SYNTHESIS

THE MAGAZINE OF **UC DAVIS COMPREHENSIVE CANCER CENTER** VOL 18 • NO 2 • FALL/WINTER 2015

MESSAGE FROM THE DIRECTOR

Dear Reader,

Great things can happen when you marry biology with technology. At UC Davis Comprehensive Cancer Center the relationship just keeps getting better.

In this issue of *Synthesis* we highlight several projects in which our biomedical science researchers are working to bring innovative technologies to physicians in the clinic and operating room so that they can better diagnose and treat cancer patients.

Our story on breast cancer innovations highlights Laura Marcu's laser technology that will be used during surgery to help physicians distinguish different types of tissue to protect healthy tissue, identify good margins around tumors, reduce patients' risk for additional surgeries and boost survival odds. Marcu's vision is also at play in a story describing the exciting work produced by our new innovation groups, which bring diverse talents together to address thorny problems in cancer.

You will also learn about the development of a dual imaging technique for breast cancer developed by Ramsey Badawi and John Boone that combines PET and CT scanning capabilities to better differentiate between tumors and healthy tissue.

We feature imaging technologies again in our story about Simon Cherry, whose work on a PET scanner that can view the entire body all at once could revolutionize cancer diagnosis, measure disease progression and effectiveness of therapy in less time, at a lower cost and with less radiation exposure.

These, plus an introduction to our new chief of Pediatric Oncology and an important program to find out why some Asian-Americans vary in their response to the hepatitis B virus and rates of related liver cancer are all included in your new issue of *Synthesis*.

Ralph de Vere White
Director, UC Davis Comprehensive Cancer Center
Associate Dean for Cancer Programs
Distinguished Professor, Department of Urology

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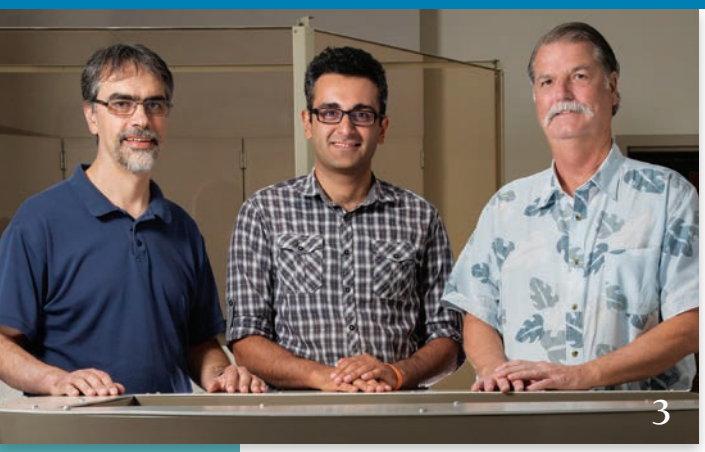

Breaking Barriers to Beat Cancer℠

INSIDE THIS ISSUE

UCDAVIS COMPREHENSIVE CANCER CENTER

A National Cancer Institute-designated comprehensive cancer center

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Tracking down breast cancer

Three advances in diagnosis and care

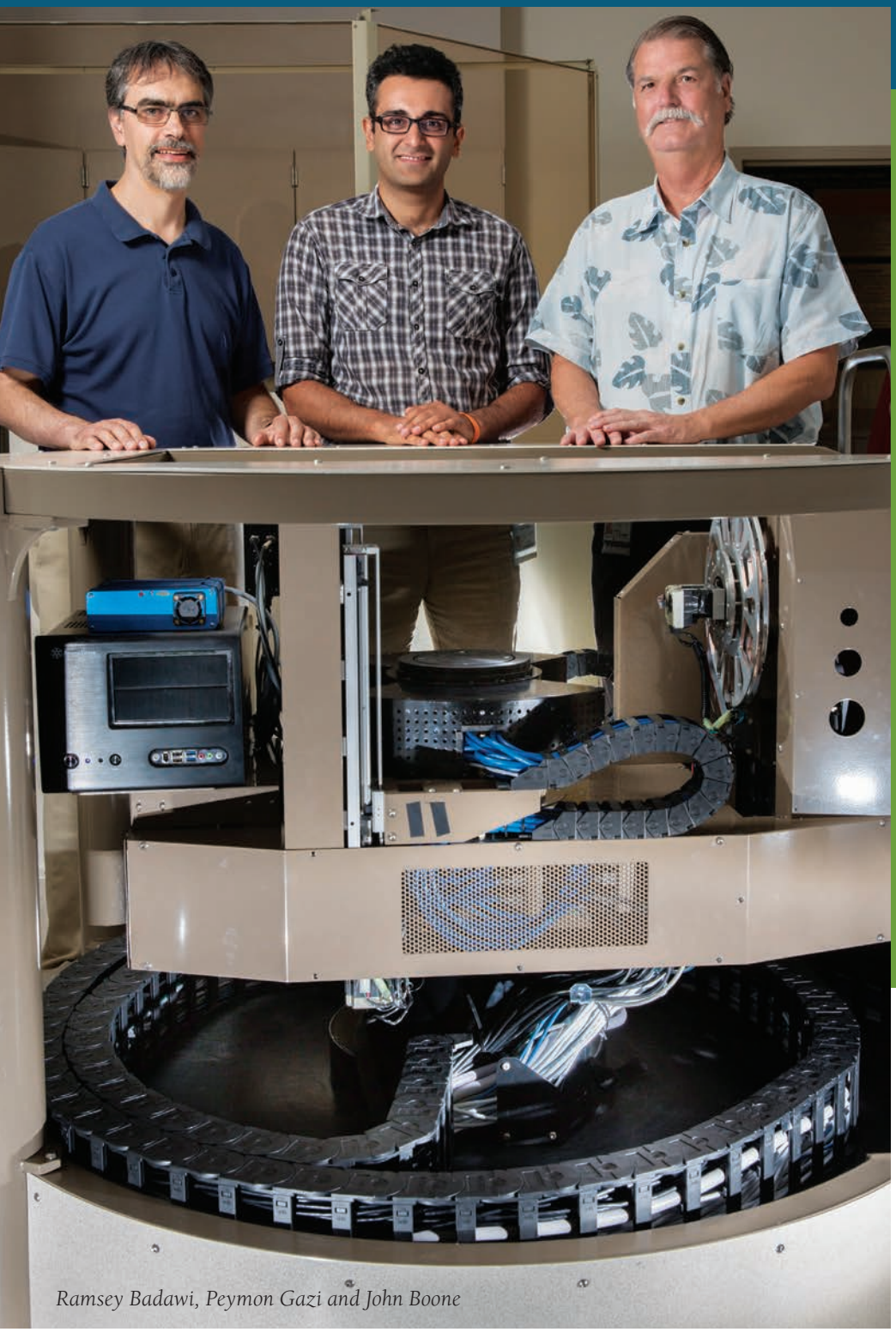
Detecting and treating breast cancer is like a biological game of hide-and-seek.

Clinicians must figure out whether a patient has cancer, how far the cancer has spread, and how much tissue to remove during surgery.

Precisely mapping tumors can translate into better outcomes. But cancer is good at this game. It knows how to evade detection, sometimes until it's too late.

To overcome cancer's advantages, researchers at UC Davis are developing advanced technologies to (sometimes literally) shine a light on tumors, differentiating malignant cells from normal tissue. Armed with these new approaches, clinicians will soon have better tools to seek out and destroy tumors, and improve the quality of life for breast cancer patients.

The scanner's high resolution and three-dimensional capabilities **could better differentiate** between tumors and healthy tissue.



Ramsey Badawi, Peymon Gazi and John Boone

To overcome cancer's advantages, researchers at UC Davis are **developing advanced technologies** to (sometimes literally) shine a light on tumors, **differentiating malignant cells from normal tissue.**

Beyond mammography

For women over 40, regular screening mammograms are an expected, albeit uncomfortable, inconvenience. The procedure can find small lumps and pre-cancerous calcifications that a self-exam might miss. Going one step further, diagnostic mammograms can help determine whether a suspicious lump is actually cancer.

