In a nonsensical yarn, Mercutio accuses Romeo of consorting with Queen Mab, an imaginary Lilliputian wonder. Among other excursions, Mab gallops “O’er ladies’ lips, who straight on kisses dream,/Which oft the angry Mab with blisters plagues/Because their breaths with sweetmeats tainted are.”

So it seems that Shakespeare knew of herpes, and there are much earlier reports of the disease. Hippocrates used the term to describe the spreading of lesions on skin. And today, Queen Mab still gallops. One in four women and one in five men have HSV-2, the herpes simplex virus that occurs in the genital region; 90 percent of those with HSV-2 do not know they have it and may never experience symptoms—however, they can infect others. The similar HSV-1, which commonly results in fever blisters, is estimated to be carried by 50 to 80 percent of adults in the United States. Although painful, unpleasant, and full of social stigma, HSV is often manageable, yet it’s not to be taken lightly. If pregnant women become infected late in term, their fetuses are at great risk of not surviving. And HSV is the leading cause of infectious blindness.
Still, 2,500 years after identifying the disease, science has not offered a cure. But it seems to be inching closer, and now investigators at Pitt have repositioned the yardstick.

Virologists consider herpes simplex virus to be one of the most fascinating organisms known to us. But we don’t know it very well. One source of HSV intrigue is its ability to remain dormant then somehow reawaken. The viral DNA survives during latency by camping out in the nervous system, where it’s protected. In the case of ocular infection, the virus travels up the optic nerve connecting the eye to the brain, the viral DNA making itself at home in the cell bodies of ganglia. In most people, the virus never seems to assert itself. Others suffer from recurring infections—no one knows why, but stress and ultraviolet light probably have something to do with it.

Scientists had pretty much decided that the immune system didn’t play a role during the latent period. The viral DNA didn’t appear to be producing proteins during latency, so there was nothing for the immune system to do, no antigens to launch a response against. Herpes research focused on the neuron hosting the DNA. When virologists attended herpes latency meetings, they didn’t talk about the immune system. Then Robert Hendricks’ lab gave them something to talk about.

Ting Liu, who had been an ophthalmologist in China, came to the University of Pittsburgh School of Medicine several years ago and pursued a postdoctoral fellowship with Hendricks, a professor of ophthalmology interested in ocular latency. In 1996, Liu and Hendricks found T cells hanging around cell bodies during initial latency in mouse ganglia. T cells are sent by the immune system to shut down intruders. But what was the immune system responding to if the viral DNA wasn’t producing proteins?

Then Kamal Khanna found out. Khanna completed his PhD in immunology at the School of Medicine this spring. Under Hendricks’ guidance, he monitored herpes in a latent state in a mouse. Building on Liu’s work, he discovered that T cells remained not just a couple of days into latency but appeared for the life of the mouse. Further, Khanna found highly suggestive indications of persistent, low-level production of viral glycoproteins, which can be thought of as viral building blocks. The immune system appeared to be operating after all—very subtly squashing these glycoproteins and the beginnings of a full-blown infection.

These findings were published in the Journal of Experimental Medicine and Immunity. Khanna’s efforts brought him an American Association of Immunologists award usually reserved for postdocs. The lab’s work has been called paradigm shifting. And it recently was translated to a human model by German investigators.

It makes sense that the immune system plays a role in latency, Khanna notes, pointing out that herpes is known to readily reinfect people with HIV, a population with compromised immune systems.

Herpes vaccine development has met with little success. But Hendricks suspects a vaccine would be effective if it targeted the glycoproteins that subtly appear during latency. “These are the most important ones to stop the virus from recurring,” he says. He speculates that such a vaccine could be used therapeutically for people who suffer from recurrent infections.

