



A native of Canada, Britten attended medical school at the University of Toronto. She trained in medical oncology at the British Columbia Cancer Agency in Vancouver, and then did a fellowship in drug development at the Institute of Drug Development in San Antonio, Texas, where she participated in more than 40 Phase I clinical trials in two years.

Britten then returned to the BC Cancer Agency, where she continued to administer Phase I studies before coming to UCLA.

In addition to running four Phase I studies at the Jonsson Cancer Center, Britten also sees patients with liver, breast and head and neck cancers. She also works with basic scientists to help design early phase studies, taking compounds from the lab and testing them for the first time in humans.

Britten currently is leading two Phase I studies for people with advanced breast cancer. One study pairs the monoclonal antibody Herceptin with the experimental compound Tarceva, a pill designed to block a growth receptor

Molecularly targeted therapies have been splashed across the news in recent years as scientists use what they know about the biology of cancer to zero in on what makes a healthy cell become a cancer cell.

Name any of those high profile experimental therapies and chances are good that Dr. Carolyn Britten has tested them on the very sickest of cancer patients to see if they offer new hope.

Britten, an adjunct assistant professor of hematology/oncology and associate director of the Cancer Transitional Therapeutics Program Area at UCLA's Jonsson Cancer Center, which tests the newest experimental therapies on patients for whom all conventional treatments have failed.

"I really like Phase I studies because you're right at the interface between the lab and the clinic," said Britten, a medical oncologist who joined the UCLA faculty in 2001. "You get all of the interesting compounds coming through Phase I clinical trials first. There's a lot of excitement here."

Phase I studies—the earliest phase of human clinical trials—are designed to determine an effective dose of a drug and discover what, if any, side effects it may cause. Typically, Phase I studies involve between 15 and 25 patients and take about 12 to 18 months to complete.

"Researchers need to see how well patients tolerate a new medicine and cancer patients participate with the hope that a new drug will have activity in their diseases," Britten said. "The drugs we bring to Phase I trials have shown a lot of promise in the lab, but we don't know if they're going to have activity in humans."

In Phase I studies, researchers treat a few volunteers at a dose they think should be safe based on laboratory data and follow those patients very carefully, Britten said. If there are no serious side effects, researchers increase the dose in a new group of volunteers. Each new group or cohort of volunteers receives a larger dose until the optimum dose is found.

That maximum tolerated dose can then be tested to see how well it fights cancer in larger Phase II and III studies.

Dr. Carolyn Britten

**Scientific
STAND
OUT**

Testing the newest, leading-edge therapies on the patients who need them the most.

that prompts the excess cell proliferation associated with cancer. The other breast cancer study is testing a tyrosine kinase inhibitor in pill form that researchers hope will work similarly to Herceptin.

Britten also is heading up two Phase I studies for people with all advanced cancers. One is testing the experimental drug SU11248, an angiogenesis inhibitor designed to cut off a tumor's blood supply, hopefully starving the cancer to death. The other pairs Xeloda with LY317615. Xeloda is a chemotherapy pill, while LY317615 is another angiogenesis inhibitor.

Additionally, Britten is leading a Phase II study of the angiogenesis inhibitor Avastin in patients with advanced liver cancer who are undergoing chemoembolization, a process in which chemotherapy agents are injected directly into the blood vessels that feed the tumor.

"This is an exciting time to be doing Phase I clinical trials," Britten said. "There's an explosion of knowledge about the basic biology of cancer, and we can use that to identify new targets for novel anti-cancer therapies. One of the problems we have, and it's a great problem to have, is how are we going to use all these new agents and how do they fit in? If you look at oncology 20 years ago, researchers were desperate for new agents. Now we have so many we're almost overwhelmed."

Britten said one of the best things about her work is the patients she treats, those who could not be saved with conventional cancer therapies but who are willing to enter a clinical trial.

"Patients on Phase I clinical trials are hopeful the drugs will have some benefit, but there's a lot of altruism involved as well," Britten said. "They're amazing people, because patients on a Phase I trial have to come into the clinic a lot more often than those receiving standard treatment. They have a limited life expectancy, but they're willing to give their valuable time to help future patients." ★

Some viruses can live within the human body forever.

Scientist Ren Sun wants to know how these viruses achieve this and hopes the answer may shed new light on the development of certain cancers.