But mammograms have limitations. They produce two-dimensional images of three-dimensional structures. This can be problematic, as normal glandular tissue and tumors have similar densities, giving cancer an opportunity to hide, particularly in women with dense breasts.

Researchers Ramsey Badawi and John Boone are working on a new system that could help — a small PET/CT scanner designed specifically to detect breast cancer. The scanner's high resolution and three-dimensional capabilities could better differentiate between tumors and healthy tissue.

"The whole idea behind this scanner is to unobscure the

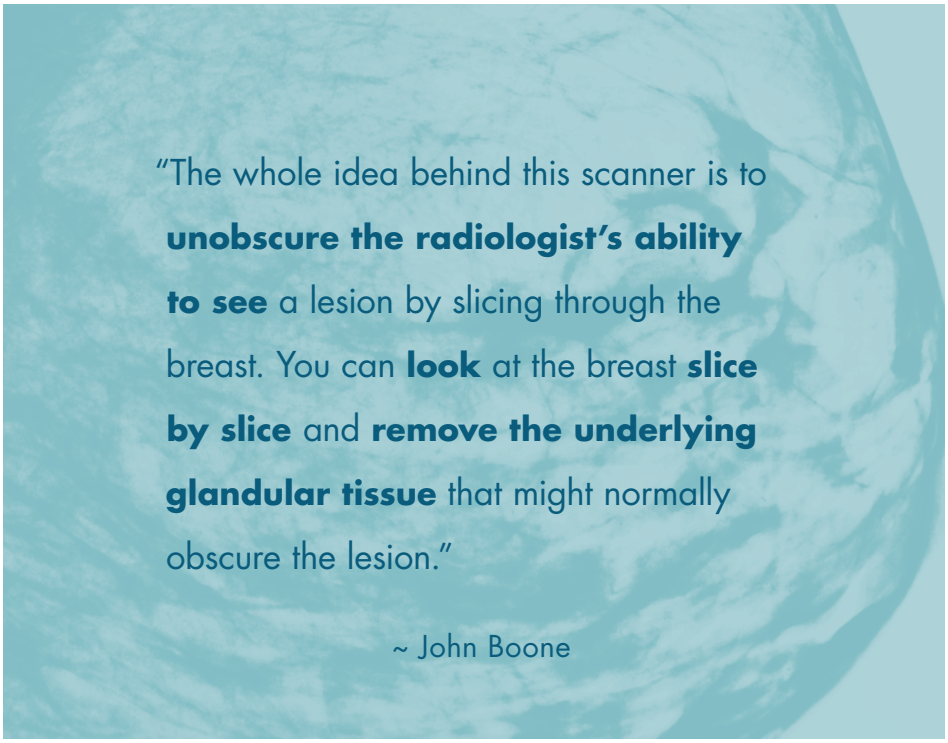
radiologist's ability to see a lesion by slicing through the breast," says Boone, professor of radiology and biomedical engineering, who manages the CT side of the project. "You can look at the breast slice by slice and remove the underlying glandular tissue that might normally obscure the lesion."

The positron emission tomography (PET) scanner makes the system even more powerful. Because malignant cells divide so rapidly, they tend to have bigger appetites. Patients are given an injection of a sugar tagged with a radioactive isotope. The radioactive sugar concentrates in hungry tumors, lighting them up for the PET scanner.

"You can really tell the difference between cancer and normal tissue," says Badawi, chief of nuclear medicine. "If you have cancer and milk-producing tissue right next to each other, it can be difficult to tell them apart. With a PET scan you can see the cancer more clearly."

Because the dual machine is built to detect breast cancer it must have high resolution, and each succeeding prototype has gotten better. With the current system, the PET can detect lesions as small as 1.2 millimeters, while the CT picks up calcifications as small as .1 millimeter. This technology could be especially useful for diagnostic imaging, determining if a lump is actually cancer. In addition, PET/CT could help oncologists track whether a treatment is working, giving them better data to make mid-course corrections.

Because the **dual machine** is **built to detect breast cancer** it must have **high resolution**, and each succeeding prototype has gotten better.

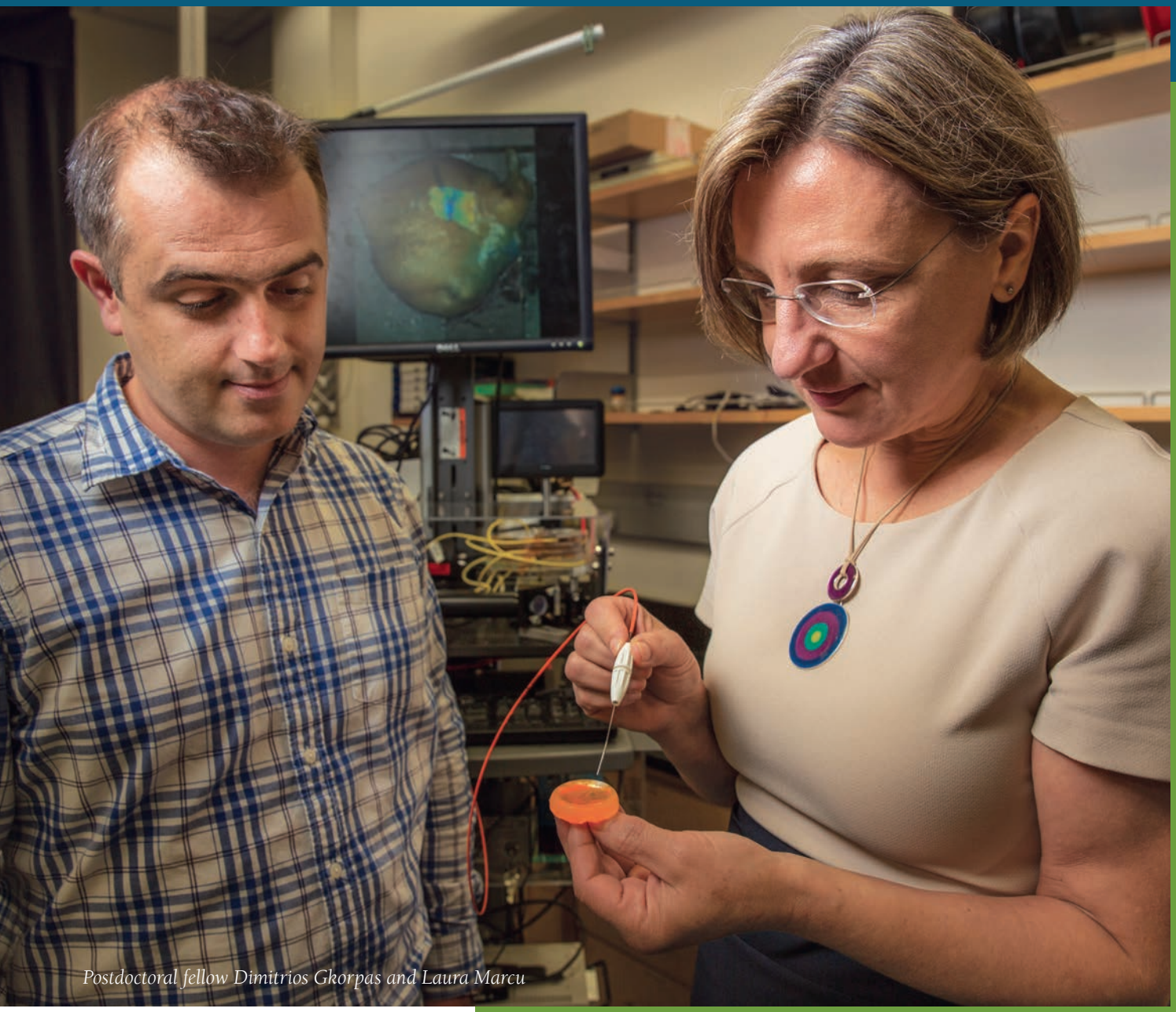


Surgical spotter

Once cancer is confirmed, it needs to be eliminated. In many cases, women receive a lumpectomy, followed by additional chemotherapy or radiation. During lumpectomies, surgical teams work diligently to get every bit of the cancer.

