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Square one in CFS

By Lev Osherovich, Senior Writer

The **Chronic Fatigue Initiative** is moving on to new approaches to identify the true cause of chronic fatigue syndrome after a consortium of American researchers failed to reproduce a 2009 study linking CFS to a virus called XMRV.[1]

The Chronic Fatigue Initiative (CFI), a venture philanthropy organization, announced plans last week to fund epidemiological studies of CFS, build a biological database of tissues from subjects with CFS and generate hypotheses to stimulate academic research into the molecular mechanisms of the condition.

The initiative plans to spend more than $10 million on these projects over the next three years.

CFI hopes to help affiliated researchers test their ideas using blood and tissue samples from a well defined CFS cohort, said executive director Scott Carlson.

In the past, CFS research has been stymied by heterogeneous clinical criteria for illness and a lack of openly accessible biological sample collections. Carlson expects that CFI's efforts will spur further investment in the indication by academic funding agencies and companies.

"We look at our effort as seed capital to stimulate other institutions with deeper pockets to bring their resources to bear," he said.

CFI's announcement of its funding efforts coincides with a setback in the CFS space, as the link between XMRV and the condition has essentially evaporated.

In 2009, a team led by Judy Mikovits at the **Whittemore Peterson Institute for Neuro-Immune Disease** and collaborators at the **Cleveland Clinic** and the **National Cancer Institute** (NCI) published evidence that people with CFS had a higher incidence of XMRV infection than healthy controls.[2]

That finding caused concern about the possibility of transmission of CFS through blood products and triggered efforts by companies including **Abbott Laboratories** and **Gen-Probe Inc.** to develop research-use diagnostics to detect the virus.

Skepticism about the findings emerged soon after, with several academic groups challenging Mikovits' methodology and reporting the absence of XMRV in their own analyses of tissue from subjects with CFS.[3] However, Mikovits' case was bolstered by a 2010 study by NIH and FDA researchers that detected evidence of the virus in an independent cohort of individuals with CFS.[4]

To resolve these controversies, Mikovits joined with teams at Abbott, Gen-Probe and six academic and government labs to retest samples from subjects with CSF and controls. The results strongly suggest that her team's original data and the resulting hypothesis about the etiology of CFS are incorrect.

The consortium was led by Michael Busch, director of the Blood Systems Research Institute at the **University of California, San Francisco**.

Blood from 14 affected individuals who tested positive for XMRV in previous studies, plus one more XMRV-positive sample from an individual without CFS symptoms, were distributed to Abbott, Gen-Probe and seven academic laboratories. Also distributed were 15 samples from healthy individuals and five positive controls spiked with XMRV DNA.

The samples were blinded and the laboratories tested them for the presence of viral DNA, serum antibodies to the virus or infectious particles of the virus itself. All laboratories identified the five spiked positive controls. However, in seven laboratories, all of the samples from affected individuals came up negative for the virus.

Two laboratories—those of Mikovits and of Francis Ruscetti, senior investigator at NCI and a coauthor on the 2009 *Science* paper—detected XMRV in a fraction of samples. However, those laboratories also found the virus in negative control samples at roughly the same frequency as in the samples designated as XMRV positive.

Results were published in *Science*. The report was accompanied by a partial retraction of the original 2009 study.

Rethinking CFS

The new research suggests Mikovits' original findings were artifacts arising from problems in laboratory practice, such as sample cross-contamination by the mouse-borne virus. XMRV and related viruses are thought to be widely distributed in the murine world, and their traces can be readily detected with PCR-based assays.

For companies, the findings mean XMRV screening of blood could be unnecessary from a public health standpoint. Abbott has filed for patents on the detection of XMRV nucleic acids and proteins.

John Hackett, Jr., research fellow and manager of emerging pathogens and virus discovery at Abbott, told *SciBX* the company began developing XMRV detection assays "soon after discovery of the virus."

"These prototype assays were developed in order to facilitate research studies to gain a better understanding of the virus and to provide insight as to the geographic distribution of XMRV and its prevalence in various normal and clinical human populations," said Hackett.

Even though the involvement of XMRV is human disease is now in doubt, Hackett said the company will continue to collaborate with academic researchers in answering basic science questions about the virus.

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—Mady Hornig, Columbia University

Fishing expedition

For patients and researchers, the findings mean it's back to the drawing board to identify the true cause of CFS.

There is clinical evidence that CFS is likely to be triggered by an infectious agent, said Mady Hornig, associate professor of epidemiology at **Columbia University**.

"Many features of CFS are highly suggestive of an infectious illness, including lymph node swelling, sore throat and malaise. A substantial proportion of CFS patients have very clear viral onset with fever and other signs of acute viral illness," she said.

Indeed, the disease may come on like a common cold, but because it takes at least six months for full blown CFS to develop, it's hard to obtain blood or tissue samples at the time of infection.

To find the pathogenic triggers of CFS, Hornig and her collaborators are launching a retrospective analysis of CFS tissue samples gathered by CFI to look for latent viruses and immunological signs of chronic infection.

The team will use a PCR technique developed by Ian Lipkin, professor of epidemiology, neurology and pathology at Columbia, to screen samples against a panel of 30–40 viruses. The team then will use other molecular diagnostic techniques to test for other pathogens, such as bacteria, fungi or parasites, that might be common among people with CFS.

Hornig's team also will look for altered cytokine levels and other plasma biomarkers that might be indicative of immune activation in patients with CFS.

She said it remains to be seen whether a single pathogen is responsible or whether CFS has an inflammatory or autoimmune component triggered by any of a number of infectious agents.

Hornig also is principal investigator at CFI, which is funding her project.

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COMPANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.
Chronic Fatigue Initiative, New York, N.Y.
Cleveland Clinic, Cleveland, Ohio
Columbia University, New York, N.Y.
Gen-Probe Inc. (NASDAQ:GPRO), San Diego, Calif.
National Cancer Institute, Bethesda, Md.
University of California, San Francisco, San Francisco, Calif.
Whittemore Peterson Institute for Neuro-Immune Disease, Reno, Nev.