Sun, director of the Viral Carcinogenesis Program Area at UCLA's Jonsson Comprehensive Cancer Center, is focusing on two herpes viruses, the Epstein-Barr virus (EBV) and the human herpes virus 8 (HHV-8), both of which are associated with cancers.

"It's fascinating that these viruses, once they get in, stay with us for the rest of our lives," said Sun, a native of China who earned his doctorate at Yale University. "We want to know how they do that."

Viruses cause about 15 percent of cancer cases, Sun said, including cervical and liver cancers. EBV and HHV-8 are associated with Burkitt's lymphoma, a high-grade B-cell lymphoma and one of the fastest growing malignancies in humans, as well as Kaposi's sarcoma, a type of endothelial cancer found primarily in those infected with HIV. The viruses also have been linked to two types of rare B-cell lymphomas, Sun said.

"The ability of viruses to promote tumor growth originates from their capacity to establish latent infection and their ability to evade the immune system," Sun said. "We are studying their mechanisms in mouse models and addressing this from two perspectives, molecular biology and immunology."

The life cycle of the herpes viruses Sun and his colleagues are studying have two phases, an active phase called lytic replication and an inactive or latent phase. They evade the immune system, Sun said, by shutting down their own expression, in effect disguising themselves. In an early study of Kaposi's sarcoma-associated herpes virus (KSHV), Sun and his colleagues identified a key protein called Rta, which regulates viral gene expression, causing the viruses to either become active or remain latent.

When Rta is activated, the virus switches to the active or lytic replication phase. When it's switched off, the virus goes into latent phase. Sun discovered that Rta is the first gene turned on when the virus begins to replicate, and that activation causes a cascade of other gene reactions along the cell-signaling pathway, perhaps leading to cancer.

"We are working to identify the downstream target genes, the mechanism of activation by Rta and the cell signaling pathways that control the expression and function of Rta," Sun said.

Perhaps the more challenging question, Sun said, is how Rta gets switched on and off in the first place. Since it's the first gene activated in the cascade, perhaps a targeted therapy could be developed that would help the body recognize the virus hiding inside the cancer cell.

"In tumor cells caused by a virus, the virus is latent so the tumor cell is not recognized by the immune system," Sun said. "If we could turn Rta on, the virus would begin to replicate and tumor cells could be recognized by the immune system and destroyed."

Sun and his colleagues are taking their basic science discoveries from the lab to the bedside. They are initiating three clinical trials—for nasal pharyngeal carcinoma, B-cell lymphoma and kaposi's sarcoma—in an effort to unmask the cancer by causing the virus in the tumor cells to become active.

Sun and his colleagues also are studying how viruses exist in the human body at the molecular level, how they interact with our immune systems.

"The virus has complicated interactions with the host. It can persist and replicate in the presence of the immune system," Sun said. "We're trying to understand why. The virus appears to use our own weapons against us, encoding a protein called IL-6 that we use to fight infection, disguising itself."

Using a mouse model with a genetically engineered latent herpes virus, Sun and his colleagues compared virus

Scientific
STAND
OUT

Dr. Ren Sun



Exploring
the links
between
viruses and
cancers.

replication in mice with the protein IL-6 and in those without IL-6. The virus with IL-6 replicates better and persists in our body longer than the virus without IL-6, Sun found. He also found that the mouse infected by the virus with IL-6 was healthier, that there was less damage to the host.

"This is a very elegant event in evolution," Sun said. "Furthermore, it's noted that IL-6 appears to play a critical role in the development of Kaposi's sarcoma and B-cell lymphoma. The HHV-8 virus encodes IL-6 in those tumors. It will be gratifying to link this viral evolution with tumor development in humans." ★



Dr. Lawrence Bassett

When Dr. Lawrence Bassett joined the UCLA faculty in 1975, mammogram technology was in its infancy and the procedure was used only to diagnose cancer in patients with breast abnormalities.

The images were grainy and difficult to interpret, and the news they contained was often grim. Women were frequently diagnosed with large tumors that doctors don't see today, sometimes three and four centimeters. Skin retraction—the skin being pulled in by the tumor—was not uncommon, and most patients had lymph node involvement, a sign the cancer was spreading. Survival rates were not good.

