INFECTIOUS DISEASES

New XMRV Studies Bring Closure—and Fresh Dispute

What went wrong? Robert Silverman had to figure out how XMRV contaminated his samples.

Most of the scientific community long ago pronounced dead the theory that a newly discovered gammaretrovirus, dubbed XMRV, was linked to chronic fatigue syndrome (CFS). The idea, launched in a *Science* paper in 2009, quickly garnered headlines because it might explain the baffling disease and suggest ways to treat and prevent it. But since then, study after study has demolished the claim, and last year, *Science* retracted the paper (23 December 2011, p. 1636).

But the results of the biggest study of all had yet to come out. Funded by the U.S. National Institutes of Health (NIH) and led by Ian Lipkin of Columbia University, the $1 million multicenter project finally published its results on Tuesday in *mBio*—and not surprisingly, it concludes that the XMRV theory is really, really dead. What *is* surprising, scientists say, is that Judy Mikovits, the main author of the 2009 paper and the staunchest defender of a role for XMRV—or something closely related—is won over. Mikovits, who participated in Lipkin's study, concedes it is "the definitive answer. … There is no evidence that XMRV is a human pathogen."

Meanwhile, another group has also wrapped up some unfinished business. XMRV was first reported in *PLoS Pathogens* in 2006 by Robert Silverman of the Cleveland Clinic in Ohio, along with colleagues at the University of California, San Francisco (UCSF); at the time, they linked the virus to prostate cancer. A new paper by many of the same authors, published in *PLoS ONE* this week, soundly refutes that link as well and describes their meticulous detective work to explain how the spurious findings arose.

But these authors have sparked a new controversy by saying that XMRV remains a potential pathogen and refusing to retract their 2006 paper. Indeed, two high-impact journals gave the new paper a thumbs-up but refused to publish it unless the authors retracted their original work, says UCSF's Charles Chiu, who didn't participate in the 2006 study but whose lab did most of the analyses for the new paper.

Lipkin's study is one of two similar projects NIH funded after Mikovits published her 2009 paper. One, by the Blood XMRV Scientific Research Working Group, set out to discover if labs could reliably detect XMRV infection in people and whether the U.S. blood supply was in danger. The Lipkin study, which used 10 times the number of samples, was designed to get a definitive answer on the link to CFS.

To most scientists, the blood study, in which Mikovits also participated, definitely ruled out XMRV as a pathogen—even more so because a 2011 paper by John Coffin and Vinay Pathak of the National Cancer Institute (NCI) had shown that the virus was a hybrid of two mouse viruses, accidentally created in the lab in the 1990s (*Science*, 23 September 2011, p. 1694). As a result, NIH received an "enormous amount of criticism" for continuing his study, Lipkin says. But Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, says it was worth going the extra mile to disprove it, especially because CFS patients had become so emotionally invested in the XMRV theory. "Now, it's clear to everybody that it is really over," Fauci says.

Three groups took part in Lipkin's study: Mikovits, formerly at the Whittemore Peterson Institute (WPI) in Reno, Nevada, and her collaborators Francis Ruscetti at NCI and Maureen Hanson at Cornell University; a team led by Shyh-Ching Lo at the Food and Drug Administration, which in 2010 linked CFS to a related group of viruses called MLVs (*Science*, 27 August 2010, p. 1000); and a group at the Centers for Disease Control and Prevention that had failed to find any new virus in CFS patients. The samples were blinded, and each team chose their own methods to analyze them so no one could complain that the right procedures weren't used, Lipkin says.

This time, none of the groups found any evidence of XMRV or MLVs in 147 patients or 146 controls. Mikovits and Ruscetti did find that about 6% of patients and controls had antibodies to XMRV, a result they chalk up to aspecific binding effects rather than XMRV infection. No previous study had tried to replicate her findings using her exact methods, Mikovits says. "I'm forever grateful to Ian Lipkin for making it possible to participate," she says. Lipkin says he is "proud" of Mikovits for accepting the outcome.

The controversy around CFS had its origins in the 2006 study by Silverman and the UCSF team that first reported XMRV in prostate cancer patients. As the link to CFS unraveled, Silverman realized that his work might also have problems, he says, and the 2011 paper by Coffin and Pathak convinced him his results were due to contamination. From then on, "I felt like I couldn't rest until

Final answer. Judy Mikovits (*left*) says she's "forever grateful" to Ian Lipkin (*right*), who led a big study of the link between XMRV and CFS.

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I figured out how it happened," he says.

The researchers took tumor samples from 39 new prostate cancer patients and tested them for XMRV using three different techniques; they also went back to tumor tissue still available from the 2006 study. This time, they found no XMRV in any of the samples. They did find it in archived RNA extracts from the 2006 study, indicating that contamination had happened during sample processing.

Further studies—some using techniques unavailable at the time of the original study—revealed that the virus originated in LNCaP, a cell line infected with XMRV that Silverman's lab used for other studies. The LNCaP cells, in turn, had become contaminated by 22Rv1, another widely used cell line that also harbors XMRV.

Silverman's group "deserves a medal," says Kim McCleary, head of the CFIDS Association of America, a patient advocacy group. In the long history of pathogens falsely blamed for CFS, McCleary says she's never seen scientists so scrupulously retrace their steps. "These scientists put their egos aside … to get to the truth," Pathak adds.