Immediately after it's removed, the tumor is sent to pathology and the outside cells closely examined. If pathologists find no cancer cells on the outer edge (negative margin), the procedure has been successful. However, if they do find cancer (positive margin), it's likely there are still malignant cells in the body, and additional surgery may be necessary.

But what if surgeons had a simple device that could differentiate between malignant and normal tissue in real time? That's the vision behind a device being developed by Laura Marcu, professor of biomedical engineering and neurological surgery. Using a technology called time-resolved fluorescence spectroscopy (TRFS), the device uses light to excite molecules in tissue and to measure how long they emit light of their own after they are excited. Different types of molecules emit light at different rates. TRFS can



Postdoctoral fellow Dimitrios Gkorpas and Laura Marcu

measure these rates, and identify malignant and healthy tissue.

"Using fiber optics to deliver and collect light, we can remotely characterize the tissue," says Marcu. "Surgeons can determine in real time whether they have healthy margins. It would save time, money and be better for patients."

Marcu's team is currently working in the lab on tissue specimens, but the technology is ready to be used in patients.

"Using fiber optics to deliver and collect light, we can **remotely characterize the tissue**. Surgeons can **determine in real time** whether they have healthy margins. It would **save time, money and be better for patients.**"

~ Laura Marcu

The all-important sentinel node biopsy

For decades the trend has been to reduce the amount of tissue taken out during breast cancer surgery. Radical mastectomy, which removes the entire breast and some of the underlying muscle, made way for lumpectomies.

Unfortunately, the desire to minimize surgery runs up against a hard reality: cancer spreads. For a lumpectomy to succeed, clinicians must make sure tumor cells have not infiltrated the lymphatic system. In the past, cancer surgeons removed all the lymph nodes in an area under the shoulder called the axilla. But this led to severe side effects, such as painful swelling in the arm from fluid buildup.

The better solution has been to find the node most likely to contain cancer cells — the sentinel node. Currently, surgeons inject a radioactive solution near the tumor and use a small Geiger counter to track where it goes. But UC Davis researchers are working on a better way to find the sentinel node using a metal solution and magnetism instead of radiation.

"We're trying to move away from unnecessary radiation exposure," says Richard Bold, chief of surgical oncology and lead researcher on the project. "The radiation is low — we don't think it's a health risk — but if we can eliminate it, we should."

But the new approach, called

"We're trying to move away from **unnecessary radiation exposure.** The radiation is low — we don't think it's a health risk — but **if we can eliminate it, we should.**"

~ Richard Bold

But UC Davis researchers are **working on a better way to find the sentinel node** using a metal solution and **magnetism instead of radiation.**

Sentimag, has another advantage: less discomfort for patients. Radioactive injections must be given an hour before surgery and are notoriously painful. The magnetic tracer used for Sentimag identification, however, is given during surgery when the patient is under anesthesia.

Mary Willian, who was diagnosed with invasive breast cancer, is an early advocate. As part of a clinical trial to validate Sentimag she experienced both methods.

"When they injected the radioactive liquid, that hurt," says Willian. "But with the magnetic stuff, I didn't even know they did it."

Willian's procedure produced only good news — the cancer had not spread. For Bold, the added rewards come in the days following surgery.

"Patients walk in a week after lumpectomy and lymph node biopsy and tell me they just went shopping. That's the kind of recovery we like to see."

Mary Willian, who was diagnosed with invasive breast cancer, is **an early advocate.** As part of a clinical trial to validate Sentimag, she experienced both methods.

"When they injected the radioactive liquid, that hurt. But with **the magnetic** stuff, **I didn't even know they did it.**"

~ Mary Willian

Thinking outside the box

Innovation groups attack thorny cancer problems

As the saying goes, "It takes a village to raise a child," and nurturing cancer research toward maturity and independence is no different.

At UC Davis Comprehensive Cancer Center, where individual discoveries are made in exam rooms, far-flung laboratories, operating rooms, radiology suites and even on desktop computers, harnessing and exploiting that knowledge to improve patient care and survival can be challenging.

That's why Karen Kelly, a lung cancer specialist and associate director for clinical research at the cancer center, launched seven clinical "innovation groups," which meet regularly to discuss cancer challenges,

A lunchtime meeting of the "Brain Innovation Group" includes clinical and research faculty from left, James Boggan, Laura Marcu, Brad Hartle (biomedical engineering graduate student), Jian-Jian Li and Robert O'Donnell. Not pictured, Ruben Fragoso. Staff *(not facing camera)* include Edson Kong and Karol Kyte.

propose ways to tackle them, apply jointly for grants to fund the research, and work together to accomplish the projects.

"What we are trying to do is leverage the talent at UC Davis so that it can translate to improved patient outcomes," says Kelly. "That is the ultimate goal."

Bringing together multidisciplinary teams to approach problems of a particular type of cancer can speed and streamline the process of discovery — and its translation to the clinic, where patients can more quickly benefit from it. Each group includes at least one laboratory scientist, medical oncologist, pathologist, radiologist, radiation oncologist, surgeon and other specialists, as appropriate.

"This way, we get all of the stakeholders at the table to try to come up with the most innovative, impactful grant and/or investigator-initiated trial that our patients have an opportunity take advantage of," Kelly adds.

After just one year of operation, the groups already have been awarded four research grants and submitted an additional two now under consideration for funding. In addition, the groups have launched five investigator-initiated clinical trials (trials of new drugs or treatment approaches designed by physicians and not sponsored by industry), and have seven other such trials in the works.

> "What we are trying to do is **leverage the talent** at UC Davis so that it can **translate to improved patient outcomes.** That is the ultimate goal."
>
> ~ Karen Kelly

The brain innovation group sparked development of one of the grants. Biomedical engineer Laura Marcu attended a meeting and talked about her fluorescent probe that can differentiate various tissue types in ways that the human eye cannot. That prompted a discussion about a specific challenge in brain tumor treatment that involves tissue that has died as a result of radiation treatment.

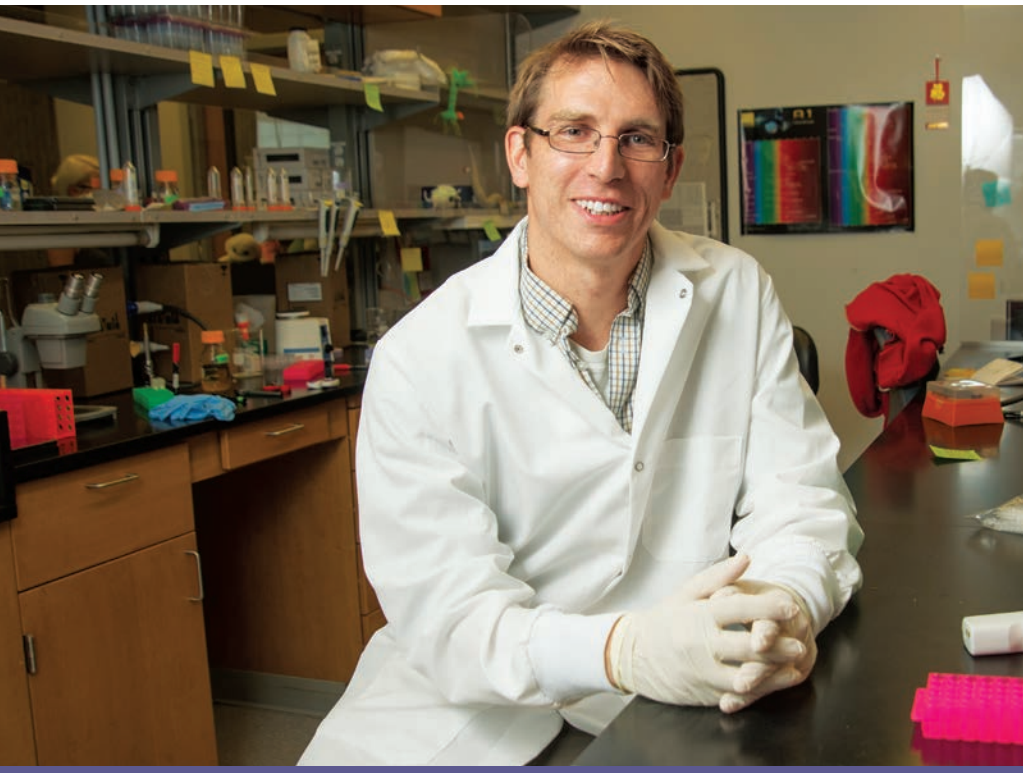
"I had been dealing with a patient with radiation necrosis," explains Ruben Fragoso, a radiation oncologist. "It's difficult to tell the difference between necrosis and tumor. We wondered if there was anything we could use to try to tell the difference."

