

# Bioengineering Bacteria for Drug Delivery

## Osel Turns *Lactobacillus* into a Local Drug Factory for the Prevention of HIV Infection

Carol Potera

Osel (www.oselinc.com) in Santa Clara, CA, works in the emerging field of bacterial therapeutics, focusing on the development of live bacterial products for the prevention and treatment of urogenital and gastrointestinal diseases.

The term bacterial therapeutics distinguishes Osel's approach from probiotics. "People think of probiotics as health-food store products," says co-founder Peter P. Lee, M.D., an immunologist at Stanford University and acting CEO at Osel. "We apply a tremendous amount of science to our products and want to shift the mindset."

Osel's newest product uses a bio-engineered bacterium that lives in the vaginal tract of healthy women to deliver a potent drug to block HIV. "It's a novel way to think about drug delivery," Dr. Lee says.

Dr. Lee co-founded Osel in 1998 with Gary Schoolnik, M.D., an infectious disease expert at Stanford University; David Ho, M.D., director of the Aaron Diamond AIDS Research Center in New York City; and Peter Kim, Ph.D., president of Merck Research Laboratory in West Point, PA.

### Pioneering Platform

Osel's patented MucoCept platform uses genetically engineered microbes to deliver protein-based therapeutics to mucosal surfaces. The first product for this platform

### At-a-Glance

#### Osel

#### Location

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#### Phone

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#### Website

www.oselinc.com

#### Principals

**Peter P. Lee, M.D.**  
chairman and acting CEO

**Qiang Xu, Ph.D.**  
director, MucoCept research

**Tom Parks, Ph.D.**  
director, product development

#### No. of Employees

12

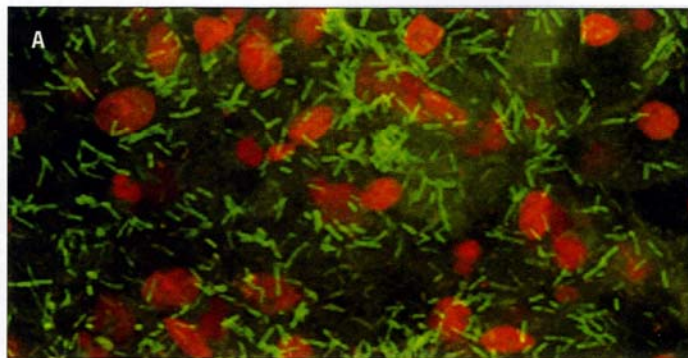
#### Focus

Osel focuses on bacterio-therapeutics, which harness the protective properties of mucosal bacteria.

uses *Lactobacillus*, the most common bacteria dwelling naturally in the vaginal tract of healthy women, protecting them from vaginosis and urinary tract infections.

Researchers at Osel inserted the gene for cyanovirin-N (CV-N), a potent inhibitor of HIV, into *Lactobacillus*. Scientists at the NCI discovered CV-N while screening natural substances to find antiviral molecules.

The bio-engineered *Lactobacillus* expresses CV-N at levels high enough to block HIV infection.



**Lactobacilli shown adhering to vaginal epithelial cells (Panel A). For visualization, lactobacilli were stained green with Syto-9, whereas epithelial cells were stained red with propidium iodide. A human vaginal isolate of *Lactobacillus jensenii* may be genetically modified as a self-renewing vehicle for mucosal delivery of a protein-based HIV inhibitor (Panel B).**

Osel researchers spent five years studying how to program *Lactobacillus* to express CV-N in large quantities. "We spent a lot of time understanding the vaginal microflora, as well as how to genetically manipulate these human strains," Dr. Lee says.

### Collaboration

They collaborated with Lawrence Berkeley National Laboratory to sequence the genome of *Lactobacillus* to identify regulatory elements and sites for chromosomal insertion. Bioinformatics and promoter-trapping strategies helped them to locate endogenous promoters to increase the secretion of CV-N. The Osel team selected a strain dubbed *L. jensenii* 1153 to manufacture CV-N.

After building an efficient expression cassette, they inserted a single copy into the *L. jensenii* 1153 chromosome in a way that stabilizes the gene, yet does not disrupt the normal functions of the bio-engineered microbe.

An endogenous promoter controls the expression of the CV-N gene, while an endogenous signal sequence directs the bac-

terium to secrete CV-N onto the mucosal surface. The bioengineered *L. jensenii* 1153 produces high levels of structurally intact CV-N. When female mice are treated with *L. jensenii* 1153, the microbe grows in the vaginal tract and produces active CV-N.

In an ongoing study, *L. jensenii* 1153 also has been shown to grow and release CV-N in Chinese rhesus macaques after vaginal inoculation. The next step is to evaluate whether *Lactobacillus* colonization prevents HIV infections, or whether macaques already infected with simian HIV show reduced viral loads after treatment. "We're trying to race toward an IND submission for clinical testing in a year," Dr. Lee says.

protest genetically engineered corn want a modified bacterium inserted into their bodies? "It's a pioneering program, and the FDA will probably raise safety concerns," says Dr. Xu.

Osel plans to address potential safety and environmental issues before seeking FDA approval. For instance, the European group designed a unique biological containment system to prevent their bacterium from entering the environment.

Osel researchers have demonstrated that their human *Lactobacillus* strain replicates poorly outside the body. The success of the MucoCept platform lies in proving that "the genetic modifications we make do not alter the bacterium's pathogenic potential or growth properties," Dr. Lee says.

A now defunct biotechnology company tried previously to develop an HIV microbicide for women by expressing CV-N in *E. coli* bioreactors, purifying it, and formulating a gel. This approach, however, proved difficult, costly, and impractical. Osel's bacterial product that colonizes the vaginal mucosa and expresses the microbicide locally will be self-renewing, inexpensive to manufacture, and able to treat women globally.

Dr. Lee foresees a tablet form of the microbicide to preserve its activity during shipping. Once inserted into the vagina, the body's fluids will trigger bacterial growth and CV-N production.

### Product Pipeline

Before the MucoCept technology, Osel designed first-generation products for women's health based on natural bacteria living on mucosal surfaces. Currently, two products, which are not genetically modified, are in clinical testing.

Osel's Lactin-V is in two Phase II trials, one for recurrent urinary tract infections and the other for recurrent bacterial vaginosis, which combined plague 15 million women yearly in the U.S. and Europe. Lactin-V contains human *Lactobacillus crispatus*, which lives naturally in the vaginal tract and secretes substances to combat infections.

Osel's CDAActin-O for the prevention of antibiotic-associated diarrhea is in Phase II/III trials. The active ingredient in CDAActin-O is a proprietary strain of *Clostridium butyricum*, which prevents and treats gastrointestinal disorders caused by the overgrowth of *Clostridium difficile*. "Both products are well-tolerated and well-received by patients, and there have been no adverse events," says Dr. Lee. The success of Lactin-V and CDAActin-O will pave the way for regulatory and consumer acceptance of bio-engineered MucoCept products, Dr. Lee predicts.

Osel says it has perfected the fermentation, preservation, and packaging of Lactin-V and CDAActin-O tablets. It is capable of manufacturing enough of the products for Phase II trials and it is in the process of selecting a commercial manufacturer for larger quantities. "After that, we're interested in partnering with bigger companies to do marketing and distribution," Dr. Lee says.