

SYNTHESIS

THE MAGAZINE OF UC DAVIS CANCER CENTER

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Making their mark against breast cancer

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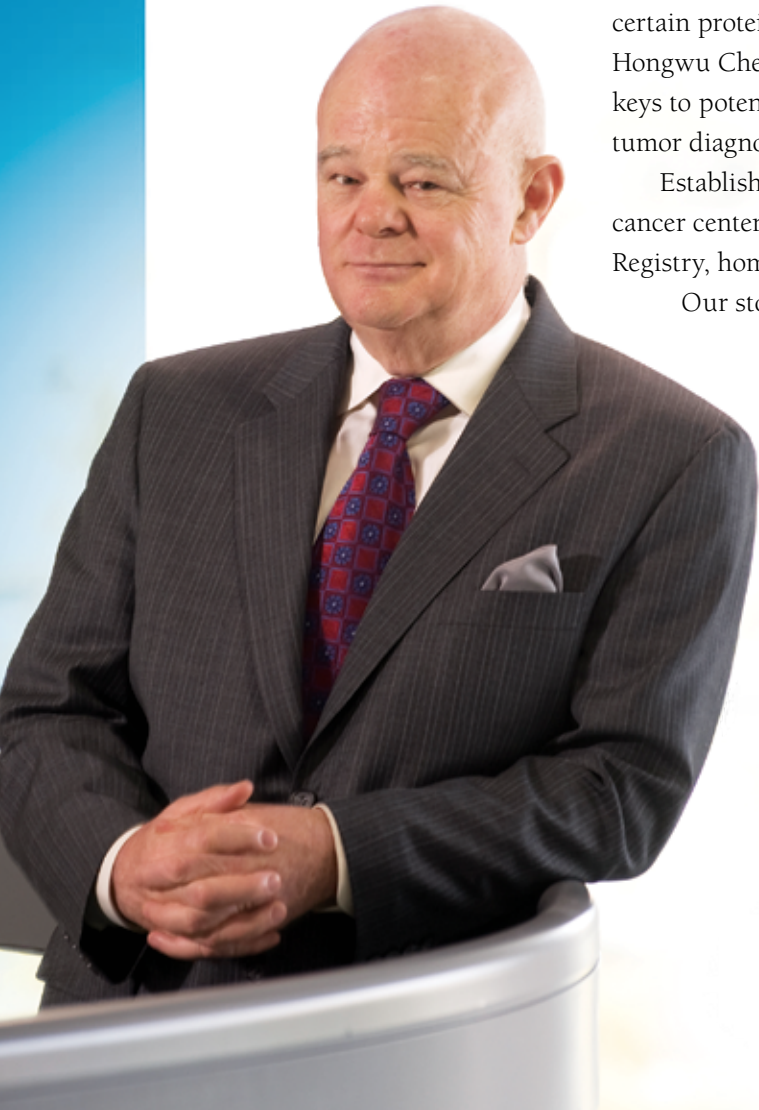
New Phase I clinical trials director aims to offer patients more promising therapies

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Major findings open doors in DNA repair research

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Dear Reader,

Welcome to the spring/summer 2011 *Synthesis*, UC Davis Cancer Center's biennial magazine designed to keep our extended community informed about how we are breaking barriers to beat cancer through leading-edge research, comprehensive care and critical outreach to underserved populations.

In this issue we are delighted to bring you several articles that highlight the cancer center's growing focus on breast cancer, a disease that will touch one in eight women sometime during their lives.

Breast cancer work at UC Davis spans the gamut from basic research and breast cancer treatment to innovative outreach to those on whom the disease places an especially high burden, including rural Northern California women and American Indians.

This issue features the work of scientists Wolf-Dietrich Heyer and Stephen Kowalczykowski, who have made important discoveries about certain proteins in the repair of DNA and their role in breast cancer, and Hongwu Chen, Alexander Borowsky and Sheryl Krig, who are uncovering keys to potential breast cancer biomarkers that could lead to more specific tumor diagnoses and treatments.

Establishment of an epidemiological "shared resource" will help the cancer center formalize our ongoing interactions with the California Cancer Registry, home to the largest collection of cancer patient data in the country.

Our story on this collaboration describes some of the efforts already under way to use this data to better understand cancer and improve care and outcomes for patients.

Finally, in this issue you will meet two terrific contributors to our cancer center: newly hired Karen Kelly, a lung cancer specialist who is spearheading efforts to enhance our trials recruitment efforts, and Robyn Raphael, a fundraising dynamo who works tirelessly on behalf of children with cancer at UC Davis and throughout the country.

We hope you enjoy this issue of *Synthesis*.

RALPH DEVERE WHITE

*Director, UC Davis Cancer Center
Associate Dean for Cancer Programs
Professor, Department of Urology*

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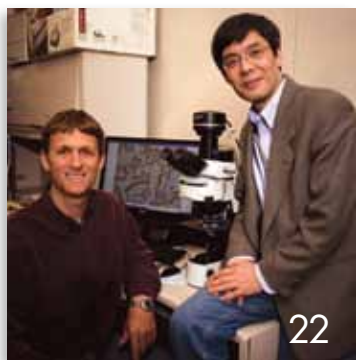
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UCDAVIS
CANCER CENTER

*A National Cancer Institute-
designated cancer center*



Karen Lindfors

Better images for better outcomes

Radiologist brings modern mammography, screening expertise to Kosovo

It took about 20 men to push the new mammography machine up the stairs for installation in a hospital in Kosovo.

But the effort was worth it. In a country where most breast tumors are detected too late and where 50 percent of women with breast cancer die from their disease, the prospect of saving more lives was good motivation.

In a country where **most breast tumors are detected too late** and where **50 percent of women** with breast cancer **die from their disease**, the prospect of **saving more lives** was good motivation.



Karen Lindfors, professor of radiology and member of UC Davis Cancer Center, recently returned from a medical mission to Prishtina, capital of the Balkan republic, where she helped teach local doctors and technicians how to use the newly donated machine to screen women for breast cancer.

It was the second such trip for Lindfors through Radiology Mammography International, a nonprofit organization that provides technical assistance, donations and training in underserved parts of the world to support breast cancer prevention, detection and treatment. Lindfors made a similar trip to Macedonia in 2009.

Upon her return from Kosovo, Lindfors described what she saw as a system for breast cancer screening that lacks technological sophistication, clinical expertise and medical record management. Complicating matters, she says, is that patients don't have health insurance; there are wide disparities when it comes to

access to care; and radiologists in the public system earn less than \$500 a month.

Lindfors says screening for breast cancer is very limited and, if available, done using ultrasound or old mammography machines that make it almost impossible to accurately detect lesions. Technicians

Lindfors says screening for breast cancer is very limited and, if available, done using ultrasound or old mammography machines that make it almost impossible to accurately detect lesions.

are trained using textbooks – not in clinical practice. And because most patients are diagnosed late, they usually undergo full mastectomies rather than breast-sparing lumpectomies.

“What really struck me was how large the cancers were that we saw in Kosovar women who were sent in for evaluation, and how interested the radiologists were in really improving their skills,” Lindfors says. “But what a tough road that is going to be because of the lack of infrastructure and support.”

And because the clinics do not set up appointments for screening, Lindfors says, “it’s absolute chaos because everyone is trying to get in the door. Some patients waited three days for a screening.”

In addition to daily lectures with medical personnel, Lindfors taught them how to do wire localizations,

a procedure used to pinpoint breast lesions that are not palpable. She also worked with surgeons who performed the first wire-localized lumpectomy ever done in the country as well as the first sentinel lymph node biopsy.

All told, she says, in two weeks the team performed 200

Because the clinics do not set up appointments for screening, Lindfors says, “it’s absolute chaos because everyone is trying to get in the door. Some patients waited three days for a screening.”





ABOVE: Karen Lindfors demonstrates to clinic personnel the proper way to perform a mammogram using modern technology.

mammograms and found seven cancers, five of which could be surgically removed with lumpectomy.

