Will Heat of Debate Thaw Latest Freeze on Gain-of-Function Viral Research?

Jeffrey L. Fox

Last October, the White House imposed a “pause” on gain-of-function (GoF) research involving the influenza and two coronaviruses, SARS and MERS, pending a two-part review of safety and security concerns that is aimed at developing a new policy for dealing with such research. One part of that review continues within the federal National Science Advisory Board for Biosecurity (NSABB), while the second part took place more publicly last December during the symposium “Potential Risks and Benefits of Gain-of-Function Research,” convened by the National Academy of Sciences in Washington, D.C. This latter phase apparently helped persuade officials late in December to exempt some MERS projects from the pause, which otherwise remains in effect.

During the symposium, differences between those who want to move ahead with such research and others who prefer its being restricted seemed palpable. The depth of those differences is no real surprise. Some insiders consider this moratorium to be the third time several research groups studying GoF influenza were stopped cold, albeit the first time for those studying MERS and SARS. Regardless of the validity of these shutdowns, they are intensely disruptive for those whose labs and lives are directly affected. Meanwhile, those favoring this pause in GoF research see the public health threat from making these already deadly viruses even more dangerous—more virulent or more readily transmissible—as too much to risk.

Proponents of this research are asking, why stop and start that influenza research, which already was subject to careful scrutiny? And why halt SARS and MERS studies at this juncture? The “pause” comes amid the ongoing Ebola outbreak in Africa and following disclosures in mid-2014 that several federal labs were found to be holding “improperly registered” cultures of select biological agents or toxins (Microbe, February 2015, p. 49). Although those recent mishaps may not account for the pause, surely they set a tone that was not helpful for the set of experts trying to persuade skeptics of the wisdom of resuming GoF research.

Another difficulty underlying this debate is the terminology itself, says influenza expert Robert Webster of St. Jude Children’s Research Hospital in Memphis, Tenn., among others. “It’s too associated with doomsday scenarios,” he says. “Is there another, better term?” Adds David Relman of Stanford University in Stanford, Calif., “The broad term GoF doesn’t capture what we’re most concerned over.” This quest, however, remains unmet.

A central argument invoked for resuming GoF research is that it provides insights needed to safeguard the public against natural pandemics. “For some questions, only GoF can provide accurate answers,” says Yoshihiro Kawaoka of the University of Wisconsin, Madi-
son, some of whose influenza research efforts are again on hold. Results from his earlier GoF research on the H5N1 influenza virus led Japanese officials to stockpile a vaccine to protect against the emergence of this strain, he says.

“But everything we saw about H5N1 prior to those experiments should have led to vaccine stockpiling,” Relman says, cautioning against a hasty lifting of the pause. “When we talk of benefits, they must be potent and immediately available to all. There are some experiments that should not be done at all, but we’re talking of a very, very small set. We have to be good stewards of the ecosphere.”

The vehement opposition to some kinds of influenza research does not seem to extend to GoF research involving MERS and SARS. “MERS is not as high profile as flu,” says Mark Denison of Vanderbilt University in Nashville, Tenn., who called for a more case-based approach to imposing pauses. Unlike the influenza virus, “there is no vaccine, therapeutics, or small-animal model” for MERS. The pause “endangers the development of a vaccine for MERS,” adds Ralph Baric of the University of North Carolina, Chapel Hill. “Coronaviruses and flu are different, and I hope regulators will recognize the differences between them.”

Beyond this focused debate about benefits from specific types of GoF research are broader safety and security concerns. What if GoF research produced a more dangerous flu or SARS virus, and it fell into the wrong hands? “We’ve been kicking the can down the road,” says Robert Lamb of Northwestern University in Evanston, Ill. “What is the path forward? We need to develop enduring structures to air diverse points of view.” Whether NSABB can again serve that purpose or another forum needs to be developed remains an open issue.

RESEARCH ADVANCES

Pathogenesis Puzzle: Norovirus Infects B Cells, Needs Bacterial Factors

Carol Potera

The notorious norovirus, long known as an agent responsible for causing debilitating gastrointestinal disease, surprisingly infects B cells of the immune system that lie beneath the gut epithelium rather than the gut itself, according to virologist Stephanie Karst of the University of Florida, Gainesville, and her collaborators there and at the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga. Details appeared November 7, 2014 in Science (doi:10.1126/science1257147). Its targeting of immune system cells raises questions about norovirus pathogenesis and poses new challenges to efforts to prevent or combat infections that this virus causes—an estimated 20 million each year in the United States.

This research began more modestly with efforts to cultivate norovirus in vitro, according to Karst. After trying mouse B and epithelial cells, she and her collaborators learned that the virus will replicate only in B cells, provided they are supplemented with bacterial histo-blood group antigen (HBGA). Subsequently, they learned that mutant mice lacking B cells resist norovirus infection better than mice with intact B cells. Additionally, norovirus replication is reduced 60-fold in antibiotic-treated mice. These findings suggest that norovirus infects B cells and intestinal bacteria enhance these infections, she says.

Human norovirus behaves similarly. GI.4-Sydney, the current dominant human strain circulating worldwide, replicates in human B cells, but only when H antigen, a type of HBGA carried on the surface of the common gut bacterium Enterobacter cloacae, is present, allowing norovirus to attach to B cells, according to Karst. Escherichia coli, which lacks H antigen, fails to stimulate norovirus infection. Other viruses, including poliovirus, reovirus, and mouse mammary tumor retrovirus, also require bacteria to replicate, she says. “Bacterial stimulation of viral intestinal infections is a new emerging theme,” says Karst.

“The missing link needed to move the norovirus field forward is now in hand,” says Stacey Schultz-Cherry of St. Jude Children’s Research Hospital in Memphis, Tenn. The system for culturing norovirus in vitro along with the realization that it infects B cells “will allow us to create vaccines and antiviral treatments,” she adds. “This is incredibly exciting.”

MINITOPIC

Treating Mice with Modified Aminoglycoside Avoids Hearing Loss

By modifying and thus interfering with the ability of aminoglycoside antibiotics to enter “hair” cells within ears, hearing loss attributable to these drugs can be reduced by as much as 17-fold, according to Anthony Ricci and Alan Cheng of Stanford University Medical Center in Stanford, Calif., and their collaborators. “We targeted sites on the drug molecule that were not involved in the antimicrobial activity that kills off infection,” Ricci says. “This allowed us to reduce toxicity to the ear while retaining antimicrobial action.” He and his collaborators made nine derivatives of sisomicin, a widely used aminoglycoside, the majority of which retained their antimicrobial activity. One of them, designated N1MS, is considered the most promising thus far, and it remains effective at treating urinary tract infections when tested in mice, but no longer causes deafness. Details appeared January 2, 2015 in the Journal of Clinical Investigation (doi: 10.1172/JCI77424).