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RNAi wins an Ebola challenge

By Tim Fulmer, Senior Writer

A team of North American corporate, academic and military researchers has used RNAi to treat Ebola virus infection in nonhuman primates.[1] With proof of concept in hand, the researchers now hope to carry out additional animal studies to get a better handle on the applicability of the approach in the field.

Ebola, an RNA virus that causes hemorrhagic fever, is highly virulent. Patients present with general flu-like symptoms and rapidly develop severe bleeding and coagulation disorders as well as significant liver damage. At least 50% die from hypovolemic shock 14–21 days postinfection.[2]

There are no vaccines or therapeutics available to treat Ebola. However, the viral genome is well characterized and encodes only eight proteins, two of which—the L protein and VP35—comprise the RNA polymerase complex. Targeting those proteins could block viral RNA synthesis and thus prevent viral replication.

To explore the feasibility of blocking expression of the proteins that drive viral replication, RNAi company **Tekmira Pharmaceuticals Corp.** teamed up with Ebola researchers at the **Boston University School of Medicine** and the **U.S. Army Medical Research Institute of Infectious Diseases** (USAMRIID).

In previous work, the team found that short interfering RNAs targeting the L protein, as compared with scrambled siRNA, completely protected guinea pigs against viremia and death when given one hour after a lethal Ebola challenge.[3] Importantly, the siRNAs needed to be encapsulated in stable nucleic acid lipid particles (SNALPs), which are liposome-like vesicles designed by Tekmira that improve delivery of siRNA to target tissues.

SNALPs also avoid off-target immunostimulatory effects and toxicity that can accompany delivery of nonencapsulated siRNA.

Following the guinea pig data, the question was whether the siRNA-SNALP construct could treat Ebola infection in nonhuman primates. However, rather than test the same siRNA-SNALP combination used in the guinea pigs, the researchers chose to study a modified SNALP that encapsulated siRNAs targeting L protein and two additional Ebola proteins—VP24 and VP35.

The expectation was that the cocktail would have a better chance of showing a therapeutic effect than a single siRNA. Indeed, 100% of rhesus macaques survived after 7 treatments. The therapeutic was dosed 30 minutes after Ebola challenge and then on each of the 6 days following infection. The control animal that received SNALPs containing nonspecific siRNA died on day 10.

Another challenge study showed a 66% survival rate for macaques that received 4 postexposure treatments. Results were published in *The Lancet*.

The animal studies were led by Thomas Geisbert, professor of medicine and associate director of the National Emerging Infectious Diseases Laboratories at the Boston University School of Medicine, and Lisa Hensley, chief of viral therapeutics in the virology division of USAMRIID. The design of the siRNA-SNALP formulations was carried out by a Tekmira research team led by EVP and CSO Ian MacLachlan.

Studying scenarios

The university and USAMRIID researchers plan to run additional primate studies, and Tekmira will produce the siRNA-SNALP formulations.

Corresponding author Geisbert said it will be important to look at administering the SNALP cocktail beginning at later time points following infection.

"One of our macaque studies shows 100% survival when treatment begins 30 minutes after Ebola challenge. While that result provides excellent proof of principle for the strategy, we now want to look at scenarios where treatment begins 24 or 48 hours postexposure or even later. Those studies should give us a better idea of the strategy's flexibility in the field, where you potentially face a wider variety of postexposure scenarios," he said.

Additional studies in guinea pigs and macaques also could be useful for showing the relative contributions of each of the siRNAs to the overall therapeutic effect of the cocktail, Hensley told *SciBX*. "We thus plan to study the three siRNAs individually and under different treatment regimens. It may turn out that two of the siRNAs have just as potent antiviral activity as the entire cocktail. If so, we could simplify the formulation," she said.

In the longer term, the researchers would like to combine the siRNA-SNALP constructs with other compounds that treat the bleeding and coagulation pathologies characteristic of later-stage infection. "In particular, we might combine our siRNA approach with coagulation-modifying compounds that help restore vascular homeostasis in clinical-stage disease," said Hensley.

Meanwhile, Tekmira plans to develop SNALP-siRNA formulations that target other, undisclosed filoviruses in addition to Ebola, according to president and CEO Mark Murray.

Since the beginning of 2009, Tekmira has nonexclusively licensed its SNALP siRNA delivery platform to **Bristol-Myers Squibb Co.**, **Pfizer Inc.** and **Roche**.

The U.S. government, Boston University and Tekmira have filed for two patents, one covering siRNA silencing of filovirus gene expression and one covering compositions and methods for silencing Ebola. The licensing status of the Ebola-related IP is undisclosed.

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REFERENCES

1. Geisbert, T. *et al. Lancet*; published online May 29, 2010; doi:10.1016/S0140-6736(10)60357-1
Contact: Thomas Geisbert, Boston University School of Medicine,

Boston, Mass.
e-mail: geisbert@bu.edu

2. Sullivan, N. *et al. J. Virol.* **77**, 9733–9737 (2003)
3. Geisbert, T. *et al. J. Infect. Dis.* **193**, 1650–1657 (2006)

COMPANIES AND INSTITUTIONS MENTIONED

Boston University School of Medicine, Boston, Mass.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Tekmira Pharmaceuticals Corp., (TSX:TKM) Burnaby, British Columbia, Canada
U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Md.