Lindfors says the challenge now is to keep the program sustainable in Kosovo, which requires government support and continued funding for supplies. She hopes to return to Kosovo some day, as long as those things are in place.

“I’ve received several positive e-mails from the radiologists I trained in Kosovo,” Lindfors says. “They report reasonable progress on their breast cancer screening program. If that continues, I’ll return to Kosovo for a follow-up mission.”

“What really struck me was how large the cancers were that **we saw in Kosovar women** who were sent in for evaluation, and **how interested** the radiologists were **in really improving their skills.**”

~ Karen Lindfors

Cancer by the numbers

California registry resource bolsters cancer center research

Tucked away in an unremarkable building on the outskirts of Sacramento is one of California's most precious – and hidden – scientific assets. With demographic details and other information on more than 3.9 million cancer cases, the California Cancer Registry is a powerful surveillance tool, the biggest and most diverse data reservoir of its kind in the nation.

For more than a decade, a handful of UC Davis cancer researchers have collaborated with the registry on a variety of projects. But the potential of the partnership far exceeds the results produced so far.

Recognizing the gold mine at their doorstep, leaders of UC Davis Cancer Center now want to formalize their relationship with the registry by designating it a “shared resource.” They hope to obtain funding to fortify the partnership under the center’s anticipated new five-year National Cancer Institute grant.

“Even without a formal shared resource, a tremendous number of meaningful papers have been written,” says Ralph deVere White, cancer center director. “A partnership that allows for joint grant submissions will contribute to even more important research and will help boost research revenues for the state in these financially challenging times.”

If approved, the shared resource will help fund the salaries of cancer epidemiologists trained to access and interpret the complex registry data. These epidemiologists will mentor

Recognizing the gold mine at their doorstep, leaders of UC Davis Cancer Center now want to **formalize their relationship** with the registry by designating it a **“shared resource.”**



Monica Brown

The state's demographics **allow researchers to analyze incidence, treatment, mortality, survival and trends of rare cancers and cancers among small or unique populations.**

junior faculty in developing projects, and collaborate with clinicians and translational scientists interested in mining the registry for research ideas.

Clinicians who have teamed up with registry staff on past projects are universally enthusiastic about the possibilities.

"Developing a shared resource in epidemiology would be a tremendous step toward building a fruitful and long-term collaboration between the cancer center and the registry," says Rudolph Schrot, assistant professor in the Department of Neurological Surgery and co-author of a study using registry data to examine brain tumors. "This partnership provides a great opportunity to expand our understanding of cancer incidence in California and investigate a wide range of population-based research questions."

Already, use of the registry has allowed researchers to document cancer trends, illuminate disparities in treatment and produce a string of findings that are helping guide patient care. Work anchored in registry data has targeted a wide range of cancers, from ovarian and kidney to lung, pancreas and nasopharyngeal cancers. Many of the projects have led to peer-reviewed publications and grant funding.

The registry first began gathering data in 1988, after the California Legislature required health officials to establish a statewide cancer reporting system. Each year, more than 162,000 new cases of cancer are added to the database, and both its size and tremendous diversity make it unique in the nation. State law permits the use of registry data by qualified researchers for cancer

surveillance and research into the causes and cures of cancer.

Californians represent 12 percent of the United States' population and are rich in their racial/ethnic, economic and cultural diversity. The state's demographics allow researchers to analyze incidence, treatment, mortality, survival and trends of rare cancers and cancers among small or unique populations. Thus the registry is a powerful resource for health-disparities research, a major focus at UC Davis.

The registry's voluminous files include information on patient characteristics, cancer type, extent of disease at diagnosis, treatment and survival. The data are extremely reliable and representative, says Monica Brown, a registry epidemiologist who also has an adjunct faculty appointment at UC Davis.

"We receive reports on cancer cases from the tiniest doctor's office right on up to the biggest hospital in the state, and we have excellent documentation of each case," Brown says. "The data are completely representative, and that's very important for statistical analysis."

Registry staff members also

routinely link their database with other administrative databases, including Medicare, MediCal and the state hospital discharge database. These connections allow the registry to enhance its files with information about treatment and the presence of other illnesses that can affect survival.

Schrot teamed up with Brown on a descriptive study examining brain tumors catalogued in the registry between 2001 and 2006. The study, which led to two articles published in April 2009 in the *Journal of Neuro-Oncology*, was the first large-scale population-based report that included malignant and benign tumors.

Schrot's study also examined tumor incidence according to gender, race/ethnicity, socioeconomic status, and level of urbanization – rural

or urban – based on census tracts.

“The broad diversity of the registry allowed us to do not just a comprehensive study, but also an in-depth analysis across various demographic groups,” Schrot says. “So we were able to show, for example, that glioblastoma has the highest numbers in non-Hispanic white males, and incidence rates for benign tumors, such as meningioma, are very high in black females.”

Beyond their intrinsic value, such descriptive studies form the foundation for future investigations and provoke new research questions, Schrot says, “such as why would some tumors be higher in some groups than in others? Is it genetics? Is it access to health care? Are there environmental factors?”

Primo Lara Jr., a medical oncologist,

professor of medicine and associate director for translational research at UC Davis Cancer Center, has partnered with the registry to investigate stage migration in non-small-cell lung cancer. The phenomenon describes a change in cancer staging because of technological advances that allow for more sensitive detection of tumor spread. He also has worked with the registry to study disparities in non-small-cell lung cancer therapy and outcomes, and trends in kidney cancer epidemiology in both the cytokine era and targeted therapy era. Much of this work has been published in major cancer journals.

Lara values the registry for its ability to “provide the investigator with the ‘30,000-foot view’ of the state’s cancer landscape, allowing one to identify and pursue research



“My hope is that this will **substantially increase the research collaborations** between the registry and clinical researchers at the cancer center, **leading to improvements in treatment for cancer patients and reductions in health care disparities.**”

~ Rosemary Cress



“Developing a **shared resource in epidemiology** would be a tremendous step toward **building a fruitful and long-term collaboration** between the cancer center and the registry.”

~ Rudolph Schrot

gaps in public health as it relates to oncology.” Formalizing the partnership, he says, would give UC Davis researchers more tools to generate and test hypotheses and “pursue team-based science in cancer epidemiology.”

Perhaps the most fruitful area of research involving registry data has focused on women’s cancers, an emphasis aided in 1999 when former Sen. Debra Ortiz (D-Sacramento) and other lawmakers set aside about \$300,000 for the work. Most recently, in January’s online edition of the journal *Gynecologic Oncology*, UC Davis and registry researchers reported that more than a quarter of women with apparent early ovarian cancer do not receive the lymph node biopsies proven to improve patient survival.

Only 72 percent of patients with presumed early stage disease had lymph nodes from the pelvis and abdomen tested for signs of cancer spread, despite published professional guidelines for proper staging of the disease. Their findings were based on an analysis of medical records and registry data on more than 700

patients in California and New York. The results also showed that the five-year survival for women who, in the early stage of the disease, had the node biopsies was 84 percent, compared with 69 percent for those who did not have the tests.

The study’s lead author was Rosemary Cress, an epidemiologist and research program director at the registry, and an associate adjunct professor in the Department of Public Health Sciences at UC Davis. The senior author was Gary Leiserowitz, chief of gynecologic oncology at UC Davis Cancer Center.

It was not the first time the pair used registry data to produce important findings. Leiserowitz, benefitting from the linkage of registry files with a database of hospital deliveries, found in an earlier study that although ovarian masses are relatively common during pregnancy, they are not typically malignant, a conclusion that has allowed many women to avoid surgery while pregnant.

In another seminal finding,

Lloyd Smith, professor in the Department of Obstetrics and Gynecology at UC Davis, teamed up with a registry research scientist to dispel the myth that ovarian cancer is a “silent disease,” announcing itself only in late stages, when prognosis is poor. Instead, their study found that patients with ovarian cancer were more likely than two groups of other patients to report symptoms such as abdominal swelling and pain.

Cress and Brown, the duo of registry epidemiologists who have worked most closely on projects with UC Davis, are optimistic that the shared resource will pay off handsomely in terms of research and, ultimately, patient well-being.

