infections, mapping the HPV genome, and studying how best to treat cervical disease in HIV-positive women.

Vaccine Dreams

Of the approximately 15 different types of HPV that cause cervical cancer, just two account for most cases: HPV 16 (which causes 60 percent of all cases) and HPV 18 (10 percent of cases).

Thanks to widespread use of the Pap smear screening test as well as effective therapies, cervical-cancer deaths in the U.S. are relatively low—fewer than 4,000 annually. But cervical cancer is the second most common cancer in women worldwide and the leading cause of cancer death among women in developing countries. Each year in the rest of the world there are 400,000 new cervical cancer cases diagnosed and 200,000 deaths.

It has been known for more than 100 years that cervical cancer is a sexually transmitted disease, but not until the 1980’s was cervical cancer linked to viruses—the HPV family of viruses in particular. These viruses cause other health problems as well, including anal and penile cancers, common skin warts, genital warts, and laryngeal papillomas (benign tumors that can obstruct the airways unless surgically removed).

About a dozen Einstein scientists are aggressively investigating the HPV’s and their link to cervical cancer. Among other things, they’re using vaccines to halt the cervical cancers associated with HPV infections, mapping the HPV genome, and studying how best to treat cervical disease in HIV-positive women.

Making Prevention a Priority

Which cancer is most strongly linked to an “outside” cause that we’re exposed to in our environment? You might guess lung cancer, since 80 percent of all cases are due to smoking. But the strongest of all connections between cancer and something external involves cervical cancer: More than 95 percent of all cases of cervical cancer result from infection by human papilloma viruses (HPV’s).

Thanks to widespread use of the Pap smear screening test as well as effective therapies, cervical-cancer deaths in the U.S. are relatively low—fewer than 4,000 annually. But cervical cancer is the second most common cancer in women worldwide and the leading cause of cancer death among women in developing countries. Each year in the rest of the world there are 400,000 new cervical cancer cases diagnosed and 200,000 deaths.

It has been known for more than 100 years that cervical cancer is a sexually transmitted disease, but not until the 1980’s was cervical cancer linked to viruses—the HPV family of viruses in particular. These viruses cause other health problems as well, including anal and penile cancers, common skin warts, genital warts, and laryngeal papillomas (benign tumors that can obstruct the airways unless surgically removed).

About a dozen Einstein scientists are aggressively investigating the HPV’s and their link to cervical cancer. Among other things, they’re using vaccines to halt the cervical cancers associated with HPV infections, mapping the HPV genome, and studying how best to treat cervical disease in HIV-positive women.
An electron micrograph of the protein surface of HPV

immune response that eliminates HPV 16 infections in these women before cervical cancer can develop.

Even though the vaccine is targeted against HPV 16, participants weren’t restricted to women with HPV 16 infections. The hope, says Dr. Einstein, is that the HPV-16 vaccine will rally antibodies and immune cells that will “cross react” with other cancer-causing HPV’s such as HPV 18, HPV 33 and HPV 35.

Last March, Dr. Einstein reported what he describes as “very encouraging results” involving the initial group of 36 women, 31 of whom completed the vaccine trial. Ten of the 31 patients had a complete response to the vaccine—no HPV could be found in their now normal-looking cervical cells; 12 women had a partial response, i.e., their lesions had shrunk by more than 50 percent; and disease in the remaining nine patients was unchanged.

“What’s gratifying is that the vaccine seemed to be effective in women infected with HPV 16 as well as those infected with other types of HPV,” says Dr. Einstein. “In addition, for each woman for each month of the trial, we have blood samples that reveal their immunological response to the vaccine, so we can correlate measures like the patients’ T cell responses with regression of their disease. This information may allow us early on to identify a subset of patients who are “vaccine responders” and can expect a complete cure and also sheds light on the still mysterious role of the immune system in combating HPV infection.”

Recently, several “prophylactic vaccines” have shown promise in preventing HPV infections from developing in young women who haven’t yet developed such infectious. But this is the first time that a therapeutic vaccine—for suppressing cervical cancer in women already infected with HPV—has shown some success.

Deciphering HPV’s genome

Dr. Robert Burk can trace his long career in HPV research at Einstein to lunch in the Lubin Dining Hall on the Einstein campus. “It was 20 years ago—back when most of the faculty ate there—and I was chatting with Dr. Sy Romney [professor of obstetrics & gynecology and women’s health],” recalls Dr. Burk, professor of pediatrics, microbiology & immunology, obstetrics & gynecology and women’s health, and epidemiology & population health.