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G O O D I N K

Editorial commentary is infrequent in peer-reviewed journals. It’s reserved for papers that are likely to shake things up a bit, or at least turn heads. Among these lines, the School of Medicine’s PhD program has scored a hat trick. Three papers on herpes submitted by doctoral students from the school as primary authors were judged worthy of editorial commentary in the past couple of years: two by Kamal Khanna, whose adviser is Robert Hendricks (see story above), and one in the Proceedings of the National Academy of Sciences (June 24, 2003) by Sara Jackson. Working with her adviser, Neal DeLuca, professor of molecular genetics and biochemistry, Jackson reported that the herpes virus does not replicate from a circular genome, as was previously assumed, but instead appears to replicate from a linear template. This finding has implications for understanding DNA repair in viruses. In that paper, Jackson and DeLuca also identified a protein that seems to determine the fate of the viral genome’s configuration. —EL

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C O M M E R C I A L I Z A T I O N

FOR BEGINNERS

A N G E L S A N D A N E W O F F I C E H E L P

B I O M E D S T A R T - U P S

I

B Y D O T T I E H O R N

Sometimes business was almost too good. In 2001, Theresa Whiteside was director of a specialized University of Pittsburgh Cancer Institute laboratory. UPCI researchers running clinical trials came to Whiteside, and she’d help them develop—and would then run—series of tests to indicate whether an experimental therapy was effective. For example, after a patient had received...
a drug for two months, were his immune cells more active? What about at four, six, and eight months? Further, the test results obtained at point A had to be exactly comparable to results obtained at point B.

Whiteside, professor of pathology, immunology, and otolaryngology, and her colleagues developed a reputation for such testing. The lab, initially created to support UPCI scientists, began taking on industry clients. There was so much corporate interest that Whiteside began to wonder: Could we offer these same services outside the University to industry clients, and could we make a profit?

That was about the time Carolyn Green came to UPCI, as the director of the newly created Limbach Entrepreneurial Center. Her job was to foster the commercialization of technology developed at UPCI.

One day, Whiteside showed up in Green’s office, asking about the possibility of starting a company. Intrigued, Green visited Whiteside’s Immunologic Monitoring and Cellular Products Laboratory. She made phone calls, hired consultants, asked questions. How much did it cost the lab to do its testing? What laws would regulate the company? Who would be the company’s competitors? Most important: Could the company turn a profit? After 10 months of research, Green decided the answer to this last question seemed to be yes.

It’s a process in which Green specializes. When a University faculty member comes to her with a new technology or process developed at Pitt, she evaluates its commercialization potential. (She currently has some 70 such “cases.”) In 2003, Mark Nichols, assistant professor of pharmacology, and Richard Steinman, associate professor of medicine and pharmacology, talked to Green and her team about a new method they’d developed for making random siRNA molecule libraries. (These molecules can silence a single gene in a cell.) The technology is now the focus of a new start-up company, Cellumen. That same year, Michael Buckley, associate professor of oral and maxillofacial surgery, and Eric Beckman, Bayer Professor of Chemical Engineering, spoke to Green about a new polymer they’d developed that could act as a surgical adhesive. Cohera Biomedical Adhesives is about to be launched to manufacture the surgical “glue.”

There are many steps in between an initial meeting with Green’s staff and the creation of a new company. After researching Whiteside’s idea, Green wrote a business plan and brought the company, dubbed ImmunoSite, into legal existence. Although the laboratory tests used by Whiteside were not patentable, the know-how for running the lab belonged to the University and UPMC. Green met with Pitt and UPMC officials and worked out an agreement to transfer the intellectual property surrounding Whiteside’s lab to ImmunoSite.

Eventually, Green went in search of money. In many cases, a new service company is unlikely to generate the high rate of return on investment sought by venture capitalists. In such instances, Green looks for angel investors, wealthy individuals interested in placing private funds in promising opportunities like start-ups.

Green’s office works with several angel networks in Pittsburgh. Some of her angels are School of Medicine faculty or alumni. “Angels are typically very quiet people. You’d never know they were there if you didn’t know how to find them,” she says.

Green also may approach UPMC Health Ventures, the investment arm of UPMC, which funds start-up companies.

It took Green two months to secure more than $1 million in support for ImmunoSite. In September 2002, a little more than a year after Whiteside first approached Green, ImmunoSite began operations.

Green likens the process of starting a company to having a baby. “[But] once it is born, I have to let someone else raise it.”

Her office has itself recently grown. In February, the Limbach Entrepreneurial Center became the Office of Enterprise Development, Health Sciences (OED). Instead of serving just UPCI, the new office serves all of Pitt’s health sciences schools. Green, who was once a one-person office, now has a staff of five, including an immunologist and neurobiologist.