“My hope is that this will substantially increase the research collaborations between the registry and clinical researchers at the cancer center, leading to improvements in treatment for cancer patients and reductions in health-care disparities,” Cress says.

Adds Brown: “It’s really smart of UC Davis to continue building bridges between the campus and the registry. They recognized that they had a huge asset right in their backyard, and the staff at the registry are ready and willing partners.”

Focus on finding a cure

New Phase I clinical trials director aims to offer patients more promising therapies

Karen Kelly's office walls are still bare, but her desk and shelves are piled high with research articles and study proposals. The new professor and Phase I clinical director has wasted no time working on ways to make UC Davis Cancer Center a national leader in early clinical trials accrual.

"Clinical trials are enormously important, and the more that we can offer, the better," Kelly said in an interview just one month after she arrived at UC Davis Cancer Center.

"Conducting clinical trials is the only way we will cure cancer."

Kelly is an internationally recognized lung cancer expert at the forefront of evaluating anticancer agents, primarily for small-cell and non-small-cell lung cancer. Before coming to UC Davis, she served as deputy director of the University of Kansas Cancer Center, where she built an infrastructure that revitalized their clinical trials program to better serve patients and streamline the process for physicians.

"We are extremely excited about bringing Karen Kelly to UC Davis Cancer Center," says Ralph deVere White, associate dean for cancer programs at UC Davis School of Medicine and cancer center director. "She is a seasoned investigator who more than doubled patient accrual to clinical



“Clinical trials are **enormously important**, and the **more that we can offer, the better**. Conducting **clinical trials is the only way we will cure cancer.**”

~ Karen Kelly

trials in just three years at the University of Kansas Cancer Center. She is also an outstanding clinician as well as mentor to physician-scientists.”

According to Kelly, Phase I studies can be the most challenging among clinical trials. Phase I trials are designed to determine the most effective dose and to evaluate a drug’s safety; often a Phase I drug is being used in humans for the first time. (Phase II trials help determine whether the drug actually helps fight

a disease, and in Phase III trials, the new drug is tested against the current standard therapy.)

Although Phase I trials typically involve as few as three patients, they are extremely costly. Subjects must be monitored very closely in a clinical setting by an expert team of scientists, physicians, pharmacists and nurses, who regularly evaluate patients for changes in their blood chemistry and other target tissues.

Kelly says that her top priority

in her new job is to enhance access for patients to many more leading-edge drugs. She hopes to make the process of getting promising new agents – many being developed at UC Davis – to clinical trials more efficient. She also aims to build partnerships with small biotechnology companies that need an academic medical center and large patient base to test new compounds.

UC Davis Medical Center holds a National Cancer Institute grant for

Phase I clinical trials, which Kelly acknowledges is a privilege given to only a few institutions in the country.

“We already have a stellar program here, and I just hope to enhance and expand it,” she says. “I have been so impressed with everyone’s willingness to work together collaboratively – at the

end of the day that is the most important ingredient for success.”

Kelly also intends to design curriculum in Phase I clinical trials development to be offered as a subspecialty of the existing hematology-oncology fellowship program. Not many institutions have such a program, she says, and more are

desperately needed to increase the nation’s capacity to test new therapies.

In addition to her responsibilities at the Cancer Center, Kelly serves on numerous national committees: as chair of the board of directors for the International Association for the Study of Lung Cancer (IASLC), as a member of the board of scientific

“Patients understand that they are **contributing to science**. Curing cancer is about **an entire team** of absolutely critical components – **scientists, physicians and patients**. But most importantly, clinical trials **offer hope**.”

~ Karen Kelly



ASK
ME ABOUT
**CLINICAL
TRIALS**

counselors for the National Cancer Institute, and on several program committees for the World Conference on Lung Cancer. She has been the medical oncology track leader for the Lung Cancer Committee in the Southwest Oncology Group since 2002. She also has authored or contributed to more than 150 papers, reviews and book chapters, and frequently lectures on lung cancer topics at conferences worldwide.

“Karen is a top-notch lung cancer researcher and a dynamic leader,” says Joan Schiller, deputy director of Simmons Cancer Center at the University of Texas Southwestern Medical Center, who has worked with Kelly at IASLC and on several other national committees. “UC Davis is extremely lucky to have her.”

Along with her administrative duties, Kelly continues to practice medicine in the oncology clinic. “My patients motivate me,” Kelly says. “Lung cancer is the leading cause of cancer deaths – both in this country and worldwide. Patients desperately need more options.”

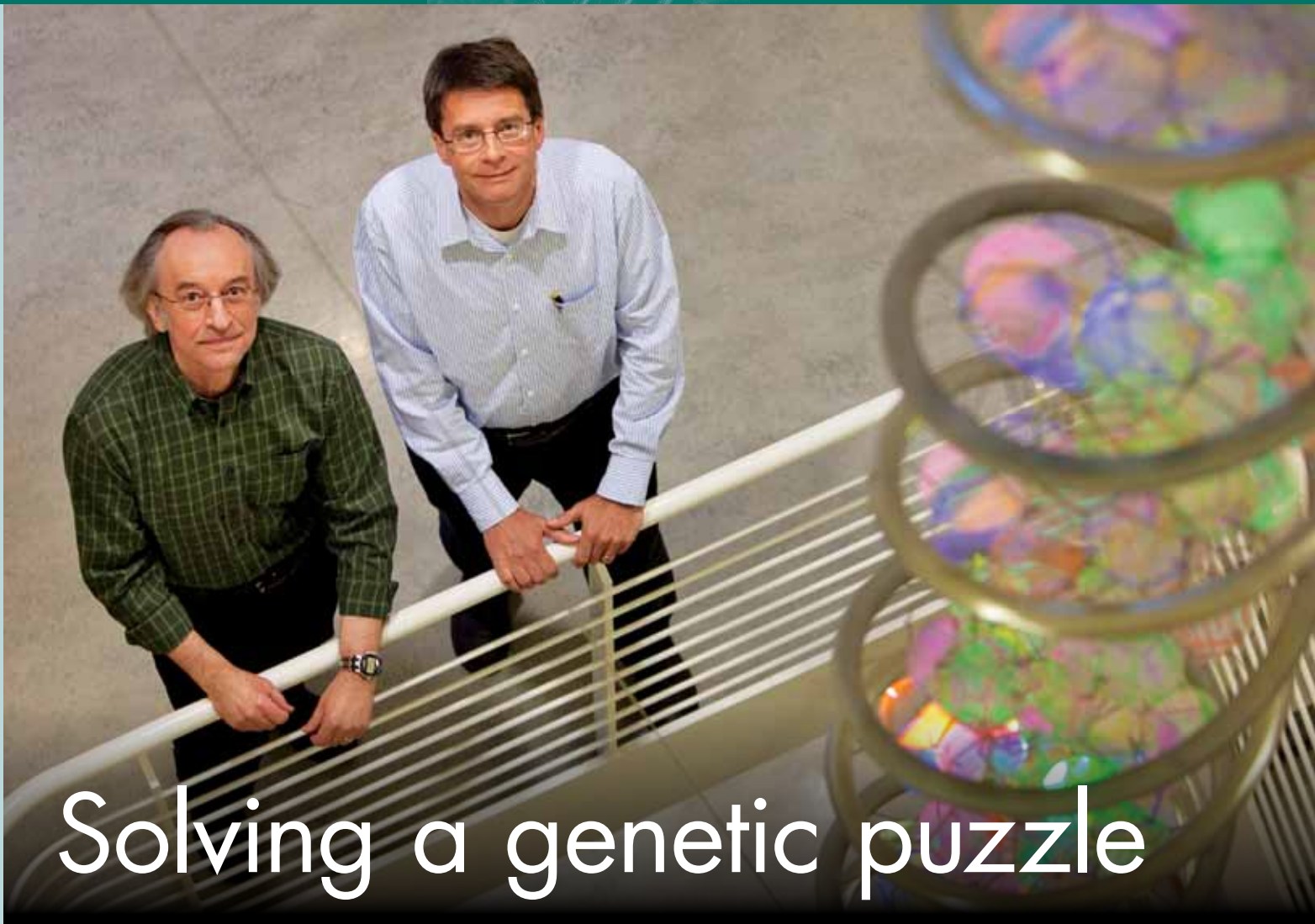
How does she convince someone that it is a good idea to enter a trial that will only determine whether a drug is safe?