Fragoso's dilemma was developed

into a grant proposal, which was later funded by the National Cancer Institute. A clinical study is under way to see if the probe could spare patients unnecessary additional surgery by informing the surgeon whether the tissue is cancerous before incisions are made.

"These innovation groups bring people with different perspectives together," Fragoso says. "You get new ideas and bridge different disciplines you wouldn't otherwise. Who would have thought about an optic biopsy probe?"

Brian Jonas, a hematologist who specializes in and researches adult blood cancers, considers the groups "think tanks." He is an active member of the hematological malignancies and phase I clinical trials innovation groups. With the hematological malignancies group, Jonas teamed with pediatric oncologist and researcher Noriko Satake to develop a bone marrow failure tissue bank to complement the cancer center's biorepository, and that could benefit research on children and adults with blood cancers.



"I work on cells in a dish. The group goes beyond the cells and asks, '**How does my work relate** to actual organisms?' Just thinking about that for an hour a month **brings you back to reality.**"

~ John Albeck

At an August meeting of the phase I clinical trials innovation group, participants discussed collaborations that could result in a grant designed for projects that involve imaging or image-guided interventions in cancer. Jonas proposed a research study on use of a novel and non-invasive imaging approach to evaluate myelofibrosis, a malignant bone marrow disorder that is currently detected through bone marrow biopsy.

"This gets everyone together to bounce ideas back and forth," Jonas says of the meetings. "Not all ideas become priorities, but all it takes is a thought, and the next thing might be, 'Hey, you should do this.' The diversity of the group stimulates that type of discussion."

For basic scientist John Albeck, who works in a laboratory on the UC Davis campus, participating in the lung cancer innovation group has been a kind of reality check.

"It forces me to think about how to make what we do useful," he says. "I work on cells in a dish. The group goes beyond the cells and asks, 'How does my work relate to actual organisms?' Just thinking about that for an hour a month brings you back to reality. When I go back to my cells, what am I going to learn from them that will be really useful and biologically meaningful?"

Albeck's research in the Department of Molecular and Cellular

Brian Jonas and Eva Meraz-Robey

"This gets everyone together to **bounce ideas** back and forth. Not all ideas become priorities, but **all it takes is a thought**, and the next thing might be, 'Hey, you should do this.'"

~ Brian Jonas

Biology focuses on certain cellular pathways common to lung cancer. Along with David Gandara, director of thoracic oncology at the cancer center, and Phil Mack, who leads the cancer center's molecular pharmacology shared resource, Albeck has submitted a grant proposal to use mouse models capable of growing human lung tumors to test various treatment strategies. The goal is to find drugs that inhibit cellular pathways that allow tumors to grow and that don't eventually fail, as many ultimately do.

"For any study, if you want to do effective cancer research, you really have to know the people who are actually working with patients," he says. "I don't think you really do cancer research without a group like this anymore."

Kelly explained that the groups are successful because they are more than just brainstorming sessions. Karol Kyte, an analyst and assistant to Kelly, was tapped as administrator for each group and works hard to keep members on task and moving forward. Each group is also required to write annual progress reports.

"They are doing what we asked them to do," Kelly says. "They are finding research opportunities based on UC Davis strengths and developing weakness into opportunities."

"These innovation groups bring people with **different perspectives** together. You get **new ideas** and **bridge** different **disciplines** you wouldn't otherwise.

~ Ruben Fragoso

Man's best PET?

Cherry leads international development of new scanning technologies

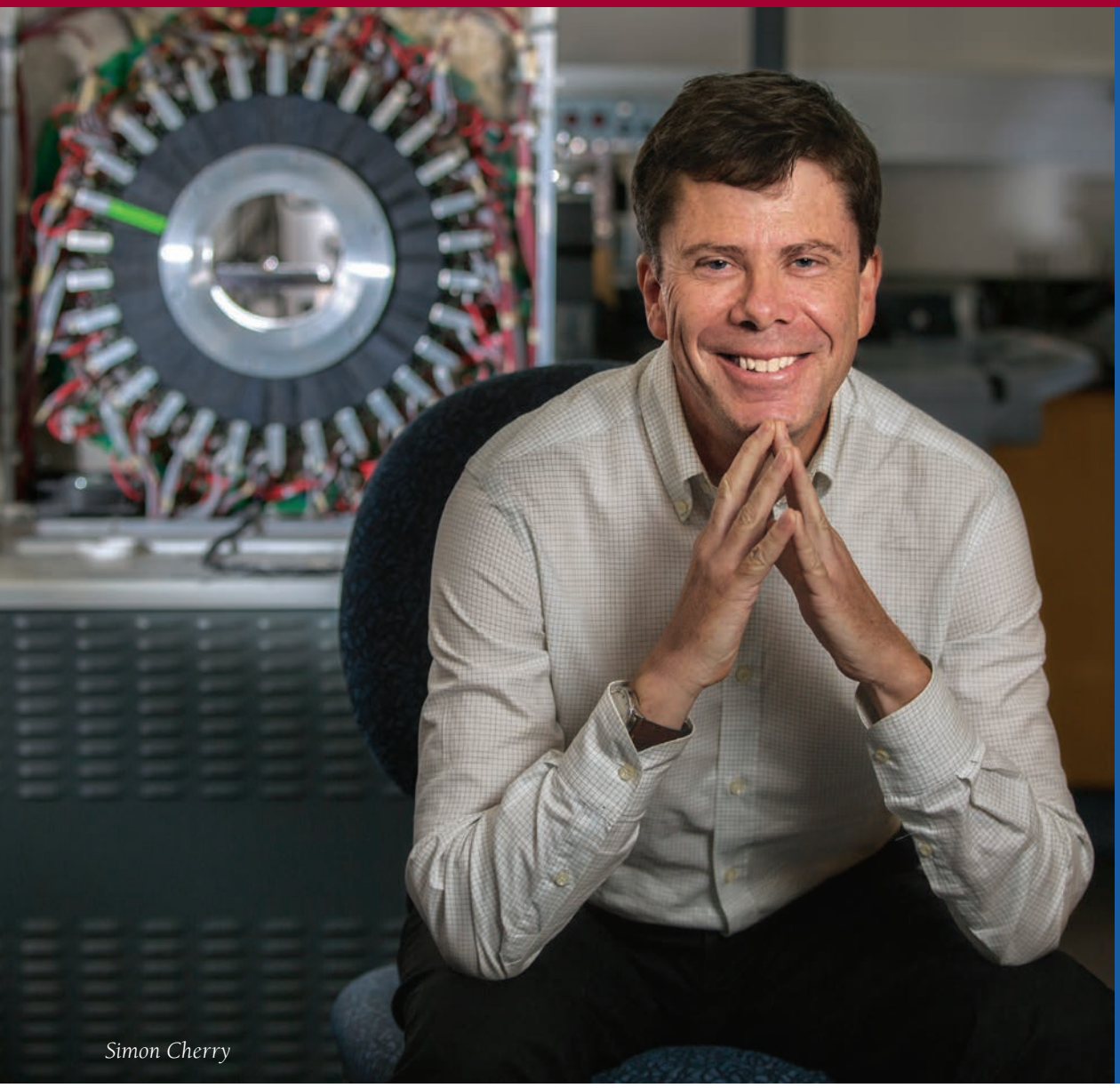
Clinicians have a wide variety of scanners to diagnose what ails us. X-rays and CTs use ionizing radiation to visualize structures in the body.

