Small molecule, big advance against Marburg virus

Marburg virus, like other filoviruses, causes hemorrhagic fever and has a fatality rate as high as 90%. Filoviruses are normally transmitted between individuals by blood or body fluids but are also infectious in aerosol form, which means they pose the risk of becoming a global health threat as well as being used as agents of biological warfare or terrorism. Given these possibilities, the lack of vaccines or therapies for filovirus infection is a great concern. Developing filovirus countermeasures is a top priority for the US Army Medical Research Institute of Infectious Diseases (USAMRIID; Fort Detrick, MD), said USAMRIID commander Col. Erin P. Edgar in a press release, and USAMRIID scientists recently reported new progress toward achieving that goal.

The group, led by Sina Bavari, showed that a synthetic small-molecule inhibitor of viral RNA polymerase activity, called BCX4430, protected cynomolgus macaques from Marburg virus infection without adverse effects (*Nature* doi:10.1038/nature13027; published online 2 March 2014). The drug was administered intramuscularly and was effective even when administered up to 48 h after exposure to Marburg virus. These characteristics make it potentially suitable for use during outbreaks.

Guinea pigs exposed to Marburg virus either by intraperitoneal injection or by aerosol inhalation were also protected from infection by administration of BCX4430 within 48 h of exposure. BCX4430 also showed efficacy against other filoviruses, including Ravn virus and Ebola virus, as well as Rift Valley fever virus (belonging to the related family of bunyaviruses) in rodents. Intramuscular administration of BCX4430 protected mice from all three of these viruses, and oral administration was also effective against Ebola virus infection in mice. In cell-based studies, BCX4430 showed specific antiviral activity against multiple virus families other than filoviruses and bunyaviruses, including arenaviruses, orthomyxoviruses, picornaviruses, paramyxoviruses, flaviviruses and coronaviruses. The researchers are carrying out further studies to evaluate the *in vivo* efficacy of BCX4430 against these and other virulent viral pathogens.

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BCX4430 was developed by BioCryst Pharmaceuticals, Inc., in collaboration with the USAMRIID scientists. It inhibits viral RNA polymerase activity indirectly after being incorporated into viral RNA strands, causing premature termination of transcription and replication. Col. Edgar indicated that the study "demonstrates the importance of government-industry collaboration," continuing, "[w]hen federal assets like USAMRIID team up with cutting-edge partners in private industry, we can make real progress."

Monica Harrington

SPYING ON THE GUT WITH A BACTERIAL REPORTER

The human gut comprises an intricate ecosystem of trillions of bacteria that continuously sense and respond to signals from their environment. Some of these signals could provide valuable information for the detection of gastrointestinal conditions such as Crohn's disease that have been difficult to diagnose early and accurately.

Now scientists have found a way to harness these bacterial responses to the goings-on in the gut, using synthetic biology. In a collaboration between Harvard University's Wyss Institute for Biologically Inspired Engineering and Harvard Medical School, both in Boston, MA, a newly engineered strain of *Escherichia coli* bacteria was developed that can record a specific biological event in the gut and report back the information later, almost like a memory.

The team, led by Pamela Silver, genetically inserted a transcriptional switch into the *E. coli* that 'flips' when it senses a specific environmental cue. This switch came from lambda phage, a virus that commonly attaches to the bacterium. After invading *E. coli*, lambda lies dormant, its DNA biding its time in the *E. coli*'s genome. But when the bacterium's DNA is damaged, such as after exposure to an antibiotic, the genomic switch flips, changing the expression of particular proteins in the bacterial cell. Later, one can check whether the switch has been flipped in the *E. coli* by checking the cell's protein levels.

Jeff Way, coauthor of the paper, said, "Nature has a tried and true blueprint for memory systems if you know where to look." Added lead author Jonathan Kotula, "We knew the lambda switch would be a great candidate for the memory element, and we simply tweaked it to meet our needs."

The researchers tested their switch in a strain of *E. coli* isolated from the mouse's gut so that it would be robust enough to compete with the animal's native bacteria. After engineering its genome to incorporate the switch, they administered the bacteria back to the mouse, which had also been given the chemical anhydrotetracycline. Within a few hours, the bacteria sensed the chemical and flipped the genetic switch, which then stayed flipped for about a week (*Proc. Natl. Acad. Sci. USA* doi:10.1073/pnas.1321321111; published online 17 March 2014). This was long enough for scientists to recover fecal samples from the mouse and test them in order to determine whether the chemical signal had been detected and recorded. "This achievement paves the way toward living monitors programmed using synthetic gene circuits," said Silver.

Kara Rosania