“Patients understand that they are contributing to science,” she says. “Curing cancer is about an entire team of absolutely critical components – scientists, physicians and patients. But most importantly, clinical trials offer hope.”



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Building on basics>>



Solving a genetic puzzle

Major findings open doors in DNA repair research

Of all the genetic factors implicated in breast cancer, mutations in the BRCA2 gene are among the most foreboding. They're a factor in about half of all cases of hereditary breast cancer, and BRCA2 mutations are also associated with an increased risk of ovarian and a number of other cancers.



“This is **very exciting** and **opens doors to understand the detailed action** of this elusive, yet dreadful, tumor suppressor. It **illustrates how basic biochemistry** in the lab can have a **significant impact clinically.**”

~ Hsing-Jien Kung

The BRCA2 protein, produced by the BRCA2 gene, which was discovered in 1994, plays a crucial role in DNA repair. It helps fix problems that can occur during cell division and, if allowed to accumulate, can lead to cancer. Scientists don't have a detailed understanding of the protein's function, largely because they haven't had a complete version of the human BRCA2 protein to work with, despite a decade and a half of research in labs around the world to purify it.

“The lack of a full-length protein was a real impediment. It really held back the field,” says Wolf-Dietrich Heyer, co-leader of UC Davis Cancer Center's molecular oncology program.

The BRCA2 protein is difficult to isolate because of its size and instability – with 3,418 amino acids, it is four or five times the size of the

average protein. Researchers have had to make do with studying snippets of it, or investigating similar proteins found in worms, flies or fungi.

But now, two groups of UC Davis researchers, working independently but collaboratively, have successfully isolated the human BRCA2 protein, and they've used it to study how the protein helps mend muddled DNA. Funding for the research came from the National Institutes of Health, the U.S. Department of Defense Breast Cancer Research Program, the Susan G. Komen Breast Cancer Foundation,

and UC Davis Cancer Center.

Their achievement will enable scientists to study BRCA2 function in much more detail, and to investigate how the hundreds of known mutations in the gene affect the protein's vital repair role. It may also help researchers develop new tools for diagnosing breast cancer and identifying promising strategies for fighting the disease.

“This is very exciting and opens doors to understand the detailed action of this elusive, yet dreadful, tumor suppressor,” says Hsing-Jien

The BRCA2 protein is **difficult to isolate** because of its **size and instability** – with 3,418 amino acids, it is **four or five times the size of the average protein.**

Building on basics>>

Kung, basic science director at UC Davis Cancer Center and distinguished professor of biochemistry and molecular medicine. “It illustrates how basic biochemistry in the lab can have a significant impact clinically.”

There was intense and widespread interest in purification of the protein, says Heyer, whose research group – including post-doctoral researcher Jie Liu, staff research associate Tammy Doty, and Bryan Gibson, now a doctoral student at Cornell University – produced the BRCA2 protein from genetically engineered yeast, adding protein tags to help stabilize it and make it more soluble. The work, which Heyer says involved “an enormous amount of expertise and dedication,” was reported in the journal *Nature Structural and Molecular Biology*. In a lab just down the hall, Heyer’s colleague Stephen Kowalczykowski, a distinguished

Having the **purified protein** also will be a **boon for researchers** looking for **new ways of battling breast cancer**. Therapies could be developed that bolster the BRCA2/RAD51 repair process, **to keep cells healthy**, or they could be **used to disrupt it in cancer cells**, leaving them vulnerable to other treatments.

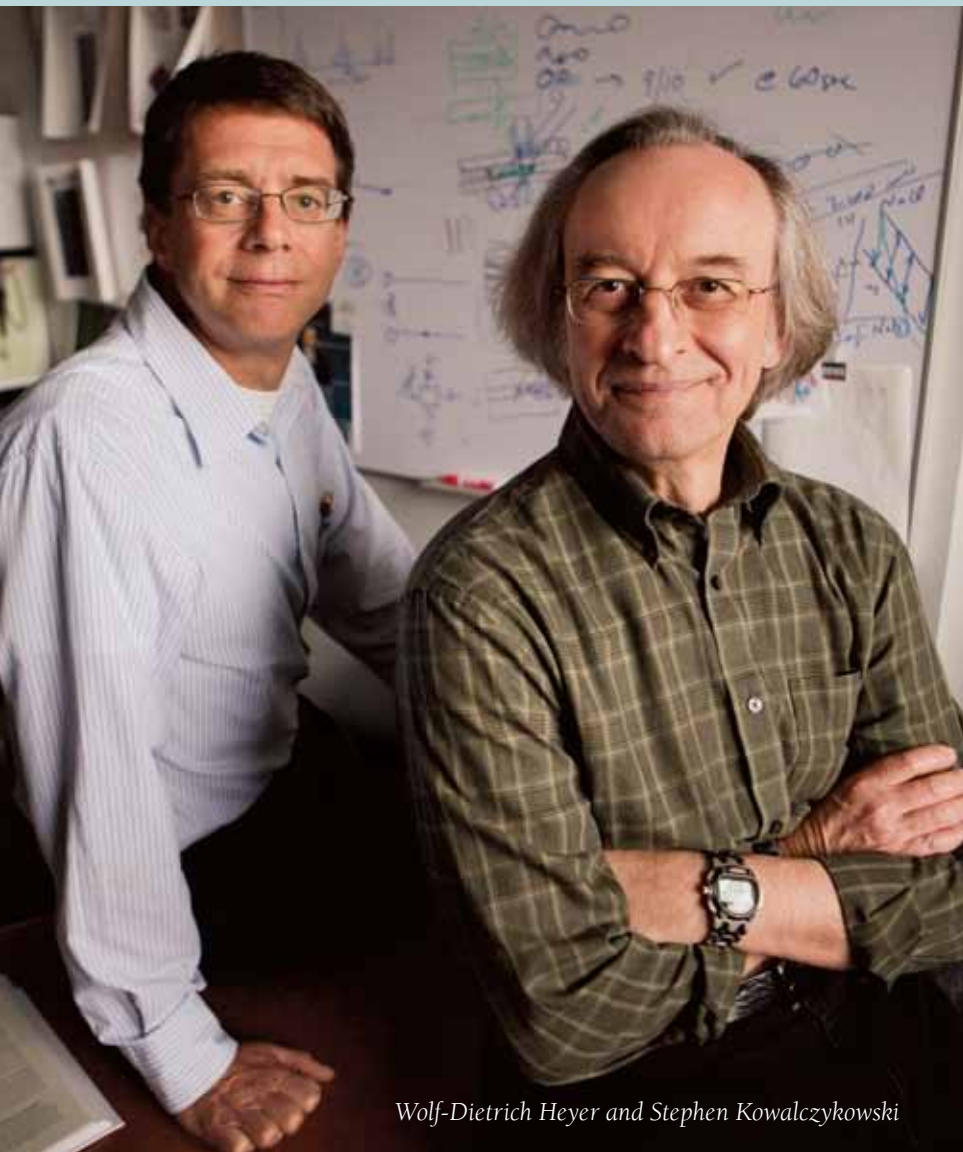
professor of microbiology who is also with UC Davis Cancer Center, led a group that isolated the BRCA2 protein from cultured human kidney cells, also using protein tags to help the process. Kowalczykowski and postdoctoral researchers Ryan Jensen and Aura Carreira reported their results in the journal *Nature*.

