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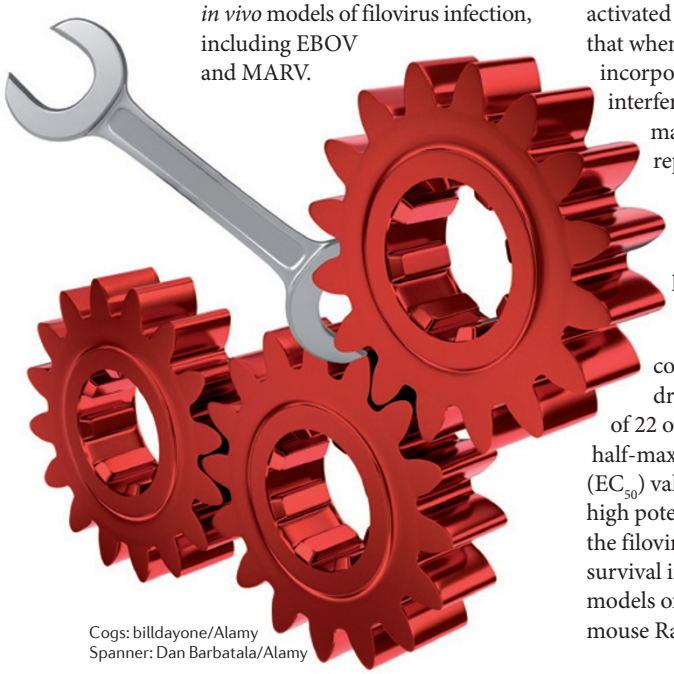
ANTIVIRAL DRUGS

Spanner in the works of filovirus infection

Filoviruses such as Ebola virus (EBOV) and Marburg virus (MARV) cause viral haemorrhagic fever and are responsible for some of the highest fatality rates of all human pathogens. At present, however, there are no drugs licensed for use against filoviruses in humans. Furthermore, potential therapies in development are based on virus-specific strategies that would limit their applicability during outbreaks involving multiple filoviruses, which have already occurred in outbreak-prone regions of the world. Warren and colleagues have now synthesized a novel nucleoside analogue, BCX4430, which confers protection in numerous *in vivo* models of filovirus infection, including EBOV and MARV.



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BCX4430 was identified from a library of small molecules that were designed to inhibit the activity of viral RNA polymerase, an enzyme that is essential for the reproduction of RNA viruses such as filoviruses. The authors found that BCX4430 is phosphorylated in cultured cells, just as naturally occurring nucleosides are, to BCX4430-TP (triphosphate), which is subsequently combined into nascent viral RNA. Moreover, BCX4430-TP inhibited the transcriptional activity of the RNA polymerase of hepatitis C virus by inducing premature termination of RNA chain synthesis. These results support the author's hypothesis that BCX4430 is activated by phosphorylation, and that when the active BCX4430-TP is incorporated into the viral RNA, it interferes with RNA transcription machinery and blocks virus replication.

The authors went on to test BCX4430 against a range of both negative- and positive-sense RNA viruses (including five filovirus variants) using high-content image analysis. The drug inhibited the replication of 22 of the 24 tested viruses, with half-maximal effector concentration (EC_{50}) values below 70 μM and with high potency (EC_{50} <12 μM) against the filoviruses. BCX4430 increased survival in four different rodent models of filovirus infection; in the mouse Ravn virus model, 75–100% protection was conferred when the 9-day treatment was initiated 4 hours before, or up to 96 hours after, infection.

Finally, the authors tested the drug in the cynomolgus macaque MARV model, which more accurately mimics the filovirus-induced disease observed in humans. Animals (six per group) were treated twice daily with intramuscular doses (15 mg per kg) of vehicle or BCX4430, starting 1, 24 or 48 hours after MARV infection. The virus was lethal in all six animals treated with vehicle; however, all but one of the 18 animals that were treated with BCX4430 survived. Serum levels of viral RNA and markers of virally induced liver damage were lower in BCX4430-treated animals than in controls. In addition, treatment with BCX4430 prevented the blood coagulation disorders observed in control MARV-infected macaques, indicating that the drug may help protect against haemorrhaging.

BCX4430 was well tolerated *in vivo*, showed good metabolic stability in a human liver enzyme assay, and exhibited no mutagenicity or incorporation into human RNA or DNA *in vitro*. The authors also emphasize that the drug's intramuscular route of delivery means it can be rapidly absorbed and easily administered in the event of a filovirus outbreak. BCX4430's effects against EBOV and other filoviruses in non-human primates are currently being evaluated to support its entry into Phase I trials.

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ORIGINAL RESEARCH PAPER Warren, T. K. *et al.* Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. *Nature* http://dx.doi.org/10.1038/nature13027 (2014)