“Many research discoveries cannot achieve their full impact on human health without going through the commercialization process,” says Green.

But the office does not focus just on moving technology out of the University. OED also gets industries to invest money in technologies still under development at Pitt. In addition, the office educates faculty about commercialization—sponsoring seminars and publishing an e-mail newsletter, which has 900-plus subscribers.

“The most significant lesson our scientists can learn [is] that the business world requires intellectual property to be legally protected. If you don’t take the time to disclose and protect it, it may be impossible for industry to promote your idea and to commercialize it.”

FOR MORE INFORMATION: WWW.OED.PITT.EDU
Every month, staff from the nation’s largest and longest-running cancer screening trial sends out about 1,200 birthday cards. Yes, birthday cards. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial involves 155,000 participants at 10 locations across the country, including nearly 17,000 in the Pittsburgh area. Study administrators send cards as a personal reminder of how much they value the participants' involvement. “We get nice feedback,” says Betsy Gahagan, an administrator for the Pittsburgh site. “In fact, one woman called to tell us that ours was the only card she received that year.”

Aside from adding a spot of cheer to a sometimes lonely day, the cards serve another, more scientific purpose: They’re one of the tactics Joel Weissfeld, principal investigator for the Pittsburgh site, and his staff have developed to keep in touch with their many study subjects and encourage ongoing participation in the trial. Launched in 1992, the $150 million study was designed to determine whether certain screenings help reduce deaths from prostate, lung, colorectal, and ovarian cancer. (Together, these cancers account for about half of all cancer deaths in the United States.) By 2001, the study had enlisted the army of men and women between the ages of 55 and 74 needed for a statistically relevant sample. Participants agreed to a random assignment to one of two groups. Those in the intervention group visit a designated center every year for six years for screening, while those in the control group simply continue routine care with their own doctors. Through 2006, all intervention group participants are expected to provide blood samples. They also fill out questionnaires each year. (In response to another required questionnaire that happened to be 39 pages long, one participant included a worn-away pencil stub with his returned tome.)

To obtain solid data, study organizers need at least 85 percent of the participants to cooperate with the trial’s requirements. The Pittsburgh site has been able to maintain 90 percent compliance for the annual screening and 98 percent for the surveys, but this achievement is hard won. It requires the daily efforts of staff to set up appointments with participants and catch up with those who have been remiss in following through with other requirements; this can involve dozens of calls and letters to a single person.

If it’s hard to keep tabs on 155,000 active participants, imagine how tricky it can be to get appropriate information about those who’ve died. Since the whole point of the trial is to determine whether there are fewer cancer deaths in the intervention group than in the control group, it’s critically important to know the precise cause of each participant’s death.

When someone enrolled in the study dies, organizers need authorization to access the deceased participant’s medical records; however, the next of kin are often not aware that the deceased was part of a clinical trial. Specially trained staff members are charged with convincing families to authorize a release of information. Information about anybody whose death may have resulted from one of the target cancers—or whose cause of death is unclear—is turned over to a national death review committee.

The committee’s job is to make sure that errors in determination of death don’t skew the trial’s results. “For instance, a death certificate might indicate that the patient died of pneumonia, but the pneumonia might have actually resulted from a progression in the patient’s lung cancer,” says Christine Berg, an oncologist who is the National Cancer Institute’s project officer for the study. “That kind of error will underestimate the true number of cancer deaths.”

The committee also looks out for the so-called “sticky-diagnosis bias,” which can skew trial results in the opposite direction. In any screening trial, participants in the intervention group could be diagnosed with a cancer that might never have even presented symptoms. Still, the diagnosis from the screening tends to “stick,” so that though the person dies of another cause, hospital staff in charge of determining cause of death assume that cancer is the culprit. The death review committee double checks to find out if the cancer is, in fact, the actual cause of death.

“People ask why we go through all this trouble,” Berg continues. “They say, ‘You’ve got the death certificate—why not just go with that?’ But ... errors creep in.”

Determining the cause of death of participants in a huge cancer screening clinical trial is not always straightforward, yet it’s key to the trial’s results.