Having obtained the complete protein, the Davis researchers then

turned their attention to investigating its function and how it interacts with other proteins to perform vital repair work. They determined that it works with the RAD51 protein to fix breaks in double-stranded DNA in a process called homologous recombination, which is practically universal, occurring in everything from yeast to plants to primates. The RAD51 protein winds around a single strand of DNA and uses the matching DNA section from the paired chromosome as a template to perform repairs. BRCA2 mediates this process, the researchers found, by helping RAD51 bind to damaged DNA and stimulating its activity. Heyer and his colleagues also discovered that another protein, DSS1, is directly required for this repair process, which is the best means a cell has of maintaining the quality of its DNA.

Now, with the BRCA2 protein purified, researchers will be able to investigate how mutations in the BRCA2 gene can hobble homologous recombination, forcing cells to resort to the more error-prone repair process – predisposing women

Having obtained the complete protein, the Davis researchers then **turned their attention** to investigating its **function** and how it **interacts with other proteins** to **perform vital repair work**.



Wolf-Dietrich Heyer and Stephen Kowalczykowski

“For any type of drug targeting, one will need the protein to develop the approach. We’ve only really scratched the surface.”

~ Wolf-Dietrich Heyer

carrying the mutations to breast and other cancers.

Genetic tests can be used to detect BRCA2 mutations, but the results can be difficult to interpret. With a clearer picture of the protein’s functioning, Heyer says, scientists should be able to better understand the effect and significance of a particular mutation. Kowalczykowski adds that with the complete BRCA2 protein available, “it should be

possible to make good antibodies that could be used in inexpensive screening tests.”

Having the purified protein also will be a boon for researchers looking for new ways of battling breast cancer. “Knowing the molecular basis of BRCA2 malfunction can help researchers develop therapies for malfunction,” Kowalczykowski says. Therapies could be developed that bolster the BRCA2/RAD51 repair

process, to keep cells healthy, or they could be used to disrupt it in cancer cells, leaving them vulnerable to other treatments.

“For any type of drug targeting, one will need the protein to develop the approach,” Heyer adds. For now, though, he and Kowalczykowski are focused on understanding BRCA2 functioning.

“We’ve only really scratched the surface,” Heyer says.



Robyn Raphael: Unstoppable advocate

Memorial philanthropy thriving 13 years after Keaton's death from cancer

Childhood cancer is a journey no parent expects to take.
And it's a journey no parent should travel alone.

“To date, we’ve helped more than 850 families with financial assistance, resources and education. We really try to deal with the full journey: the beginning diagnosis, treatment, survivorship or loss.”

~ Robyn Raphael



Keaton Raphael
Memorial’s Childhood
Cancer Family
Navigator Program
**links families to
the resources they
need to stay afloat
financially and
emotionally during
this trying time.**

That’s the mantra of Robyn Raphael, a pioneering advocate for families enduring the arduous, emotionally wrenching and isolating journey through a child’s cancer diagnosis, treatment and, sometimes, death.

Raphael, 46, of Roseville, Calif., knows firsthand the pain and confusion a family endures when a child receives a diagnosis of cancer. She lost her 5-year-old son, Keaton Raphael, to neuroblastoma in 1998 after a nine-month battle with the illness that included treatment at UC Davis Cancer Center and a stem cell transplant in Boston.

The loss of Keaton was a turning point for Raphael on many levels, she says. It forced her to dig deep and find the fighting spirit within herself that now energizes her to help others, including many families at UC Davis Cancer Center, moving through the painful journey of childhood cancer. Raphael also now advocates on the state and national levels for increased funding for childhood cancer research.

“After we lost Keaton and we came home, it became more about fighting back and doing something,” recalls Raphael.

Raphael, who holds a master’s degree in public policy administration,

has been “doing something” about childhood cancer ever since. As founder of the Roseville-based non-profit organization, the Keaton Raphael Memorial, Raphael and a cadre of volunteers and employees have made immeasurable contributions to UC Davis Cancer Center and Children’s Hospital. The organization has donated nearly \$600,000 for childhood cancer research and vital services and cash assistance to struggling families maneuvering through the day-to-day rigors of childhood cancer treatment.

“To date, we’ve helped more than 850 families with financial assistance, resources and education,” says Raphael, a petite blond with seemingly boundless energy. “We really try to deal with the full journey: the beginning diagnosis, treatment, survivorship or loss.”

Accompanying a child through the maze of cancer care takes not just an emotional toll, but a financial one as well. Not many people are aware of the financial drain of the disease, says Raphael.

Even if a family has health insurance, the cost of caring for a child with cancer adds up. Frequent trips to the hospital for chemotherapy or other treatments can result in

higher fuel bills, time off from work to stay at a child's bedside, and increased child-care expenses for siblings who need care while parents are at the hospital are just a few of the added costs.

Keaton Raphael Memorial's Childhood Cancer Family Navigator Program links families to the resources they need to stay afloat financially and emotionally during this trying time. The non-profit receives many of its referrals from caseworkers at local children's oncology centers or through word of mouth. Families may be offered anything from gas cards to help pay for fuel to additional funds to make the rent or mortgage. At Christmas, some families are given gifts to help defray holiday expenses.

The Family Navigator Program also provides families with the names

"Your world is upside down. You feel as though you are the only one on earth going through this. You find out you are not."

~ Michael Jeffries

and phone numbers of other families on the same journey.

"What I was committed to was linking families to resources," says Raphael, who worked as an administrator in a city recreation department early in her career.

Cherie Trout's family is one of the many families getting through their cancer journey with the help of Raphael's non-profit. Trout's 2-year-old son Cooper Cochran is undergoing cancer treatment at UC Davis Cancer Center. The single mother has two older children at home, and feared that the frequent trips to the cancer center clinic would cause her to lose her job.

"I had been at my job for less than a year, so I didn't qualify for leave under the Family Medical Leave Act," Trout says. "I had to be by his bedside, and I had to make the trip four days a week."



Cooper Cochran

One of the **signature gifts** given by the Keaton Raphael Memorial is a **hope chest**, filled with **books and gifts for all family members coping** with the anxiety induced by a cancer diagnosis.



Cherie Trout
and son, Cooper

Accompanying a child through the maze of cancer care takes not just an emotional toll, but a financial one, as well. Not many people are aware of the financial drain of the disease.

The non-profit provided Trout with a \$500 check to help defray costs associated with her son's treatment. Members of the group also found a local car dealership to donate labor to help repair Trout's car.

"Anything I need, I call," says Trout.

One of the signature gifts given by the Keaton Raphael Memorial is a hope chest, filled with books and gifts for all family members coping with the anxiety induced by a cancer diagnosis. If a child succumbs to the disease, the family is given a bereavement box with helpful books, as well as names and phone numbers of people to lend support.

"They sent us a hope chest," says Trout. "It was great for the older kids to not feel left out of the process."

Michael Jeffries, whose son William was diagnosed with cancer five years ago, remembers coming home one day after one of his son's treatments.

"I got home and there was this great big box on the front porch," says Jeffries. "I had no idea... I sat there and cried. I was so touched by it."

The box was filled with books, gift cards, gas cards and homemade blankets, says Jeffries. But it contained so much more, he adds,

remembering the referrals to other families who had gone through or were going through the same thing.

"Your world is upside down. You feel as though you are the only one on earth going through this," says Jeffries. "You find out you are not."

Jeffries' son is now 17 and cancer-free, but he lost much of his eyesight from the cancer treatments. William attends the California School for the Blind.

"He's a very positive kid," says Jeffries.

The Keaton Raphael Memorial also raises money for cancer research through donations, sponsorships and co-sponsorships of various fundraisers, such as the Chipping Away at Childhood Cancer Golf Tournament, and the St. Baldrick's hair-shaving event. The non-profit also is a partner in the Beads of Courage program, which awards specific beads to cancer survivors and their families at certain milestones along the cancer journey. Those milestones could be a first treatment of chemotherapy or recovery from a surgery.

Raphael's organization also provides beads, paints and other crafts materials – as well as a cadre of volunteers – for the annual holiday

party put on at the cancer center for young patients and their families.

