Genetically modified bacteria to protect against HIV in women

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Never before has humanity faced a disaster on such a scale as HIV/AIDS. The disease has killed around 20 million people. If the pandemic continues unchecked, there will be 45 million new infections by 2010 and nearly 70 million deaths by 2020. Prevention of infection and care for the infected are the key elements of today's massive fight against HIV.

The cause of the disease was identified as a human retrovirus. Several key scientific developments resulted in the identification of CD4, a membrane protein on human immune cells[1] (the 'helper T cells' of the immune system) that HIV specifically binds before infecting the cells. Since then, scientific research has successfully produced an impressive array of antiretroviral drugs that can control HIV and delay the onset of AIDS and death. However, these drugs are not a cure, and can cause a host of side effects from prolonged use, and may encourage the emergence of drug-resistant strains of HIV. Scientists are therefore pursuing the design of more effective drugs. An important goal is the development of a simple, affordable and effective vaccine against HIV, which has been on the anvil for the last two decades; but a successful product still appears to be many years away[2,3]. In the absence of a vaccine, and the lack of condom use in many settings, researchers are hoping that microbicides – also called *chemical condoms* – may prove a viable option[4]. These are substances that can be applied as a cream, gel or pessary to the vagina or rectum, to kill or immobilize HIV. If proved feasible, microbicides would put women in control of their reproductive health. There are now some 60 different microbicides in the pre-clinical and clinical pipeline, with three undergoing large-scale clinical trials. No final product has been approved yet.

Recently, a novel approach that exploits a naturally occurring defence mechanism within the vagina was conceived by Peter Lee and colleagues for the prevention of HIV[5]. The hypothesis proposed was that trapping HIV by bacteria that normally coat the interior of the vagina, would prevent transmission by stopping the virus from reaching target cells. The trapping of the virus could be enhanced by adding the gene for CD4, a protein that specifically latches on to HIV by interacting with the envelop protein gp120 that projects from the surface of HIV. This simple idea was based on the premise that all women carry HIV-fighting *Lactobacillus* bacteria in the vagina at the main site of HIV infection. These bacteria excrete the antimicrobial chemicals, lactic acid and hydrogen peroxide (Figure 1). Research has shown that women with little or no lactobacillus have a higher risk of contracting HIV than those with high levels of the bacteria[6]. Osel, a company based in California, already markets freeze-dried tablets of unmodified *L. jensenii* to fight vaginal infections.

The results[6] reported by these scientists supported their hypothesis (Figure 2). There are three major species of lactobacillus[4]. *L. crispatus*, *L. jensenii*, and *L. gasseri*, that could be isolated from the vaginal mucosa of healthy women. *L. jensenii* was used to produce the protein CD4, which binds to the HIV virus. The protein was expressed in native conformation as shown by its ability to interact with monoclonal antibodies directed at conformational epitope/s and interacted with HIV type 1 (HIV-1) gp120. *In vitro* tests showed that the genetically engi-

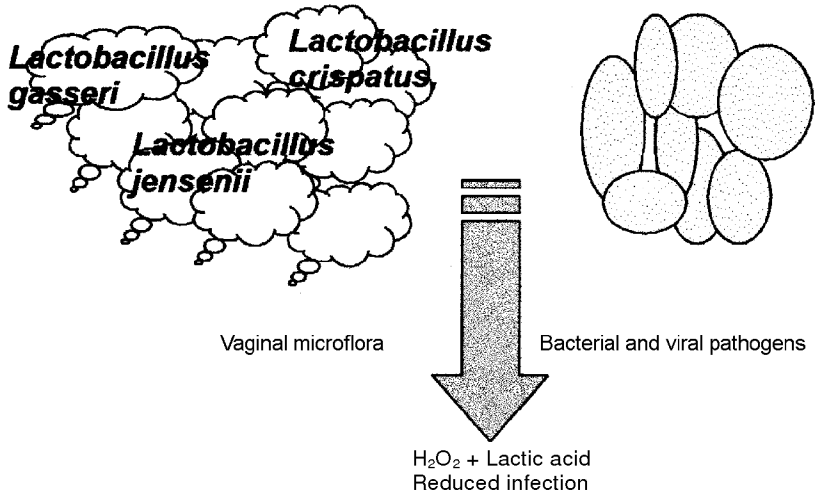

Figure 1. Schematic representation of natural defence offered by vaginal microflora.

