

Microbicides 2008: Third-generation microbicides might act as 'bacterial vaccine'

Gus Cairns, Tuesday, March 04, 2008

Studies are underway of genetically engineering naturally-occurring vaginal bacteria to produce microbicides against HIV, and in one case such a strategy has already proved effective in preventing HIV infection in monkeys, the Microbicides 2008 Conference heard last week in Delhi.

Qiang Xu of 'bacterial therapeutics' company Osel, Inc. of California reviewed the latest progress on getting naturally-occurring *Lactobacillus* bacteria to produce the microbicide Cyanovirin-N.

Cyanovirin-N is a protein originally derived from algae that has shown promising efficacy as both a vaginal and a rectal microbicide. However it is a large molecule that might be prohibitively expensive to develop as a gel.

Dr Xu's team inserted a gene into the genome of *Lactobacillus jensenii* 1153, a variety of the naturally-occurring bacteria that colonise the vagina. These already confer some protective effect by generating hydrogen peroxide, which has a microbicidal effect – see [this report](#) for a study of lactobacilli presented at CROI.

The researchers were able to induce the modified bacteria to colonise the vaginas of female rhesus macaques (which naturally harbour lactobacilli) for over two months. In vitro experiments showed that the Cyanovirin-N produced inhibited CCR5-tropic HIV, with a 50% inhibitory concentration one one nanomolar, which is comparable to systemic antiretrovirals.

Studies are needed to establish whether the colonizing bacteria can produce enough Cyanovirin-N in situ to have a microbicidal effect, and also on fermentation techniques to produce bulk amounts of the bacteria. Asked about the possibility of escape of genetically-modified bacteria, Dr Xu said that they could be completely cleared with a short course of the antibiotic azithromycin and did not survive outside the body in water or air.

Another novel approach is to engineer altered versions of naturally-occurring CCR5 inhibitors which act, like maraviroc and vicriviroc, the ones developed as treatments, by blocking a co-receptor molecule needed by HIV to gain entry to CD4 cells.

The natural ligand (molecule that naturally attaches to) the CCR5 co-receptor is the chemokine molecule RANTES, which acts as a means of mobilising immune-cell activity in cases of injury or infection.

Because of RANTES' immune activity and short half-life it cannot be used as an anti-HIV treatment or preventative in itself.

Dr Oliver Hartley of the University of Geneva in Switzerland has been developing an analogue or altered version called PSC-RANTES as an HIV treatment. This works by inducing CD4 cells to downregulate their CCR5 receptors, in other words to pull the molecules inside the cell surface where they can no longer act as chemokine or viral receptors.

In experiments in monkeys, PSC-RANTES was shown to protect against transmission in the macaque model – [see this report](#) for progress up to the previous microbicide conference. However PSC-RANTES still acts as an immune-signalling chemical (it excites immune activity) and would also be impossible to produce in bulk cost-effectively.

Hartley generated a variety of other RANTES analogues and has found one called 5P12-RANTES that can be manufactured in bulk by fermentation methods. It acts as a CCR5 inhibitor but it neither induced CCR5 downregulation nor immune activation. It shows equivalent activity to PSC-RANTES and in the macaque model, when applied topically as one-micromolar solutions in saline, protected five out of five female macaques from vaginal SHIV infection.

Finally, in experiments combining both approaches, Luca Vangelista of the San Raffaele Scientific Institute in Italy has engineered the same lactobacilli as in the Xu study to produce human-type RANTES and is currently engineering another variant that will produce an analogue called C1C5-RANTES, and also small peptides – sections – derived from RANTES to see if these have anti-HIV activity.

References

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