“I had come to Einstein to work on the hepatitis B virus and liver cancer,” Dr. Burk says, “but I was intrigued by the emerging evidence that cervical cancer was also caused by viruses. ‘I’m interested in cervical cancer too,’ Sy said, ‘and I run a colposcopy [examination of the cervix with a special microscope] clinic. Why don’t we get together and I’ll give you some biopsy samples?’ And starting with that lunch, we began a collaboration.”

In the years since, Dr. Burk and his Einstein colleagues have published numerous papers on HPV. One of their most significant contributions, published in The New England Journal of Medicine, involved the natural history of HPV infection and cervical disease in young women.

“We showed that HPV infections and the early, precancerous lesions that they cause are usually transient,” says Dr. Burk. “Standard practice up to then was surgical removal of these lesions, based on the assumption that they’d otherwise progress to cervical cancer. We found that 95 percent of these lesions go away within two years, which really changed the way physicians treat young women with early cervical disease.”

Dr. Burk’s specialty is using molecular hybridization—a method for comparing genetic sequences—to identify the specific types of HPV’s in cervical tissue as well as variants within those types. He is now collaborating with the National Institutes of Health in an effort to map the HPV genome as part of a 10-year study involving 10,000 women in Guana Costa, Costa Rica. Costa Rica was chosen in part because cervical cancer is about three times more common there than in the U.S.

“Since these 10,000 women were truly randomly selected, they can be considered a representative sample of the entire Costa Rican population,” Dr. Burk explains. “We’re interested in describing the genetic makeup of all the HPV types in this population and then detecting the genes that govern crucial viral characteristics such as carcinogenicity and persistence.”

One of the most interesting findings addresses a key question: Does the length of time an HPV infection lasts influence whether it will lead to cervical cancer? “Before this work, the assumption was that cancer-causing viruses were those that tended to persist longer than others,” says Dr. Burk. “We found that several HPV types cause long-lasting
infections but are not carcinogenic. So persistence is important but is clearly not sufficient to cause cancer. We have some likely suspects regarding viral genes that play a role in causing cancer, but more work will be needed to pin them down.”

HPV, cervical cancer and immunity

One good thing about HPV infections: They only rarely lead to cancer. Some 70 percent of sexually active young women are infected with one or more types of HPV, yet just a small percent of them ever develop cervical cancer—even though infections with HPV’s known to cause cancer are extremely common. In fact, HPV 16—which causes the majority of all cervical cancers—is one of the most prevalent HPV infections.

Several factors influence the survival of HPV infections—smokers, for example, are more likely than nonsmokers to develop cervical cancer—but the most important factor may well be a woman’s immune status.

“The main focus of my research is to understand how host immunity affects infection with the human papilloma virus,” says Dr. Howard Strickler, associate professor of epidemiology and population health. He is an investigator in the ongoing Women’s Interagency HIV Study Group—the nation’s largest prospective study of HIV-positive women—and chairs the HPV Working Group.

The more than 2,000 HIV-positive women in this study (and more than 500 HIV-negative women) have been examined every six months for the past decade and also provide blood samples so that their immune status can be assessed.

“With their weakened immune systems, HIV-positive women are at greatly increased risk for infection with HPV and for cervical cancer itself,” says Dr. Strickler. “This study suggests possible strategies for screening HIV-positive women for cervical cancer, and it can help us learn which treatments work best against the progressive stages of HPV infection and premalignant lesions in immune-compromised women.”

Recently, Dr. Strickler and his colleagues looked at the onset of new HPV infections in HIV-positive women. “We found that HPV infections are prevalent among HIV-positive women mainly because of a sharp increase in new infections and not because of old, persistent infections,” says Dr. Strickler. “And the chance of developing new infections relates very strongly to a woman’s immune status: the weaker her immunity, the more likely we are to find that new HPV infections have arisen between one examination and the next.”

Do these newly detected infections arise from recent sexual activity or from reactivation of previously inactive HPV infections? “Sexually active HIV-positive women definitely had a higher rate of newly detected HPV’s,” he says, “but we also found an elevated rate of new infections among the sexually inactive women.”

“This suggests,” says Dr. Strickler, “that many new HPV infections result from reactivation of earlier infections—the best evidence ever from a human study that there may be such as thing as HPV latency and reactivation and that it may not be uncommon. So we’re really getting some surprising new insights into how host immunity affects HPV infections—insights that may save lives by improving cervical cancer screening and treatment practices for immune-compromised women.”