Ultrasounds and MRIs use sound waves and radio waves, respectively. But PET scans fill a different role.

Short for positron emission tomography, PET tracks tiny amounts of radioactively labeled molecules to determine where they go in the body. The technology is less focused on the structure of the body than on metabolism and function. While CT, MRI and the other imaging techniques may depict the anatomy, PET can tell us what cells in the body are actually doing.

This can be extremely useful. For example, because cells in tumors divide faster than normal tissue and are therefore "hungrier," they tend to concentrate a radioactive sugar such as glucose. PET scans can see tumors as glowing bright spots.

The technology has other advantages, too. PET is being used as a tool to aid in the development of new drugs by determining if the drug goes where it is supposed to go or goes elsewhere in the body where it could cause toxic side effects. Finding that information early, before spending millions of dollars on clinical trials, could help stream-



Simon Cherry

line the drug discovery process.

And while PET has been around for decades, it still has shortcomings that keep it from fulfilling its potential. But perhaps not for long. Simon Cherry, distinguished professor in the Department of Biomedical Engineering, in collaboration with Ramsey Badawi, director of research in the Division of Nuclear Medicine, is working with colleagues at UC Davis and beyond to build a better PET scanner. Improved PET technology could provide faster, clearer scans, using less radiation.

One of PET's **main disadvantages is its narrow field of view.** ... To image the entire body, clinicians have to "step" it through one chunk at a time. Cherry believes **the process could be improved.**

The full-body PET scanner

One of PET's main disadvantages is its narrow field of view. PET machines can only see the body in 20-centimeter chunks, which amounts to about 8 inches. To image the entire body, clinicians have to "step" it through one chunk at a time. Cherry believes the process could be improved.

"If we can develop a scanner that covers the entire body, allowing us to see the radioactively labeled molecules we have given the patient in all organs

simultaneously, we can either drop the radiation dose by a factor of 40 or image 40 times faster," says Cherry. "Rather than a scan taking 20 minutes, it could take just 30 seconds."

The reduced radiation could benefit pediatric and other patients who might be vulnerable to radiation. It could be particularly helpful for patients who require several scans to track cancer progression or determine if a treatment is working. In addition, capturing scans much more quickly could mean images will be less blurred by movement of the patient, allowing physicians to get a clearer view of smaller tumors.

"If you ask someone to lie still for 20 minutes, they'll do their best, but they move," says Cherry. "Twenty or 30 seconds is more doable. Someone could even hold their breath for that long to eliminate motion caused by breathing."

Cherry has been collaborating with Badawi on the EXPLORER program to build a two-meter PET scanner. The group is part of an international effort to make dramatic improvements to PET. Cherry and Badawi recently received a $15.5 million Transformative Research Award from the National Cancer Institute and other federal programs to complete construction of what will be the world's first whole-body PET scanner.

The **advantages of a bigger PET scanner** are so obvious, many people wonder why it hasn't happened yet. The simple answer is the **technological challenges** are quite daunting.

Fast scanning and **reduced radiation** are only some of the benefits **full-body PET scanners** bring to patients. These devices could **better track** how far metastatic cancer has spread, monitor **how patients are responding** to treatment, or **clarify how immuno-therapy activates** the body's ability to attack cancer.

The fruits of international collaboration

The advantages of a bigger PET scanner are so obvious, many people wonder why it hasn't happened yet. The simple answer is the technological challenges are quite daunting. For example, a larger scanner means handling huge amounts of data.

To overcome this and other issues that prevent PET scanning from reaching its full potential, Cherry's team is collaborating with researchers and companies around the world. The EXPLORER program, for example, also involves scientists at the University of Pennsylvania and the Lawrence Berkeley National Laboratory, as well as consultants from the United Kingdom.

Other collaborations focus on developments further into the future. In another ongoing partnership, the group is working with the Shenzhen Institutes of Advanced Technology (SIAT) in China to develop better data-handling technology.

"SIAT is a young institute," says Cherry. "They have a lot of interest in PET technology but not much expertise. On the other hand, they have tremendous expertise in electronics, where we could use some help. It makes for a great partnership."

The researchers also are working with scientists in Australia to perfect tracking technology that would provide clearer images when subjects are moving. They are also

Ramsey Badawi

Cherry has been **collaborating** with UC Davis colleague Ramsey Badawi, director of Nuclear Medicine Research, on the EXPLORER program, which is **building a two-meter PET scanner.**

collaborating with Imanova, a London-based company that wants to use full-body PET to test new pharmaceuticals.

Perhaps the most interesting collaboration is with the research institute Fondazione Bruno Kessler in Italy and an Irish company called Sensl to develop a solid-state, low-light sensor. PET scanners, while advanced, still contain a relic from the 1950s – a vacuum tube, known as a photomultiplier tube. The scanner detects gamma rays from the radioactive tracer and converts them into visible light, which is then converted into electrical signals by the photomultiplier tube.

Cherry and collaborators are searching for a solid-state alternative, which would be more efficient and easier to manufacture, and could potentially improve image quality as well as reduce cost.

Big rewards

Fast scanning and reduced radiation are only some of the benefits full-body PET scanners could bring to patients. These devices could better track how far metastatic cancer has spread, monitor how patients are responding to treatment, or clarify how immunotherapy activates the body's ability to attack cancer.

"This scanner could help with anything that's a whole-body phenomenon," says Cherry. "Think metastatic cancer, inflammation, immunotherapy – they're all systemic and all relevant to cancer."

Those are long-term goals, but in the shorter term, the technology offers another way to benefit patients: accelerated drug discovery.

A full-body PET scanner could follow a drug's path through the body, helping pharmaceutical and biotech companies determine if an agent is hitting its target and whether it's sequestered in the heart, liver or kidneys – a potential warning sign for toxicity.

The information could give medicinal chemists and pharmacologists early opportunities to redesign a molecule – or try another compound entirely – to avoid toxicity and move potentially life-saving drugs down the pipeline.

This possibility is already intriguing drug companies interested in the early prototype being developed by Cherry's team. And though direct patient care is the ultimate goal, research applications could provide great benefits in the near future.

"We're not positioning this as something that's going into hospitals anytime soon," says Cherry. "It's really a tool to conduct these unique research and pharmacological studies. If we have this kind of performance, it could really change the kind of research we can do with PET."

Clues for Kimmy

HBV study could improve outcomes for Asian-Americans

Kimmy Pham may carry clues as to why Hepatitis B causes more virulent liver cancer among some Asian American ethnicities than in others.

The study seeks to find potential biological reasons **why Hmong with hepatitis B virus** (HBV) have **higher liver cancer mortality rates** and present at younger ages with late-stage disease than other Asian Americans with HBV.

Pham, a Vietnamese American, is part of a health disparities study spearheaded by Christopher Bowlus, professor and acting chief of the Division of Gastroenterology and Hepatology at UC Davis Health System. The study seeks to find potential biological reasons why Hmong with hepatitis B virus (HBV) have higher liver cancer mortality rates and present at younger ages with late-stage disease than other Asian Americans with HBV.