A lot has changed in 28 years. It's rare today that Bassett sees tumors as large as those he saw on mammograms from the mid-1970s. Women are being diagnosed with much earlier stage cancers, when the disease is easier to treat, and their survivor rates are far better.

"It's a different world now," said Bassett, medical director of the Iris Cantor Center for Breast Imaging and a national expert on breast screening. "It's still amazing to me that anyone could find anything on those early mammograms."

And things could get better still. Bassett, along with other top researchers nationwide, is testing the latest in breast screening technology—digital mammography. The Digital Mammographic Imaging Screening Trial (DMIST) compares digital mammography to standard mammography for the detection of breast cancer.

Digital mammography uses computers and specially designed detectors to produce a digital image of the breast that can be displayed and manipulated—enlarged, magnified, lightened or darkened—on high-resolution monitors. Digital mammograms also can be printed out on X-ray film for easier comparison with conventional mammography. Unlike conventional mammography,

**Scientific
STAND
OUT**

**Improving
the next
generation
of the
life-saving
mammogram.**

the image produced by a digital mammogram can be lightened or darkened prior to being printed on film.

More than 2,000 women are enrolled in the UCLA arm of the study, which will continue to recruit participants through December. Nationwide, about 49,500 women will participate in DMIST.

"This is the next step in the digital revolution," Bassett said. "Digital mammography has incredible potential for improved image detail and contrast and it eliminates the problems with film—the long processing time, having only one original image to work from. With digital mammography, we can change the image once it's produced. We can store it electronically. We can send the mammogram somewhere else within minutes. There will be no need for huge, expensive film libraries."

Despite the improvements that radiologists have witnessed over the last three decades, screening mammography has remained a controversial topic. A spate of studies came to differing conclusions regarding the question of whether screening mammography is an effective tool. Public debate raged. However, there was never any question in Bassett's mind that women should undergo mammography.

"Nothing has gained more attention in recent years than mammography," Bassett said. "And in the long run, it has been proven to be effective."

A recent Swedish study published in the peer-reviewed journal *Cancer* compared women in seven counties that offered mammography with women in seven counties that did not have screening services. Researchers found a 30 percent reduction in mortality from breast cancer in the counties that offered screening mammography versus those that did not. This is important because women in the other counties had access to the same treatment advances, thus dispelling the argument that it is only improved treatments that lower mortality.

Among women in the study who actually were screened, mortality was reduced 45 percent when compared to women who had not undergone mammography, according to the study.

Still, mammography is far from perfect.

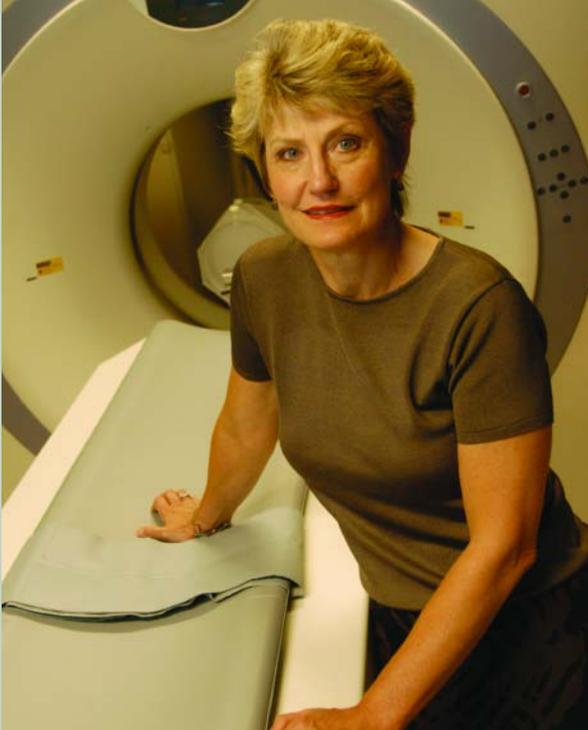
"About 15 percent of breast cancers will not show up on a mammogram, usually due to dense breast tissue," Bassett said. "But mammography remains the best way to detect cancer at this point in time."

It's been so successful, in fact, that national guidelines for breast cancer staging had to be changed largely because so many cancers were being detected at earlier stages through mammography, said Bassett, who served on the American Joint Committee on Cancer, which develops the staging system.

