. 14, 2012, in *PLoS ONE*. While the study met its primary endpoint of increased exercise tolerance, the improvement of just 108 seconds for the treatment group, compared to 27 seconds for the placebo group, was disappointing. Secondary endpoints of patient-rated measures did not show much improvement either, although the manufacturer considers the study a success.

Compared to reports heard at public meetings and research conferences over the years, the data did not seem to match the anecdotal testimonies. This suggests that the key to understanding the Ampligen response may lie hidden in data and that a subset of patients may fare better than the group as a whole, as has been the case with many drugs, including Benlysta, recently approved for a subset of lupus patients.

Updates on Grantees Funded by The CFIDS Association

Markers Differentiate CFS from MS:

A new study from the team of Kathleen and Alan Light at Univ. of Utah shows unique post-exercise markers in CFS compared to patients with MS and healthy controls. Increases in metabolite-detecting receptors after a moderate, but sustained exercise challenge were unique to patients with CFS, whereas both patients with MS and patients with CFS showed abnormal increases in adrenergic receptors. (*Psychosomatic Medicine*, Dec. 30, 2011) In Sept. 2011, the Lights were awarded a three-year \$1 million grant from NIH to continue their studies of post-exercise biomarkers in CFS.



Kathleen (top) and Alan Light, University of Utah

Upright Posture Impairs Cognition: Marvin Medow, Ph.D., and colleagues at New York Medical College conducted cognitive tests during tilt table testing and made other circulatory measures of brain blood flow on 25 CFS patients with POTS and 20 healthy control subjects. “Overall, our data show that blood flow fails to increase during [cognitive] tasking for all [levels of difficulty].” In control subjects, progressive tasking difficulty enhances blood flow. (*American Journal of Physiology — Heart and Circulatory Physiology*) Dr. Medow will continue his studies with another award from the Association (see page 2). ■

Building Awareness

Our scientific director, **Dr. Suzanne Vernon**, was interviewed by the *Saturday Evening Post* about her perspective on promising directions for CFS research. An online feature complemented an article in the Nov./Dec. print edition.



David Tuller

Journalist **David Tuller** wrote his first news story about CFS in 2007, when his byline ran under the *New York Times* headline, “Chronic fatigue no longer seen as ‘yuppie flu.’” He has written 12 articles about CFS for the *Times* since then. Tuller’s longest article about CFS was posted to virology blog, a well-read science blog hosted by Dr. Vincent Racaniello (see below). That article, “CFS and the CDC: A long, tangled tale,” represents many months of research and scores of interviews. In December, Tuller covered the two XMRV retractions for the *Times* and he did a follow-up story on the aftermath of XMRV in Feb. 2012.



Many of the year-end media wrap-ups included CFS, most often for the controversy over XMRV that peaked as 2011 came to a close. **DISCOVER Magazine** included CFS in two of its top 100 science stories of the year — XMRV and the proteome study published in Feb. 2011 by Dr. Steven Schutzer and colleagues.



Columbia University professor and host of the popular “This Week in Virology” podcast **Vincent R. Racaniello**, Ph.D., covered XMRV and CFS numerous times on his blog and podcast. On Jan. 12, 2012, Dr. Racaniello’s perspective was shared with readers of DISCOVER magazine’s blog *The Crux* in an article titled, “A Tale of Two Viruses: Why AIDS Was Pinned to HIV but CFS Remains a Mystery.” Dr. Racaniello serves on the Association’s Scientific Advisory Board. He is a go-to expert for the media on many topics in virology.



UK film critic **Scott Jordan Harris’** review of the ME documentary, “**Voices from the Shadows**,” was posted by Roger Ebert to the *Chicago Sun-Times* website on Feb. 10, 2012. Harris has ME himself and says of the film, “It’s my film of the year. It’ll be my film of the decade.” “Voices” won a prize at the 2011 Mill Valley Film Festival but it hasn’t yet attracted a distribution deal. The review, “A Howl of Desperation for Those Who Cannot Howl,” created a sensation of its own, just as the documentary has, for drawing attention to the most severely ill.

