

 INFECTIONOUS DISEASE

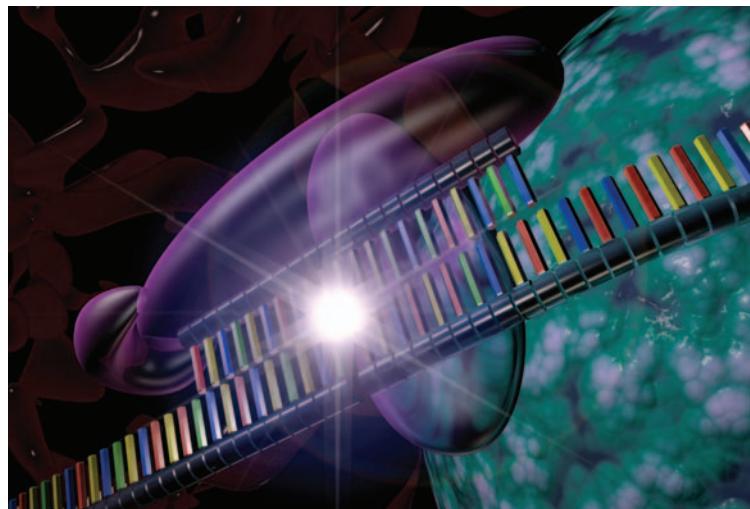
## Topical microbicide based on siRNA

The sexually transmitted herpes simplex virus-2 (HSV-2) causes infections resulting in significant morbidity, and is an important co-factor in the global spread of HIV. In a recent landmark paper in *Nature*, Judy Lieberman and colleagues describe a short interfering RNA (siRNA)-based microbicide, which proved effective against vaginal HSV-2 challenge in a mouse model. This study might lead to a breakthrough in the development of a novel type of microbicide to contain the spread of sexually transmitted viral diseases.

Several recent papers have shown impressive results for the treatment of viral lung infections with siRNA, suggesting that mucosal tissues are efficient at taking up siRNA. To explore the possibility of delivering siRNA to vaginal tissue, Palliser *et al.* treated green fluorescent protein (GFP)-expressing mice intravaginally with GFP-specific siRNA complexed with a transfection lipid. The result was an impressive downregulation of GFP expression in the vaginal and cervical epithelium, as well as submucosal tissues, and a surprisingly long-lasting silencing effect.

Extending this strategy to combat a sexually transmitted virus, several siRNAs directed against essential genes of HSV-2 were assessed for their capacity to inhibit HSV-2 replication *in vitro*. The most effective siRNAs (four- to fivefold reduction in viral replication) were intravaginally applied to mice 2 hours before and 4 hours after lethal vaginal challenge with HSV-2.

As evaluated by clinical disease scoring and by survival, the treatment regimen resulted in highly significant protection: whereas 75% of mock-



Original image from the RNAi animation by Arkitek Studios (<http://www.nature.com/focus/rnai/animations/index.html>).

treated control mice died, only 25% of mice treated with the specific siRNA died. Although just over 50% of the treated mice showed signs of infection, the surviving mice were free of disease at day 11 after challenge.

There was no evidence of inflammation caused by siRNA alone, or for the emergence of viral escape mutants after treatment. Even post-exposure treatment (3 and 6 hours after viral challenge) with a combination of two different HSV-2-specific siRNAs conferred significant protection, which is an important finding given that one of the main problems with current microbicides is their requirement to be administered before sexual intercourse.

Much work remains to be carried out to explore the effect of menstrual variation on siRNA-mediated viral silencing and the durability of this effect, to address the issue of viral sequence variability, and to formulate siRNA in a vehicle acceptable for vaginal retention. An extension of

these results to the formulation of an HIV microbicide would also require further investigation into the cell types amenable to siRNA uptake in vaginal tissues. However, the fact that these experiments were successful without optimization of the siRNA for silencing or resistance to endogenous RNases demonstrates that siRNAs can be attractive candidates for the active component of a novel type of microbicide. Targeting HSV-2 as a co-factor for HIV transmission, and the potential of extending these studies to the development of an HIV microbicide, hold promise for the development of a new weapon in the global battle against the HIV epidemic.

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**ORIGINAL RESEARCH PAPER** Palliser, D. *et al.*

An siRNA-based microbicide protects mice from lethal herpes simplex virus 2 infection. *Nature* doi:10.1038/nature04263 (2005)

**FURTHER READING** Bitko, V. *et al.* Inhibition of respiratory viruses by nasally administered siRNA. *Nature Med.* 11, 56–62 (2005)