Raphael also is California team leader and parent advocate for CureSearch for Children's Cancer, an organization that visits state legislators to advocate for increased funding for childhood cancer research. Raphael and others claim the efforts of such advocacy groups were instrumental in the 2008 passage by Congress of The Caroline Pryce Walker Conquer Childhood Cancer Act, a landmark bill signed by former President George W. Bush that earmarks \$40 million a year for five years to childhood cancer research.

Raphael says her advocacy efforts around childhood cancer are a vital part of her journey through Keaton's illness and passing.

"It was part of my healing journey to jump in," she says. "It felt like my way of fighting back."

Raphael has been an inspiration to Trout, who says she'd like to form her own organization some day to help other single mothers like herself cope with the difficult diagnosis and treatment of a child's cancer.

For more information on the Keaton Raphael Memorial visit www.childcancer.org.

Making their mark against breast cancer

UC Davis researchers zero in on molecular targets

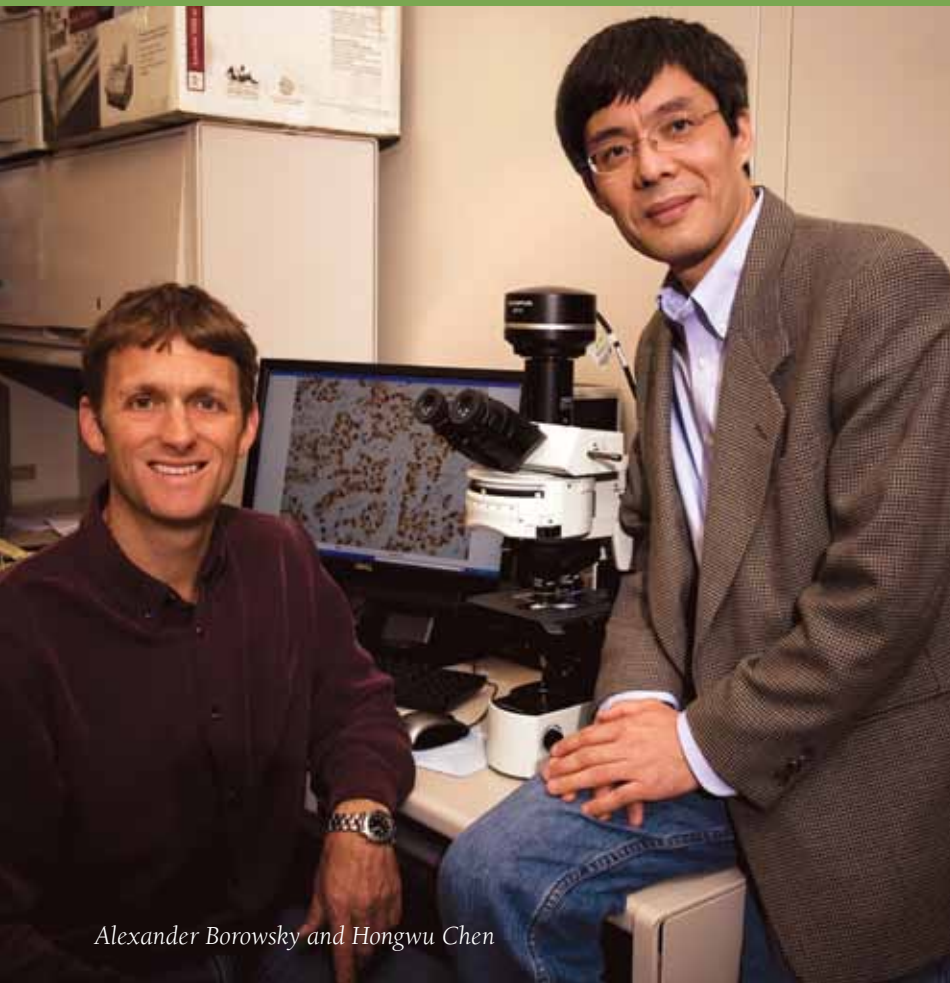
How best to treat each case of breast cancer is a thorny problem for doctors. Although breast tumors all originate in one type of tissue, the mechanisms behind their uncontrolled growth can be wildly different. Pinpointing what has gone awry can be crucial to halting breast cancer in its tracks.

Yet for many decades, the treatment for most patients was essentially the same. Doctors removed tumors via mastectomy or lumpectomy, sometimes added radiation to treat the site, administered chemotherapy to reduce the risk of metastasis, then both patient and doctors hoped for a cure.

That treatment scenario is now much more individualized. Researchers have found ways to classify tumors by their molecular characteristics. Now every breast tumor biopsy is subjected to three tests to determine whether the tumor produces estrogen receptor (ER), progesterone receptor (PR) or human epidermal growth factor receptor 2 (HER2). The results help steer clinicians toward therapies directed at these molecules.

But no oncologist will claim that three breast cancer biomarkers are enough. That's particularly true for patients afflicted with triple-negative tumors. These cancers cannot be treated with drugs that knock down ER, PR or HER2. To make matters worse, triple-negative tumors are notorious for recurrence and poor patient survival rates.

That bleak outlook is set to change. UC Davis Cancer Center researchers are hot on the heels of two new and promising breast cancer biomarkers. They are demonstrating how these molecules affect breast tumor growth, and tracking how patients with these biomarkers fare. In doing so, they hope not only to increase the methods available to characterize breast tumors, but zero in on new ways to research and treat this devastating cancer.



Alexander Borowsky and Hongwu Chen

“A biomarker can be clinically useful by itself. But if at the same time it has the potential to serve as a target, then its value is twofold.”

~ Hongwu Chen

The twofold potential of ANCCA

An associate professor of biochemistry at UC Davis School of Medicine, Hongwu Chen is exposing, one by one, the nasty secrets of a protein called ANCCA. With Alexander Borowsky, an associate professor in the school's Department of Pathology and Laboratory Medicine, Chen is demonstrating a close association between ANCCA and its role in tumor grade and cancer growth. Their work may be instrumental in finding new therapies for treatment-resistant triple-negative breast tumors.

In 2009, the two reported finding high levels of ANCCA in a broad range of tumors, including prostate, liver, lung, ovarian, endometrial and brain cancers, as well as lymphoma. More recently, they have used the antibodies Borowsky developed to

detect ANCCA on 225 breast tumor samples collected at UC Davis Cancer Center.

“ANCCA is common, rampant in human cancers,” Chen says. “It was overexpressed in about 70 percent of the tumors we analyzed. That's unprecedented. Most other proteins considered to be “oncoproteins” are elevated in about 30 to 50 percent of tumors.”

Even more striking, however, is ANCCA's association with triple-negative breast tumors. More than 88 percent of the triple-negative

tumors in the study showed high levels of the protein. The finding is particularly surprising, because triple-negative tumors are not considered a homogeneous group. The fact that ANCCA is found in so many “strongly implicates ANCCA as a potential link to the vast majority of the different mechanisms already identified for triple-negative tumors,” Chen says.

When matched stage to stage, the tumors with higher levels of ANCCA also tended to be at a more advanced grade (their cells were the most

UC Davis Cancer Center researchers are hot on the heels of two new and promising breast cancer biomarkers.

abnormal) and proliferated rapidly. Patients with such tumors also turned out to have the poorest outcomes.

“It was present at lower levels in lower-grade lesions and at higher levels in higher-grade lesions,” Borowsky says. This correlation means ANCCA could serve as an excellent biomarker for breast cancer prognosis.

Several lines of evidence make Chen and Borowsky suspect ANCCA also is central to causing disease, including the fact that when the gene was suppressed, cell culture lines were less likely to grow and proliferate.

Both scientists are eager to use ANCCA as a way to gauge how well

certain treatments work. Chen already has plans to piggyback additional ANCCA studies on future UC Davis Cancer Center clinical trials. He wants to see whether ANCCA levels turn out to be a good predictor of therapy effectiveness.

“We suspect that along with the grade there are other biological factors that make them hard to treat. We want to know whether ANCCA is one of those alternate pathways that can be targeted with drugs,” Borowsky says.