The Association’s Feb. 23, 2012 press release about the **research institute without walls** (see page 1) and **Laura Hillenbrand’s \$250,000 donation** (see page 8) attracted news coverage from the *Wall Street Journal’s* Health Blog, *Philanthropy Journal* and more than 325 other news agencies. Press releases issued by Biovista (see page 4) and the University of Toronto (see page 5) helped generate additional coverage by news services that cover the pharmaceutical industry, science and biotechnology.

CEO Kim McCleary and scientific director Suzanne Vernon, Ph.D., were guests on Mar. 1 on the one-hour “**Charlotte Talks**” radio program, heard on NPR stations in the local area and now archived on WFAE’s website.



Every month (and usually more often than that!) since 2003 we have published an electronic newsletter. Its content and format have evolved, but it has always sought to connect readers with the latest research, policy and health news from a variety of reliable resources. In January 2012 it got a new name — **Research1st News** — after our **Research1st** website and blog. If you aren’t already on our mailing list, please send an email message to Research1stNews@cfids.org with “SUBSCRIBE” in the subject line. ■

Supporting the Cause

Board Transitions

At the core of every nonprofit organization is the Board of Directors, responsible for defining mission, setting policy and stewarding human and financial resources. The CFIDS Association of America has benefited from the talents and volunteer leadership of 88 individuals who have served on the Board of Directors since the organization’s founding in 1987; this diversity in expertise and experience is unmatched in our community. In 2012, the Association welcomes to its Board of Directors two new members: **Elizabeth Garfield, J.D.**, and **Christine Williams, M.Ed.**

Beth is a practicing labor attorney in Los Angeles whose interest in CFS stretches back to 1985 when she became ill while on vacation. Thanks to a treatment that provided tremendous relief, she was symptom-free for 22 years before a relapse in 2011. Chris retired from service to our federal government after 30 years in health policy, first on Capitol Hill and then for the Agency for Healthcare Research and Quality. Chris was diagnosed with CFS in 2008 and she served on the federal CFS Advisory Committee, sharing her perspective as both a professional and as a person with CFS.

Two Board members have served the full term allowed under our By-laws and retired at the end of 2011: Bruce Allshouse and Jennifer M. Spotila, J.D. Four other directors, Christoph Bausch, Ph.D., Amy Divine, Stuart Drescher, Ph.D., and Brian Smith, had personal and professional obligations that precluded their continued service at this time. We thank these six remarkable individuals for their enormous commitment and contributions over the years.

Year-End Results

The CFIDS Association has set a new course and is determined to transform the way that research is done. In the summer of 2011, we established the Catalyst Fund to fuel the next phase of our research program. By year-end, with help from benefactors who issued a series of five fundraising challenges, and nearly 2,000 gifts large and small, we raised a total of \$1,217,177. Our work is off to a brisk start in 2012 and we need your support year-round to continue the momentum. Why not make the CFIDS Association one of your first charitable donations of 2012? Our secure online donation site is ready 24/7 at <http://bit.ly/RIWW-fund>, or you can use the envelope included with this issue. Thank you for your sustaining support over these 25 years of change and challenge!

Join Us For A Catalyst Café Event

In late 2011 we were pleased to host five gatherings of Catalyst donors in San Francisco, New York, Boulder, Chicago, and Washington, D.C. In early 2012 we’ve met with groups in Dallas, Charlotte and Los Angeles to share news about the Association’s progress and to thank our supporters. We have plans to hold informal “Catalyst Café” events throughout the year — maybe in a location near you! Make sure you’re included on our invitation list and receive monthly news from Association leaders through our new Catalysts In Action e-newsletter. Simply send an email message to CatalystsInAction@cfids.org with “SUBSCRIBE” in the subject line. We’d love to see you and keep you up-to-date on the latest progress! ■

The CFIDS Association of America

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Elizabeth Garfield



Christine Williams