Pham, 22, contracted HBV at birth and is symptom-free. Her mother contracted HBV in Vietnam

Christopher Bowlus and Kimmy Pham

before immigrating to the United States. Over 10 percent of the population in Vietnam is chronically infected with the virus.

Pham, a student at San Francisco State University, says it is "really cool" to be part of Bowlus' study.

"They found a cure for Hepatitis C, and now they may find a cure for Hepatitis B," she

"To me, this is an example of a project that **expands from the community to the bedside to the bench.**"

~ Christopher Bowlus

says, adding that HBV is somewhat more "unknown and mysterious."

Using molecular and genomic diagnostics, as well as biostatistics, Bowlus and his colleagues are looking at the immune responses to HBV, as well as genetic differences in the hepatitis B virus in Hmong, Vietnamese and Chinese-Americans, hoping to understand why Hmong get liver cancer at younger ages and at more advanced stages than their Chinese and Vietnamese counterparts.

Bowlus says that discovering a biological reason for a possibly more virulent HBV strain will allow researchers to target therapies and prevention strategies.

"To me, this is an example of a project that expands from the community to the bedside to the bench," Bowlus says.

The average liver cancer survival rate is six to 12 months among Chinese and Vietnamese Americans, but it is only about one month among Hmong Americans.

The average **liver cancer survival rate** is **six to 12 months** among Chinese and Vietnamese Americans, but it is **only about one month among Hmong Americans.**

Bowlus' study is **funded by the National Cancer Institute** and is **one of seven newly funded health equities projects** highlighted by the Association of American Medical Colleges institutions.

Bowlus' study is funded by the National Cancer Institute and is one of seven newly funded health equities projects highlighted by the Association of American Medical Colleges institutions. Ultimately, Bowlus wants to enroll 50 Asian Americans from each ethnic group, for a total of 150. The subjects must be infected with HBV and not be on any treatment.

Researchers will collect blood from people infected with HBV, but have not developed cancer. They will then sequence and analyze the genome in the virus and the genes of immune cells to see if the Hmong have a specific virus strain or a response to the virus that may be associated with the worst outcome.

"We're looking at the specific immune responses or gene expression in the blood cells of those infected with Hepatitis B," says Bowlus. "We're looking to see if there are specific immune responses in Hmong, to see if they have a lower immune response."

Bowlus is using state-of-the-art sequencing technology. In the past, doctors and researchers sometimes have had difficulty drawing blood samples from the Hmong because blood is considered a nearly sacred life force. Elders in the community would have to provide consent before treatment. Bowlus says many older Hmong

Christopher Bowlus and Kimmy Pham

are still reluctant to seek medical treatment and testing, but treatment is becoming more accepted in the community.

"There is much less suspicion now, and more are seeking Western care," he says. "The times are changing also in terms of access to care in their communities."

Bowlus adds that in order to effectively study the disease among different ethnic groups researchers must have a relationship with the communities affected.

"They have to want to participate," he says.

Pham certainly wants to participate. She says it gives her great pride to be part of a research project that is "trying to make a change."

Bowlus also believes the project can reap great benefits to the communities studied.

"It's a nice example of the whole spectrum of research, clinical care and community engagement," he says.

Bowlus says that discovering **a biological reason for a possibly more virulent HBV strain** will allow researchers to target therapies and prevention strategies.

Chatting with Marcio Malogolowkin

CHIEF OF THE DIVISION OF HEMATOLOGY-ONCOLOGY IN THE UC DAVIS DEPARTMENT OF PEDIATRICS

Q: Over the past couple of decades you've held leadership positions in pediatric hematology-oncology at UCLA and at the Children's Hospital of Wisconsin in Milwaukee. Why UC Davis now?

A: We wanted to return to California but not back to a big, urban environment. Sacramento feels like the Midwest — the accessibility to outdoor activities, the easy-going people — without the long winters. We are very happy to be here.

The community at UC Davis was also very attractive to me. There's a fantastic wealth of clinical, educational and research resources and opportunities. But even more important, there is a lot of work still to be done. With a new dean we are poised for a transformation, and I want to be a part of that.

Q: What are your goals for pediatric hematology-oncology?

A: First of all, we have an excellent division, and I want to ensure that patients and families continue to receive the excellent care that they deserve, and that the medical students, residents and other trainees obtain the best education possible.

There are some programs that I want to see expanded. At the moment, we must send some of our sickest patients — those with very high-risk or recurrent cancers — to medical centers out of the area so that they can obtain novel therapies. Staying near home for treatment can make a tremendous difference for families when they are at their most vulnerable; we don't want desperate parents to be away from their loved ones and community support in order to care for their children.

UC Davis has **tremendous potential for improving outcomes for AYAs**. Unlike most cancer centers, here pediatric and adult oncology programs **share the same space.**

With some effort, we can consistently provide this very specialized care here. We have the necessary expertise, research capabilities and clinical resources to accomplish this.

Another special interest of mine is the group we call "AYAs" — adolescents and young adults from 15 to 30 years old. Nationwide, these patients have not seen the improvements in survival that the pediatric and older adult populations have seen for their cancers. Maybe it's because they are no longer under the watchful care of their parents, they believe they are invincible, they have problems with access to health coverage, or they struggle with keeping balance between life and treatment.

Most AYA cancers are more common in children so, although they are usually cared for in adult medicine, they actually tend to do better when treated according to pediatric oncology protocols. UC Davis has tremendous potential for improving outcomes for AYAs. Unlike most cancer centers, here pediatric and adult oncology programs share the same space. We have the same common areas, go to the same meetings, and often share patients. This model fosters collaboration and optimizes patient care by design.

Q: What do you see as the future in cancer medicine?

A: Genomics. I believe that we are poised to more effectively fight tumors while reducing toxicity by developing targeted, personalized therapy. UC Davis, with its deep and wide genomics research interest, is strongly positioned to move this field forward.

Q: You are an internationally recognized authority in the field of pediatric liver tumors, one of the most challenging of pediatric cancers. Can you tell us something about this work?

Rhynan Fay and Marcio Malogolowkin

A: Childhood cancers are rare, and liver tumors are rare among them. I serve on national and international committees that are working on developing standards for diagnosis and consensus on tumor classifications to assure that everyone is looking at the same problems in the same way. We are working to develop collaborative international studies aimed at improving our understanding of the biology of these diseases and to improve outcomes for these patients.

Q: What keeps you motivated?

A: The relationship you have with very sick children and their families is one that nothing matches. I am honored that parents give me the privilege to take care of their children — it is a gift. Every day I find something new and promising. I firmly believe that I'm in the right place at the right time.

The relationship you have with very sick children and their families is one that nothing matches. **I am honored** that parents give me the privilege to take care of their children — it is a gift.

From personal to precise

One tumor, a cohort of mice and a treatment target

The history of cancer is filled with promising therapies that ultimately provided only marginal benefits.

