MEDICAL RESEARCH

New Vaccines May Ward Off Urinary Tract Infections

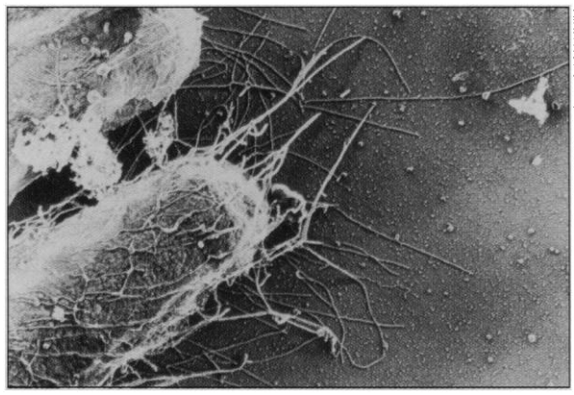
What's almost as common as a cold, but, for most sufferers, far more uncomfortable? Urinary tract infections, or UTIs. Caused primarily by *Escherichia coli*, they send 1.5 million people (mostly women) to the hospital each year in the United States alone, and 7 million more to their doctors. In most cases, the infections are not life threatening: Standard antibiotics usually offer quick relief. But UTIs can recur frequently, and, when untreated, cause kidney damage and even death. A vaccine could reduce this toll, but until now, says Harry Mobley, a microbiologist at the University of Maryland School of Medicine in Baltimore, there has been "little successful work in UTI vaccines."

On page 607 of this issue, however, researchers at MedImmune, a Maryland-based biotech company, and at Washington University in St. Louis report that they have developed a genetically engineered, injectable vaccine that prevents UTIs in mice. Meanwhile, researchers at the University of Wisconsin, Madison, are nearing completion of midstage human clinical trials of a vaccine delivered via a vaginal suppository that seems to offer at least short-lived protection. Mobley calls the new studies "very exciting." Not only do they hold out the hope of reducing the number of UTI cases, he says, but the strategy followed by the MedImmune–Washington University group—targeting a single protein that enables the bacteria to latch onto their target cells—could prove to be valuable against other infections.

These aren't the first efforts to combat UTI-causing microbes. For instance, one injectable cocktail of killed UTI-causing bugs, called Urovac, has been available in Europe since the late 1980s and provides short-lived protection. But natural toxins in the organisms often trigger painful inflammation around the injection site, among other side effects.

To minimize inflammation, the Wisconsin group—led by urologist David Uehling—uses the same concoction of killed organisms as in the Urovac vaccine, but relies on another delivery method: a vaginal suppository. The researchers hoped that by allowing killed microbes to diffuse through the entire vaginal tract instead of injecting them into one small part of a muscle, a suppository would avert inflammation. They reasoned that the killed organisms would still trigger the production of a class of antibodies known as secretory IgA, which circulate in mucosal surfaces such as the lining of the urinary and reproductive tracts and block invading microbes.

In preliminary trials of 25 women, the vaccine seems at least partially effective: Women who are prone to UTIs acquire infections less readily, and none have reported side effects. However, the vaccine's protective effect may diminish over time, says immunologist Walter Hopkins, a member of the Wisconsin team. If that is confirmed in the group's final-stage efficacy trials, says Hopkins, it could mean that women would have to readminister the vaccine, possibly as often as every few months.



S. HULTGREN/WASHINGTON UNIV.

Bug blocker. A vaccine under development prevents adhesion proteins at the tips of spaghettilike pili on UTI-causing bacteria *(above)* from latching onto host cells.

The MedImmune–Washington University team, led by MedImmune's Solomon Langermann and Washington University's Scott Hultgren, has adopted what may prove to be an even more promising strategy. Its vaccine triggers the immune system to produce antibodies that block the action of just a single, key protein on UTI-causing microbes. Administering only that protein does away with the need to expose patients to the whole organisms—and their side effect–producing toxins. The researchers targeted an "adhesion" molecule called Filamentous H, or FimH, present on *E. coli*. The microbes deploy FimH on the end of long, spaghettilike strands that extend from the cell body and latch onto sugar molecules on the surface of host cells. Says microbiologist Vince Fischetti of Rockefeller University in New York City, "If you block that interaction, you can prevent infection."

Researchers have tried to develop adhesion vaccines for other diseases such as gonorrhea, which is caused by organisms that rely on adhesion proteins. But in the past, adhesion vaccines "have not panned out very well," says Mobley. When genetically engineered bacteria are coaxed into producing the large amounts of adhesion proteins needed for a vaccine, the proteins often become degraded or clumped together, losing their ability to provoke immune cells into making antibodies targeted to the protein.

So, the MedImmune–Washington University team whipped up two separate vaccine formulations in the hope that at least one would yield suitable proteins. For the first, the researchers genetically engineered *E. coli* to express extra FimH, which they then collected and purified. As in earlier efforts to develop adhesion vaccines, these proteins ended up partially degraded. But fortunately, the part of the protein that triggers a protective antibody response remained intact. In the second formulation, the scientists modified the bacteria to express not only FimH, but also so-called chaperone proteins, which ensure that proteins fold into their proper conformation as they are made.

The team injected separate groups of mice with the two vaccines and exposed them 9 weeks later to UTI-causing *E. coli*. Both groups of vaccinated mice were able to ward off UTIs for more than 7 months, the latest time point studied. Analyses of the animals' urine showed that both vaccines had elicited blood-circulating IgG antibodies, some of which leaked into the mucosal lining of the bladder and urinary tract. These antibodies, the researchers believe, bound to *E. coli*'s natural FimH proteins, preventing the bacteria from binding to their target cells.

Despite this early success, Mobley and others say that the MedImmune–Washington University team has a long way to go before proving that its adhesion-protein vaccine can make it to market. The researchers will have to demonstrate that the vaccine can block UTI-causing *E. coli* in humans while sparing another colony of *E. coli*: the beneficial intestinal flora that keep disease-producing bugs from proliferating in the gut. Says Mobley: "The current results are still quite preliminary."

In any case, Mobley and others agree, the new adhesion vaccine's initial success could pave the way for developing a host of other such vaccines for other diseases. Adhesion vaccines might just catch on.

–Robert F. Service