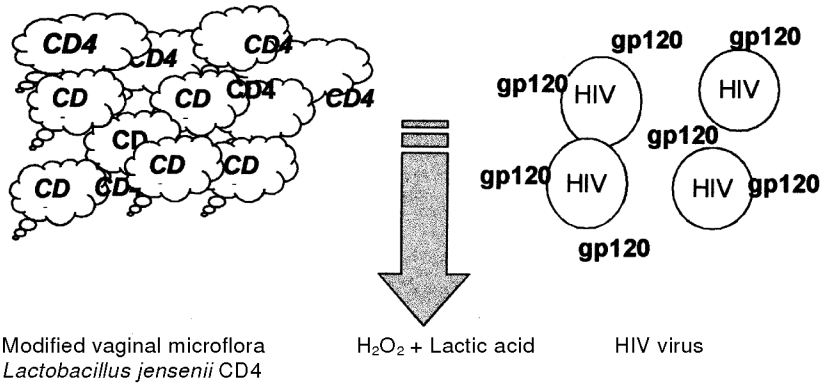

Figure 2. Schematic representation of enhanced reduction in HIV infection with modified bacteria expressing CD4.

neered bacteria secreted CD4 and reduced the rate of HIV infection in cells by at least half as assessed by single-cycle infection assays using HIV-1_{HxB2} carrying a luciferase reporter gene. Further, co-incubation of the engineered bacteria with recombinant HIV-1_{HxB2} reporter virus led to a significant decrease in virus infectivity of HeLa cells expressing CD4-CXCR4-CCR5. They are now trying to make the technique more effective by engineering *Lactobacillus* to express CD4 on its surface. Preliminary studies using monkeys showed the engineered bacteria grew well and were safe. If it works, the bacteria could be made into a vaginal suppository a woman could quietly use to protect herself. Only extended clinical trails could demonstrate if the modified bacteria work effectively in the vagina in the presence of mucus and semen, and other sexually transmitted pathogens. Other hurdles include getting clearance for the use of genetically modified bacteria.

Clearly, this technology holds tremendous promise. These bacteria could be modified to express other HIV-binding proteins, and also to prevent the transmission of other viruses, including human papilloma virus and herpes. It is also possible to prepare a vaccine by genetically modifying these bacteria. Only time will reveal if this idea could be translated into a viable product or would be forgotten as yet another promising approach buried within the covers of scientific journals.

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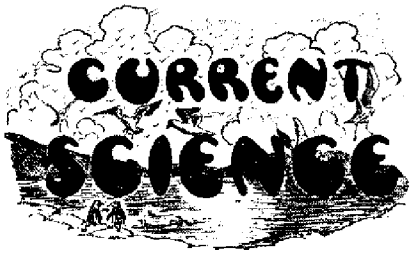

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H. E. Lord Wavell on Indian Science

Inaugurating the Thirty-first Session of the Indian Science Congress, His Excellency Lord Wavell said: "India, one of the oldest civilisations, has perhaps felt the impact of modern science later and less than any other great people. A large proportion of her population still lives the old life untouched by the vast changes of the century. Her realm has been of the spirit rather than of the earth. It may be said of the West hereafter that we took too much from India materially and too little spiritually.

But if India is to play the part in the world to which her size, her population, her history and her position entitle her, she too must make every possible use of scientific advancement.

She has already produced many great scientists, she bears many more in her fertile womb. Her contributions to science have always been on the side of peace and progress. She has everything to gain by combining modern science with her old culture indeed her traditional outlook should enable her to make an increasingly fine and characteristic contribution to natural knowledge. Indian science has made in fact a very remarkable stride forward during the last twenty-five years, as is shown by the foundation of many new societies, new journals and new departments of science in universities and under Government.

In this war science has played a great role in India as elsewhere. It has made an splendid contribution to maintaining the health of the fighting men, through the activities of such bodies as the Malaria Institute, the Indian Research Fund Association, the Nutrition Laboratories at Coonoor, and others. It has also played an important part in munitions production and in solving problems of supply. As an ex-Commander-in-Chief, I should like to thank Indian science for the invaluable assistance it has given to the armies in the field.

It must play a great part also in post-war development. The coming years will be vital to India. She must learn to make use of her abundant resources with the aid of science. Science is the most international of all human interests.

Professor Hill has himself said in an address elsewhere: 'I believe that the pursuit of knowledge for the welfare of mankind is one of the greatest agents for goodwill between men in every land.' It is in that belief that he is here to-day.

This Session of the Indian Science Congress has a momentous task to perform; to discover how best to bring the aid of science to the development of India's great resources in agriculture and industry, to the improvement of health and to social advancement and prosperity.