Antiviral Compound Protects Nonhuman Primates Against Ebola Virus

Scientists protected 75 percent of rhesus monkeys infected with Ebola virus that were treated with a compound targeting the expression of VP24, a single Ebola virus protein—suggesting that VP24 may hold the key to developing effective therapies for the deadly disease.

The study, which appears in today’s edition of mBio, the online journal of the American Society for Microbiology, was conducted by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in collaboration with biotechnology firm Sarepta Therapeutics, Inc.

For over a decade, USAMRIID and Sarepta have been collaborating to develop and test a class of antisense compounds known as phosphorodiamidate morpholino oligomers (or PMOs), according to principal investigator and first author Travis K. Warren, Ph.D., of USAMRIID.

“Antisense drugs are designed to enter cells and eliminate viruses by preventing their replication,” Warren said. The drugs act by blocking the translation of critical viral genetic sequences, preventing the protein from being made and giving the infected host time to mount an immune response and clear the virus, he explained.

In work previously published in the journal Nature Medicine, the team demonstrated that a combination PMO called AVI-6002—a product targeting genes that code for two proteins, VP24 and VP35—prevented Ebola virus infection in rhesus monkeys. The current study compared the activity of the individual components against that of the combination treatment. In this experiment, animals were treated with AVI-7537, which targets VP24 alone; AVI-7539, which targets VP35 alone; or AVI-6002, which targets both proteins. A fourth group served as the untreated control. Animals were treated once a day for up to 14 days beginning approximately one hour after virus exposure.

Seventy-five percent of the animals treated with AVI-7537 and 62 percent of those receiving the combination treatment, AVI-6002, survived, said the authors. However, all animals in the control group and those treated with AVI-7539 succumbed to the infection at a rate that was similar to the untreated group.

Sina Bavari, Ph.D., USAMRIID Science Director and the paper’s senior author, noted that this work further substantiates recent data demonstrating that VP24 may be a key virulence factor encoded by Ebola virus. “This study shows that targeting VP24 alone may lead to the
development of more effective medical countermeasures against Ebola virus,” Bavari said. “In addition, future development of these potential treatments will be greatly simplified if only one PMO is required.”

Ebola virus causes severe hemorrhagic fever in humans and nonhuman primates with high mortality rates and continues to emerge in new geographic locations, including West Africa, the site of the largest outbreak to date. Nearly 22,500 confirmed, probable and suspected cases have been reported in Guinea, Liberia and Sierra Leone, with almost 9,000 reported deaths, according to the World Health Organization.

Although several clinical trials are currently underway, there are no licensed vaccines or therapies against Ebola virus. According to Michael Wong, M.D., Senior Medical Director of Infectious Diseases at Sarepta, the AVI-7537 compound was found to be safe and well tolerated at the doses tested in a Phase 1a clinical trial. AVI-7288 and AVI-7100, two other clinical stage PMO compounds for Marburg virus and influenza, respectively, demonstrated similar safety and pharmacokinetics. Development of AVI-7537 has been suspended because of government fiscal constraints, according to Wong. Further development is planned should funding mechanisms be secured.

Research on Ebola virus is conducted under Biosafety Level 4, or maximum containment conditions, where investigators wear positive-pressure “space suits” and breathe filtered air as they work. USAMRIID is the only laboratory in the Department of Defense with Biosafety Level 4 capability, and its research benefits both military personnel and civilians.

USAMRIID’s mission is to provide leading-edge medical capabilities to deter and defend against current and emerging biological threat agents. The Institute plays a key role as the lead military medical research laboratory for the Defense Threat Reduction Agency’s Joint Science and Technology Office for Chemical and Biological Defense. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

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