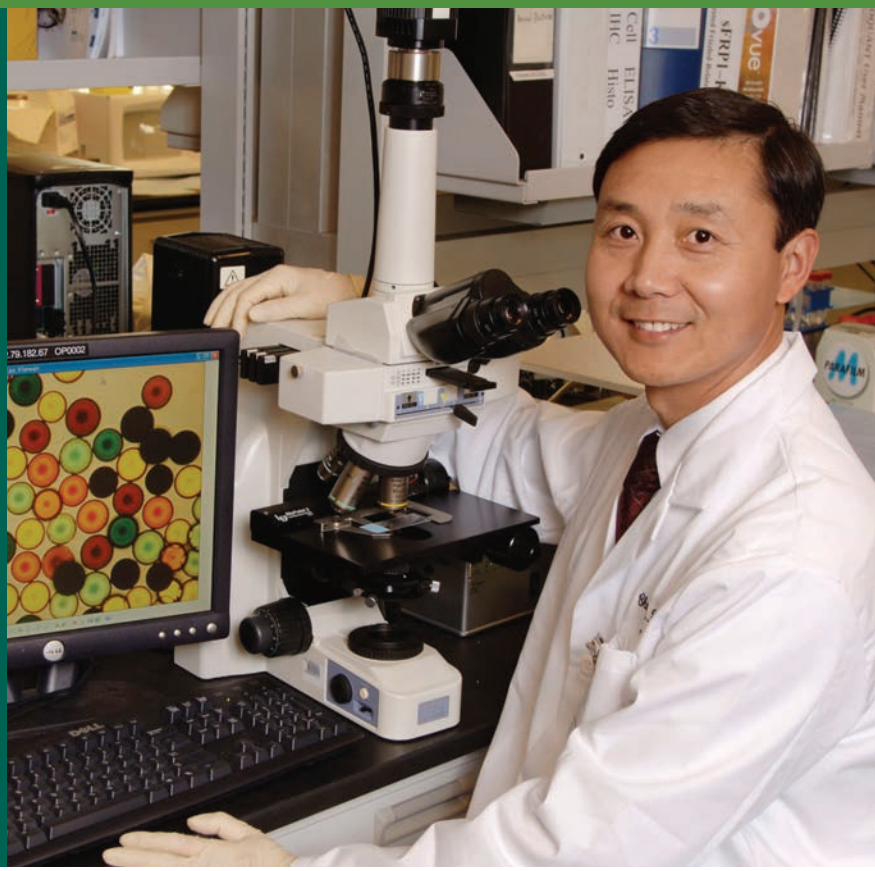
Early chemotherapy, high-dose chemotherapy and radical surgery are just a few examples.

Now we've developed a new generation of therapies that target specific mutations in tumors, undermining the genetic anomalies that drive the cancer. This approach makes perfect sense — remove the foundation and the building collapses. However, while preclinical trials were promising, the results in patients have been underwhelming.

"For most cancers, once you have failed first-line therapy, there is no standard, second line of treatment," says Ralph de Vere White, a urologist and director of the UC Davis Comprehensive Cancer Center. "We have the patient get a biopsy and send it off for genomic analysis, which will show us abnormalities that can be treated. Let's say there are four of them. Now we have to guess which one is driving the cancer, and the success rate is about 12 percent. That's putting the patient through a lot for just 12 percent."

"By **prescreening**, we can determine which medication works, providing a **much higher chance** the patient will benefit. This can **reduce toxicity, increase efficiency and lower costs.**"

~ Chong-Xian Pan



It's become obvious that simply matching tumor mutations with treatments isn't enough. Researchers and clinicians have been missing a step, but de Vere White and genito-urinary oncologist Chong-Xian Pan may have found it. The answer may be testing different therapies against a patient's unique cancer to find the right therapies to eradicate it.

Pinpointing the right mutations

The problem with basing cancer therapies on genomic diagnostics is the tests don't provide enough information. Yes, they identify mutations, but they cannot tell which mutations are driving the cancer.

"Look at how many mutations a cancer can have — from only a few in pediatric cancers to dozens or hundreds in adult cancers," says Pan. "Lung cancer probably has hundreds of mutations, and only a few of those are important. But at this point we can't always figure out which mutations are important and which are unimportant."

Oncologists must make their best guess based on the data they have. However, if that particular course of treatment proves ineffective, there's little time to backtrack and try a different therapy. Clinicians need precise information that will help them make the right choice from the beginning.

We may be on the verge of doing just that. In a recent proof-of-concept paper, Pan, de Vere White and colleagues reported that they may have found a way to pinpoint the critical mutations that drive an individual's cancer.

Working closely with The Jackson Laboratory, with headquarters in Bar Harbor, Maine and a facility in West Sacramento, the team grafted invasive bladder cancers from human patients in mice. Once the tumors grew, they analyzed their molecular characteristics then tested different cancer treatments and combinations of treatments to see which were effective. When a therapy worked in the model, it was given to the patient.

"By prescreening, we can determine which medication works,

The problem with basing cancer therapies on genomic diagnostics is the **tests don't provide enough information.** Yes, they identify mutations, but they **cannot tell which mutations are driving** the cancer.

providing a much higher chance the patient will benefit," says Pan. "This can reduce toxicity, increase efficiency and lower costs."

Though the study was small — only nine patients — the results were impressive. First, the grafts showed remarkable genetic fidelity to the original patient tumors — between 92 and 97 percent — even after several months. This is an enormous improvement over cell lines in a dish, which deviate from the mother tumor in just a few days.

But most importantly, the grafts provided amazing insights into which drugs could help patients.

"In one case, cisplatin didn't work and gemcitabine barely worked, but the combination really knocked the tumor out in the mouse," says de Vere White. "And that's exactly what happened in the patient."

Oncologists must make **their best guess** based on the data they have. However, if that particular course of treatment proves ineffective, **there's little time to backtrack** and try a different therapy.

Expanding the model

This study provides a promising pathway for researchers and clinicians and could ultimately help a lot of patients. Another team of UC Davis researchers is using similar methods to see if they can improve treatment targeting for lung cancer.

But this is not the end game. Although using patient tumor grafts in mice has proven effective in selecting cancer therapies against invasive bladder cancer, the process is somewhat cumbersome, as it can take months for a graft to fully implant.

The ultimate goal is to use computers to help select effective treatments. The UC Davis team wants to develop a comprehensive algorithm that includes the patient's genome, the tumor's genome, which therapies worked in mice and which ones worked with patients.

"We're not saying the mouse model is the answer," says de Vere White, "but presently there is a high failure rate in developing new, successful therapies, and we're trying to figure out how we can do better. In time, we'd like to be able to biopsy the patient, sequence the tumor, feed that information into the computer and have the computer tell us which therapy will work."

In a recent proof-of-concept paper, Pan, de Vere White and colleagues reported that they **may have found** a way to **pinpoint the critical mutations that drive an individual's cancer.**

News briefs>>

Long-time donor close to goal

The Auburn Community Cancer Endowment Fund (ACCEF), which has worked for 15 years raising money for cancer research at UC Davis, is close to hitting its $3 million goal.

Ralph de Vere White and the late Virgil Trainor

Founded by the late Virgil Trainor, the foundation's support funds a basic research chair.

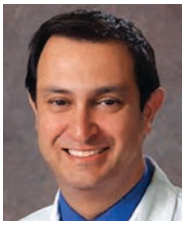
Upcoming events planned to reach the fundraising target included the opening night performance of "Mary Poppins" at the State Theater in downtown Auburn on Oct. 9, and the upcoming annual Holiday Dinner and Celebration Dec. 3 at the Placer building at the Gold Country Fairgrounds in Auburn.

Currently the foundation stands at $2.44 million, with an additional $480,000 in estate planning bequests.

"What seemed impossible is now within reach," said Betty Bennett, co-vice chair of the foundation. For information on helping ACCEF reach its goal, visit www.accef.org. Checks can be mailed to ACCEF, 11899 Edgewood Road, Suite X, Auburn, CA 95603.

Major grant awarded to treat HIV, lymphoma

A team of UC Davis researchers has been awarded $8.5 million from the California Institute for Regenerative Medicine (CIRM) to conduct a clinical trial using bioengineered stem cells to treat HIV patients suffering from lymphoma, a blood cancer associated with the disease.



Mehrdad Abedi

The grant will be used to test gene-modified hematopoietic (or blood-forming) stem cells in patients and then monitor and analyze their effectiveness on the human immunodeficiency virus (HIV).

The UC Davis team, led by Mehrdad Abedi and Joseph Anderson, developed a gene therapy strategy that in animal models showed promise as a functional cure for HIV, the virus that causes AIDS. That achievement, which involved improving a technique for purifying populations of HIV-resistant stem cells, opened the door for the human clinical trial.