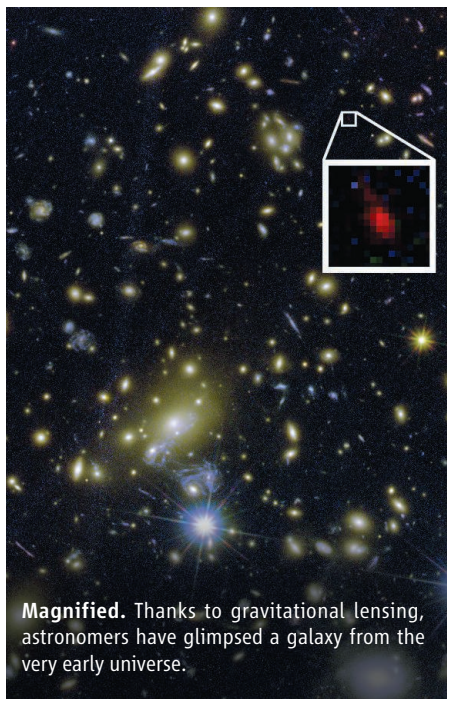
But others are less charitable. In the discussion of the paper, the authors say that XMRV is still a "genuine infectious agent" with "as-yet undefined pathogenic potential"; they point out that the virus is able to infect two primate species and mice and has interesting biological properties that may be useful, for instance, in cancer research. Lipkin says he's "astonished" by that claim. An accidental lab creation not occurring in nature is not a genuine infectious agent, he says, and he worries that the language may inspire new hope in XMRV believers: "I thought we were really done with this."

Both Lipkin and Coffin say the 2006 paper should be retracted because its findings were wrong. But Silverman, who retracted his lab's share in the Mikovits study 2 months ahead of the retraction of the entire paper, says the 2006 study reports the discovery of a new virus—and the rest has been corrected. There have been other cases in which authors corrected, rather than retracted, a spurious finding, he points out. Chiu adds that it would be odd for future papers on XMRV to refer to a retracted paper as a description of the discovery of the virus.

Pathak says that although retraction would be the best option—"just for the sake of setting the record straight"—it may not make much of a difference; any decent scientist interested in the 2006 paper would find the new one as well, he says. Silverman and his colleagues, he says, "have already done the hard part." **–MARTIN ENSERINK**

ASTRONOMY

Warped Light Reveals Infant Galaxy On the Brink of the 'Cosmic Dawn'



Magnified. Thanks to gravitational lensing, astronomers have glimpsed a galaxy from the very early universe.

Sometimes nature gives you free of charge a discovery you expected to cost billions of dollars. Just ask Wei Zheng and his fellow astronomers, who recently spotted a galaxy dating back to a mere 500 million years after the big bang.

The galaxy, some 13.2 billion light-years from Earth, sets a new record for most distant object sighted by astronomers. Such distant, ancient images are technically beyond the reach of existing telescopes. Imaging the infant universe is a primary goal of the James Webb Space Telescope (JWST), being built at a cost of $8.7 billion and expected to launch in 2018.

Yet Zheng, a researcher at Johns Hopkins University in Baltimore, Maryland, and colleagues got a sneak preview thanks to gravitational lensing: an effect in which gravity's ability to bend light turns weighty objects such as galaxy clusters into magnifying glasses for sources behind them. The young galaxy showed up in images taken by the Hubble Space Telescope because the massive gravity of an intervening cluster magnified it more than 15 times. "We got this image without additional funding from Congress," Zheng says in a joking reference to JWST, whose ballooning cost has forced NASA to ask appropriators for extra cash (*Science*, 19 November 2010, p. 1028).

From studying the image, the researchers estimate that the galaxy is less than 200 million years old and formed more than 300 million years after the big bang. Its estimated 100 million solar masses' worth of stars makes it just 1% as massive as the Milky Way.

In the timeline of cosmic evolution, the galaxy represents an era that is still filled with mystery. The universe was a soup of hot plasma for a few hundred thousand years after the big bang. Then the electrons and protons in the soup combined to form hydrogen. The first stars and galaxies are believed to have been born some 300 million years after the big bang. Over the next 700 million years or so, something reionized the universe, breaking its hydrogen back into electrons and protons.

Studies of the cosmic microwave background have broadly confirmed this timeline. But key early details are missing, including what led to the reionization. Many astrophysicists have suggested that ultraviolet (UV) radiation from early galaxies may have played an important role.

Zheng and his colleagues say that their discovery of the faint galaxy supports that idea. Because the magnifying glass that helped bring their galaxy into view covers only a small volume of the sky, Zheng says, it is possible that many other such galaxies were around at the time.

"Theoretical models of reionization associate most of UV production with galaxies of this or somewhat lower masses at exactly the same cosmic time," says Avi Loeb, an astrophysicist at Harvard University. "However, with only one galaxy at hand, it is difficult to draw robust statistical inferences." Loeb says ongoing lensing surveys or future telescopes—such as JWST—will help astronomers determine whether such galaxies were indeed the primary sources of ionizing radiation "at cosmic dawn."

Rogier Windhorst, an astronomer at Arizona State University, Tempe, and a member of JWST's science team, calls the discovery impressive but adds that "we definitely need JWST to find the main population of these objects," including more distant ones, and determine their physical properties. **–YUDHIJIT BHATTACHARJEE**

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