"When I started in the 70s, only 5 percent of cancers were detected when they were still non-invasive, before they had left the milk duct," he said. "Today, about 30 percent of diagnosed breast cancers are non-invasive, and these are almost all found by mammography screening."

Still, improving mammography remains paramount for Bassett. He believes the DMIST study will lead to further improvements in screening.

"This is the future of mammography," he said. ★



Scientific STAND OUT

Dr. Denise Aberle

Lung cancer kills more Americans every year than breast, prostate, colon and pancreas cancers combined, claiming the lives of 85 percent of those who get it.

Lung cancer is so deadly, in part, because by the time it's found, the disease has usually spread. Doctors cannot predict how patients will respond to treatment or whether some patients might respond better than others.

Dr. Denise Aberle, a Jonsson Cancer Center researcher, chief of thoracic imaging and vice chairman of research in radiology at UCLA, is on a mission to change all that.

Aberle leads a national study comparing spiral CT scanning to conventional chest X-ray to determine which is more effective at reducing lung cancer deaths. She's also among a group of UCLA researchers seeking better ways to individualize cancer therapies and predict patient outcomes through molecular targeting and imaging.

The first line of attack for Aberle is screening. She serves as national principal investigator for the National Lung Screening Trial, (NLST).

"Our hope is that this study will lead to saving lives," Aberle said.

Chest X-rays produce a two-dimensional view of the chest and can detect quarter-sized or larger abnormalities using radiation exposures that are among the lowest in medical imaging. With low-dose spiral CT, the patient moves on a table through a doughnut-shaped structure that acquires views from all angles. These views are combined to produce a three-dimensional image of the chest. With CT scanning, dime-sized abnormalities can be detected, although at somewhat higher levels of radiation.

Low-dose spiral CT is a newer approach to lung cancer screening, and has been lauded by some health professionals because of its ability to detect smaller lung lesions than conventional X-rays.

"But we don't know that detecting a small lung cancer will actually reduce deaths," Aberle said. "Genetic and biological factors—not merely tumor size—determine

whether a cancer spreads slowly or rapidly. Finding a small cancer on CT or chest X-ray is not necessarily the same as finding an early stage lung cancer."

And there's another wrinkle. Most of the lung abnormalities detected with low-dose CT are ultimately found to be non-cancerous, yet individuals with positive screening results are faced with additional tests and procedures that carry risks and have emotional consequences.

"We simply don't know whether these technologies will be beneficial, the degree to which they expose healthy individuals to unnecessary risks, or the balance between those risks and benefits," Aberle said.

As part of the NLST, Aberle and her team are collecting and storing samples of blood, urine, and sputum from study participants. These samples will provide an important resource for testing biological markers of lung cancer that might someday serve as screening tests themselves or might

On a mission to improve screening for and treatment of America's most deadly cancer.

better help identify those at risk of getting lung cancer.

Tailoring therapies to patients based on individual genetic profiles is another avenue of research under study. The depiction of physiologic and molecular events by imaging probes will make it possible to distinguish which tumors will respond to particular types of treatment.

UCLA researchers hope to be able to predict how lung cancer patients will respond to treatments, Aberle said. Tumors with certain gene mutations or protein expression profiles may respond better than other tumors to specific molecular therapies that target, for example, angiogenesis, the formation of an independent blood supply for the tumor, or tumor growth factors that drive cell division.

New imaging techniques and imaging tracers are being developed to document these novel therapeutic interventions at the cellular level. Such targeted molecular imaging, for example, can determine whether a molecular therapy is actually working in a patient by following the process as it happens. This would be a far superior method of measuring a drug's effectiveness. Doctors now gauge treatment response through tumor shrinkage. These measurements often are not representative of treatment response to molecular therapy, in which tumor bulk may not change despite profound changes in the tumor's ability to sustain growth.

For example, a form of positron emission tomography (PET) can discriminate between tumor cells capable of dividing versus those that cannot. Similarly, higher magnetic resonance (MR) field strengths may enable analysis of the chemical composition within tumors as a measure of their growth capacity. Positron and MR-labeled antibodies may be able to characterize tumors and their locations, or determine which molecular targets exist on the tumor that can be attacked with new treatment agents.

"We need to be able to visualize things on the cellular level," Aberle said. "This will help us better group patients, determine who will respond to certain treatments and who will not, figure out who will relapse and who will not." ★