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VIRAL INFECTION

New tricks to treat Ebola

Although there are currently no major outbreaks of Ebola, new ones are likely to emerge in the coming years. Ideally, treatments will be strain-adaptable. A new paper in *Nature Microbiology* demonstrates that a *Sudan ebolavirus* (SUDV)-targeting small interfering RNA (siRNA) can prevent death in non-human primates (NHPs) infected with a lethal dose of SUDV, even if administered when the animals have overt signs of disease.

> “all four animals treated with siVP35-LNP 4 days after infection… survived”

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Minor modifications to the siRNA target sequence could result in strain-specific treatments.

In comparison with *Zaire ebolavirus* (EBOV), treatments for SUDV — the cause of three outbreaks since 2010 — have been underexplored. To develop a novel siRNA-based therapeutic, the authors of the current study first used a human liver carcinoma cell line to examine the mRNA cleavage efficiency of siRNA molecules targeting transcripts of sequences within the coding regions of the viral L polymerase, viral protein 24 (VP24), VP35 or nucleoprotein. As siRNAs targeting L polymerase transcripts only modestly reduced levels of this mRNA, this target was not pursued further.

The top siRNA candidates targeting each of the other three RNAs were then chemically modified to remove immunostimulatory motifs and tested in NHP models. Hepatocytes are a major site of SUDV replication, and lipid nanoparticles (LNPs) efficiently deliver their payloads to this cell type. Although siRNA-LNPs have been tried in other filovirus diseases with limited therapeutic success, new LNP formulations have improved efficacy, so the authors used these molecules to deliver their siRNAs in NHPs. Animals were infected with a lethal dose of SUDV and treated with siRNA-LNP daily for 7 days starting at 24, 48 or 72 hours post-infection. The LNP-encapsulated siRNA targeting VP35 (siVP35-LNP) was the most effective of the three: all six animals treated with this siRNA survived, whereas 50% of the animals treated with siRNA targeting VP24 or nucleoprotein (one of two treated animals for each time point) succumbed to the disease, as did all the untreated animals.

In an outbreak setting, treatments must be effective in symptomatic patients. The authors therefore tested whether siVP35-LNP was still effective in animals with evidence of disease. NHPs succumb to the virus 8–10 days post-infection and have signs of disease by day 4–5. Remarkably, all four animals treated with siVP35-LNP 4 days after infection, and two of the four animals treated 5 days after infection, survived.

siVP35-LNP is thought to directly reduce viral load, allowing time for the adaptive immune response to resolve the infection. At 24 hours after initiation of siVP35-LNP dosing, viral loads were reduced by up to 4 log10 units. Notably, the siVP35-LNP-treated animals that succumbed to the disease had higher viral loads when treatment was initiated than did those who overcame the disease. Together, these data suggest that siVP35-LNP may be effective, but only up to a certain viral load.

Numerous treatments for EBOV are currently in development following the 2015–2016 West African outbreak. This study describes an effective treatment for SUDV that could potentially be used, with minor modifications following outbreak-specific sequencing, to treat new outbreaks of SUDV. The strategy has also been examined for the treatment of EBOV, and could potentially be adapted to other species of Ebola such as Bundibugyo or newly discovered strains of other filoviruses.

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ORIGINAL ARTICLE Thi, E. P. *et al.* Rescue of non-human primates from advanced *Sudan ebolavirus* infection with lipid encapsulated siRNA. *Nat. Microbiol.* **1**, 16142 (2016)