ANCCA also has two structural characteristics, one called a bromo-domain and the other an ATPase

domain, which are necessary for it to function. Scientists have inactivated similar domains on other proteins with small molecules engineered for the task. This makes Chen and Borowsky hopeful that this approach will result in a drug against ANCCA.

“A biomarker can be clinically useful by itself. But if at the same time it has the potential to serve as a target, then its value is twofold,” Chen says.

The implications of extra copies

Cancer is associated with the accumulation of changes in the structure of a cell’s DNA. Among those changes can be the duplication

Krig is thrilled by the twists and turns her research can take. **“It’s a daily surprise,”** she says. But what propels her into the laboratory every workday is more altruistic. **“I feel one day our work might help someone.”**



Sheryl Krig

Identifying aggressive tumors is a major headache for oncologists. Krig hopes to solve this problem by **developing a biomarker test** for early metastatic disease.



or “amplification” of long stretches of genetic material.

“That’s probably a bad thing,” says Sheryl Krig, a project scientist with the UC Davis School of Medicine Department of Biochemistry and Molecular Medicine. “That means the DNA has been aberrantly duplicated during the genomic and genetic instability that happens during the early stages of cancers.”

Roughly 20 such amplification hotspots in the genome have been found to be associated with breast cancer. Krig, who received her Ph.D. in biochemistry and molecular biology at UC Davis in 2001, is investigating whether the amplification of one area in particular, the 20q13 locus, is linked to the risk of tumor metastasis.

“Some tumors will just sit there and not go anywhere,” Krig says. “Those patients can just do chemotherapy treatment and forget about the drastic mastectomy.

“Some tumors have the capacity

to spread beyond their initial site, a step that is typically fatal.”

Identifying aggressive tumors is a major headache for oncologists. Krig hopes to solve this problem by developing a biomarker test for early metastatic disease.

Previous studies have found that about 20 percent of breast tumors have multiple copies of 20q13. This location is thought to be the chromosomal area that codes for a protein called ZNF217.

Krig and Jeffrey Gregg, a UC Davis associate professor of pathology, plan to test 100 breast tumors that show 20q13 amplification. The researchers will then determine whether the 20q13 locus in these tumors does indeed include multiple copies of the gene for ZNF217. They will try to confirm that tumors with more copies of the gene also have higher levels of ZNF217 expression, then examine how the patients with high versus low ZNF217 levels fared.

“In the samples where we see lots

of copies of ZNF217, for example, did the patient die of breast disease or survive? Were they estrogen receptor positive or negative? Were there lymph node metastases? The idea is to determine whether ZNF217 will be a biomarker for the actual degree of aggressiveness of the tumor,” Krig says.

Krig also plans to grow breast tumor cells that overexpress ZNF217 in a three-dimensional solid culture matrix. She will study whether the tissues formed by the modified cells are more invasive in a manner similar to what is seen in biopsy samples.

If at the end of the two-year study ZNF217 correlates with more aggressive cell growth in culture and patients, the test will go into clinical trials.

Krig is thrilled by the twists and turns her research can take. “It’s a daily surprise,” she says. But what propels her into the laboratory every workday is more altruistic. “I feel one day our work might help someone.”

National Cancer Survivors Week scheduled for May 31 – June 4

UC Davis Cancer Center will celebrate National Cancer Survivors Day with a week of events that conclude with the annual picnic for cancer survivors and their families – this year at a new location.

Events begin on Tuesday, May 31 with a free “learn-at-lunch” session on the WeCARE! Cancer Peer Navigator program, which pairs specially trained cancer survivors with



patients for the first three to six months after their diagnosis. The event will be held in the Cancer Center auditorium from noon until 1 p.m.

On Thursday, June 2, a free workshop on food and nutrition will be held from 2 to 4 p.m. in the lunchroom on the first floor of the Facilities Support Services Building, 4800 Second Ave.

The survivors picnic, on Saturday, June 4,

will include a barbecue lunch, a survivor art exhibit and performance by musician Danny Cocke, a cancer survivor and founding member of the UC Davis Adolescent and Young Adult Cancer Advisory Board.

This year’s picnic will take place in front of the Facilities Support Services Building from 11 a.m. to 1 p.m. Lunch, provided by Outback Steakhouse, will be available to the first 250 registered participants. To register for any of the events call 916-734-0823.

New effort to address cancer-health disparities among American Indians

UC Davis Cancer Center and the California Tribal Epidemiology Center (CTEC) of the California Rural Indian Health Board have agreed to collaborate on various initiatives to strengthen cancer education, outreach and awareness among American Indians.

The partnership, formally established in January, allows for collaboration on cancer prevention and control research,

outreach program development, undergraduate and graduate student research, scholarships and training for American Indians.

The two organizations will apply for grants to study American Indians in California and their knowledge of cancer, including barriers to prevention, early diagnosis and treatment. They also plan to research interventions that address cancer risk factors.

“Formalizing this partnership between UC Davis Cancer Center and the California Tribal Epidemiology Center gives both organizations the opportunity to significantly reduce cancer-health disparities among American Indians through collaborative education, research and training,” says Marlene von Friederichs-Fitzwater, director of the cancer center’s Outreach Research and Education Program.

Thomas Kim, a physician and medical epidemiologist with the CTEC, says the agreement will allow for a major focus on two issues, often related, that afflict the American Indian population in California: obesity and cancer.

“Difficult and complex problems such as these can only be addressed in creative collaborations and agreements such as this,” Kim says.

Partnership participants also hope to secure research funds to better understand the relationship of historical trauma experienced by American Indians and their mental and physical well-being.

“Historical trauma, described by Yellow Horse Brave Heart as the suffering of various oppressed aboriginal people, is an unexplored and potential component in understanding



American Indian/Alaska Native cancer prevention, research and treatment practices,” says Rebecca Garrow, a research associate with the CTEC. “Historical

trauma includes a legacy of numerous traumatic events over several generations, including colonialism, forced assimilation, boarding school, forced adoption programs, as well as racism, warfare, murder and cultural genocide leading to the loss of traditional life-ways.”

The California Rural Indian Health Board, founded in 1969, plans and develops Indian health programs in California. The CTEC, housed within the health board, works to reduce health disparities among American Indians in California, with funding from the Indian Health Service.

For more news stories, visit www.ucdmc.ucdavis.edu/cancer, click on “newsroom.”

Two cancer powerhouses join to lower breast cancer rates in rural Northern California

UC Davis Cancer Center and Susan G. Komen for the Cure, Sacramento Valley have joined forces to identify and respond



to the needs of California women with breast cancer in counties with some of the highest incidence and death rates from the disease.

The partnership, sealed with a memorandum of understanding in a ceremony at the cancer center, will expand the UC Davis WeCARE! Breast Cancer Peer Navigator Program into Butte, Sierra, Nevada and Plumas counties and increase the awareness and presence of Komen for the Cure.

Donna R. Sanderson, executive director of Komen's Sacramento Valley affiliate, calls the partnership an "example of everybody winning" that could become a national model.

"We have needs in rural communities. UC Davis has the navigator program," she says. "We thought if we married our programs, the peer navigators could take care of some of our volunteers' needs in the rural communities and some of our volunteers might become peer navigators themselves. All the women and their families in rural communities win."

The collaboration allows the two organizations to recruit and train volunteer breast cancer survivors to support newly diagnosed breast cancer patients through the first several months of treatment. Komen plans to use the partnership to attract more "ambassadors" for its local outreach efforts.

The two groups also work together to raise funds, host educational activities, collaborate on population-based studies on cancer prevention, control and care, and explore additional services to improve the quality of life for breast cancer patients and survivors in those communities.

Marlene von Friederichs-Fitzwater, director of the Outreach Research and Education Program at UC Davis Cancer Center, says mammography screening rates are poor and breast cancer incidence rates are among the highest in the state in rural communities.

"Many of our patients who receive care here go back to their rural communities and don't have the resources they need,"

von Friederichs-Fitzwater says. "By recruiting survivors in those communities and training them, our patients will have support when they go back home. Our specially trained peer navigators will help them identify the resources they need during treatment and through their transition to survivorship."

Cancer spread missed when early-stage biopsies not performed

More than a quarter of women with apparent early ovarian cancer do not receive the lymph node biopsies proven to improve patient survival, UC Davis Cancer Center and California Cancer Registry researchers have found.

The researchers analyzed the medical records and cancer registry data for more than 700 patients in California and New York. Their study revealed that only 72 percent of patients with presumed early-stage disease had undergone testing of lymph nodes from their pelvis and abdomen for signs of cancer spread. This oversight occurred despite published, professional guidelines for proper staging of the disease.

The study also found that the five-year survival for women with early-stage disease who had the node biopsies was 84 percent, compared with 69 percent of those who did not have the tests. Gynecologic oncologists were nearly six-and-a-half times more likely to perform lymph node biopsies than other surgical specialists, and nearly four times more likely to perform all recommended staging biopsies.

The study results were published in the journal *Gynecology Oncology*.

"Early-stage patients had nearly twice the risk of death if they didn't have the lymph nodes tested," says Rosemary Cress, an epidemiologist and research program director at the California Cancer Registry, associate adjunct professor in the Department of Public Health Sciences at UC Davis and the study's lead author.

"Hopefully, this should raise the awareness among physicians that it's really important to do lymph node biopsies in these patients."

Why some surgeons don't remove lymph nodes during ovary surgery for early-stage cancer patients is a matter of speculation, says Gary Leiserowitz, chief of gynecologic oncology at UC Davis Cancer Center, who was the senior author of the study. But the tests are important, he says, because patients with positive lymph nodes are given a more advanced-stage diagnosis and prescribed follow-up chemotherapy treatment.

Leiserowitz says he hopes the study results will help educate the medical community and patients about the value of appropriate cancer treatment.



Gary Leiserowitz

Colon cancer screening rates among different ethnic groups depend on geography

Whether or not people get screened for colon cancer often depends on where they live, in addition to their race or ethnicity, according to research by UC Davis Cancer Center oncologist Thomas Semrad.

It has long been known that racial and ethnic minorities have lower colorectal screening rates than whites, presumably because of differences in socioeconomic status, access to care and cultural issues. What hasn't been known, until now, is whether these differences also vary across geographic regions.

In a paper published online in the journal *Cancer*, Semrad and his colleagues demonstrated that while screening rates for whites rarely vary regardless of geography, location accounts for significant differences in colorectal testing among non-whites.

Semrad and his team analyzed data from 53,990 Medicare enrollees, ages 69 to 79, in eight states and 11 regions. Individuals were considered up-to-date on colon cancer screening if they had a colonoscopy or sigmoidoscopy within the prior five years, or fecal occult blood testing within the past year. The researchers controlled for sociodemographic,



Thomas Semrad

medical and environmental factors that could affect regional differences in colorectal cancer screening.

What they found was that whites were more likely to be up-to-date on screening than other races everywhere, except in Hawaii, where Asian/Pacific Islanders had significantly higher screening rates than whites (52 percent versus 38 percent).

"This is a stunning finding," says Semrad. "Screening rates among Asians in Hawaii were the highest of any group in any cancer registry area, including whites."

Semrad suspects that a potential explanation is the influence of Japanese culture in Hawaii. Since other gastrointestinal cancers are prevalent in the Japanese population, he says, this population may be more aware of the benefits of screening.

Geography also played a significant role in screening rate variations among African Americans, Semrad found. For example, in the state of Iowa, African Americans and whites had nearly identical screening rates, suggesting that access to screening is similar and that providers are recommending screening to Medicare enrollees regardless of their race or ethnicity.

The same was not true in the city of San Jose, Calif., where whites had similar screening rates to whites in Iowa (45 percent), but where screening rates among African Americans (29 percent) were among the lowest found in the study.

"The next step is to look at different geographic areas to see what the determinants are for minorities in terms of getting screened," says Semrad. "Are these culturally based? Are there problems with how health-care systems are set up? What are the barriers? If we can figure this out, we would have a target to improve some of these disparities."

Cancer screening study targets more than 1,000 American Indian women in California

UC Davis researchers have teamed up with an American Indian organization to bring an innovative program to women designed to foster understanding about the importance of breast cancer screening and, ultimately, lower the high death rate of the disease in the population.

With a grant from the California Breast Cancer Research Program, the Mother's Wisdom Breast Health Program will reach women from 26 California tribes through a network of American Indian clinics over the next three years.

"We hope to increase screening rates by 18 percent," says Marlene von Friederichs-Fitzwater, assistant adjunct professor of hematology and oncology at UC Davis and co-principal investigator for the project. "More screening should result in dramatic improvements in outcomes for American Indian women in California who are diagnosed with breast cancer."

The incidence of breast cancer among American Indian women has increased in the past 20 years, and breast cancer is now the second leading cause of death in this population. Screening rates among American Indian women are the lowest of any ethnic group, and American Indian women have the lowest five-year survival rates of any ethnic group. It is estimated that breast cancer mortality could be reduced by 30 percent if American Indian women followed routine screening recommendations.

Mother's Wisdom builds upon a successful pilot intervention tested with 161 American Indian and Alaska native women. Researchers found that participants who watched a culturally sensitive, interactive DVD increased their knowledge about breast health and the importance of early detection and, ultimately, got mammograms.

Progress reported on clinic-sized version of proton beam accelerator for cancer treatment

The long-awaited development of a proton beam accelerator that would fit into a typical radiation treatment suite has made a big leap forward, thanks to Compact Particle Acceleration Corporation (CPAC) and its collaborators at Lawrence Livermore National Laboratory.

The project, which began with the help of a multi-million dollar investment from UC Davis Cancer Center, aims to make cutting-edge radiation treatment for cancer more accessible and affordable so that more cancer patients can benefit from the therapy. Unlike X-rays, which can damage healthy tissue while traveling to a target, proton beams release their energy in a more confined way at their destination.

"We know that in 54 percent of cases treated with radiotherapy today, the patient can receive better or at least the same level of care with protons," says Anthony Zografos, vice president and general manager of CPAC, the company now building the technology. "Right now, that kind of treatment is really not available to most people in the world. We believe that when it is, this ultimately could replace most X-ray systems."

Proton beam accelerators typically take up a building the size of a basketball court, and cost up to \$200 million, making them off limits to most hospitals and cancer centers. Zografos and his Lawrence Livermore Laboratory research partners say they have overcome two major technical challenges to making the smaller prototype, and have demonstrated proton acceleration at the CPAC facility in Livermore.

Ralph deVere White, cancer center director, says he is thrilled with the progress of the proton beam accelerator. "It's exciting to see a project that experts told us had no chance of success move to a project that is swiftly moving closer to reality."

Researchers hope to have the first clinical prototype machine completed by mid-2013.

Cancer Center expansion project progressing

Claire Pomeroy (center) and other UC Davis Health System leaders joined a team of engineers, builders and architects in a "topping out" ceremony that marked the completion – on time and on budget – of the steel frame for UC Davis Cancer Center expansion project. The expansion has incorporated 700 yards of concrete, 50 tons of steel in the ground, 270 tons of steel above ground, 1,800 feet of underground piping and 5,836 bolts.



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Former Monarchs star Edna Campbell with a young fan at a women Aggies basketball game benefiting the UC Davis WeCARE! Breast Cancer Peer Navigator Program.

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Synthesis – the art of bringing together distinct elements in a way that makes them whole – is a particularly

relevant name for the magazine of UC Davis Cancer Center, which is distinct in its commitment to team science. Our research program unites clinical physicians, laboratory scientists, population specialists and public-health experts from throughout UC Davis and Lawrence Livermore National Laboratory with the goals of making cancer discoveries and delivering these advances to patients as quickly as possible. We are also dedicated to sharing our expertise throughout the region, eliminating cancer disparities and ensuring all Californians have access to high-quality cancer care. *Synthesis* – linking the best in cancer science toward the united goal of improving lives – is the name of our magazine, and our promise as your National Cancer Institute-designated cancer center.

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