"We're hoping this new hematopoietic stem cell gene therapy for HIV will provide a one-time treatment, with the possibility of controlling both the lymphoma as well as HIV itself by eliminating the reservoirs of HIV in patients responsible for persistence of the disease," said Abedi, an associate professor of internal medicine and hematologist-oncologist at the cancer center and a principal investigator for the new CIRM grant.

New combination treatment effective against melanoma skin metastases

In findings never before seen in melanoma, a novel combination therapy was found to be highly effective at treating patients with skin metastases, research from UC Davis has shown.

Emanual Maverakis

Led by Emanual Maverakis of the Department of Dermatology, the research found that Interleukin (IL)-2 combined with imiquimod and topical retinoid therapy in patients with so-called "in-transit metastases" is a promising therapeutic option.

The findings were published in the *Journal of the American Academy of Dermatology*.

"Our results demonstrate that intralesional therapy with a protein that causes immune cells to divide, given in combination with a topically applied immune activator, can be a highly effective treatment for these patients," said Maverakis.

Noriko Satake wins second Hartwell Foundation award

UC Davis pediatric oncologist and researcher Noriko Satake has been awarded a 2015 Hartwell Biomedical Research Collaboration Award from The Hartwell Foundation, which funds innovative and leading-edge biomedical research to benefit children.

Satake, an associate professor in the Department of Pediatrics, will share the three-year, $699,358 award with Neal M. Alto, associate professor in the Department of Microbiology, University of Texas Southwestern Medical Center. Both researchers were recipients of 2011 Hartwell Individual Biomedical Research Awards. Together, the scientists propose a targeted approach to kill pediatric cancers that will minimize the toxic side effects associated with typical chemotherapy regimens by virtue of the specificity of their innovative drug-delivery platform.

"I am making novel compounds for the two most common cancers in kids — B-cell leukemia/lymphoma and neuroblastoma," Satake said. "If this is successful, it would specifically target the cancers, delivering novel toxins directly to the tumors. The team is calling this an 'all-in-one treatment.'"

For more news stories, visit cancer.ucdavis.edu, click on "Newsroom."

News briefs>>

Man's best friend may also be his best weapon against cancer

A couple of rambunctious puppies are in training to use their keen sense of smell to find cancer.

Alfie, a labradoodle, and Charlie, a German shepherd, have taken up residence with two UC Davis physicians while undergoing a rigorous 12-month training program to develop their abilities to identify the scent of cancer in saliva, breath and urine. Scientists hope to find the cancer chemicals that only dogs can smell, then use that understanding to develop technology capable of detecting cancer's molecular markers.

Such an advance would help physicians detect cancer early when it is more easily treated and cured. Cancer is the second leading cause of death in the United States.

The olfactory acuity of dogs enables them to detect odorant concentration levels at 1 to 2 parts per trillion, roughly 10,000 to 100,000 times that of a human, according to sensory scientists. UC Davis physicians and researchers believe Alfie and Charlie have the potential to inform important diagnostic research to advance patient care. The introduction of the cute canines in early August sparked national interest, as dog-lovers, scientists and others grew interested in their potential to help in the fight against a devastating disease.

Alfie, a labradoodle, and **Charlie, a German shepherd,** have taken up residence with two UC Davis physicians while undergoing a **rigorous 12-month training program** to develop their **abilities to identify the scent of cancer** in saliva, breath and urine.

Although the dogs are not being trained to work in cancer clinics, UC Davis Comprehensive Cancer Center Director Ralph de Vere White acknowledges dogs' special gifts.

"For the past number of years, we have been developing very high-end, expensive new tests to try and detect the presence of cancer," he said. "Dogs have been doing this, for example, detecting disease in the urine of people suspected of having bladder cancer. This work marries sophisticated technology with low-tech, yet sophisticated, dogs' noses to see if they can help us identify the molecules that differentiate cancer from non-cancer."

Hilary Brodie, professor and chair of the UC Davis Department of Otolaryngology, hopes that the identification of these molecules will lead to innovative and readily available methods of detection.

"Much like the hand-held devices used to detect alcohol, drugs and explosives have revolutionized our safety, having a new tool to detect early-stage cancer would have incredible benefits for patient care," noted Brodie, whose department treats head, neck and throat cancer patients.

Researchers have established that dogs can recognize melanoma as well as bladder, lung, breast and ovarian cancers. Canines have been successfully trained to distinguish the breath samples of lung and breast cancer patients from those of healthy volunteers. Such promising results have cancer experts at UC Davis enthusiastic about the potential for the dogs to represent a safe, noninvasive method for detecting cancer before it is too late.

"Identifying patients at earlier stages could be extremely helpful in the fight against cancer," said Gregory Farwell, professor of otolaryngology and director of the university's Head and Neck Oncology and Microvascular Surgery program.

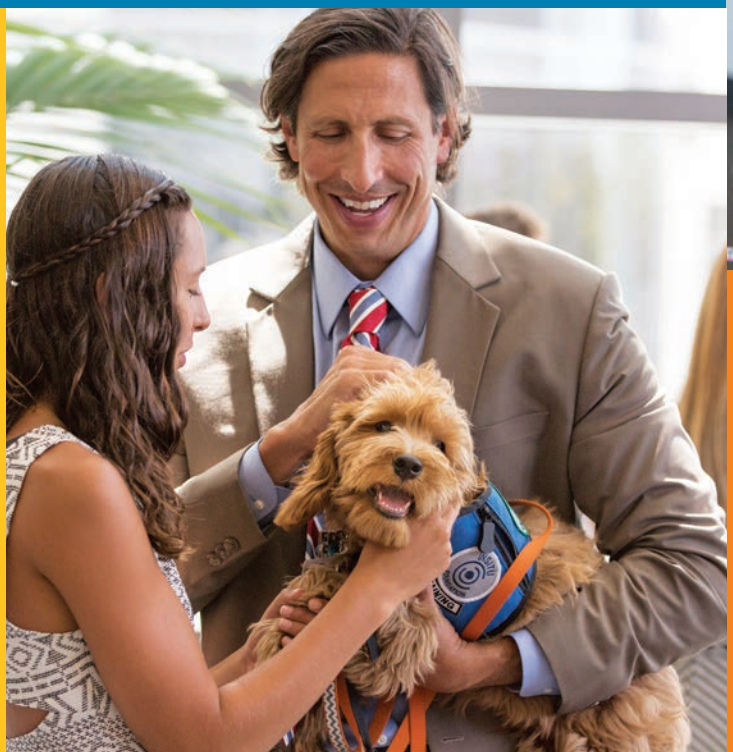
Alfie and Charlie are being trained by Dina Zaphiris, director of the In Situ Foundation in Chico, Calif. Zaphiris has trained more than two dozen dogs to detect cancer. The UC Davis canines are currently learning to distinguish samples from cancer patients and healthy individuals. Zaphiris said almost any dog can be trained to detect cancer, but she prefers German shepherds, Labradors, poodles and herding breeds because of their work ethic.

Alfie and Charlie's human-cancer screening work will begin in early 2016 with a clinical trial to establish the safety and efficacy of the new diagnostic approach. UC Davis physicians say their ultimate goal is to bring more comprehensive cancer-screening capabilities to the public.

"Despite all the advances of modern medicine, we still can't reliably detect many types of cancers in their early stages," said Peter Belafsky, professor of otolaryngology and a physician who often deals with cases involving advanced cancer. "Our new canine colleagues represent a unique weapon in the battle against cancer. It's the first of its kind at UC Davis, and the dogs' incredible talent for scent detection could offer us humans a real jump on diagnosing cancer much earlier and thus save many more lives."

"Despite all the advances of modern medicine, **we still can't reliably detect many types of cancers** in their early stages. Our **new canine colleagues** represent a **unique weapon** in the battle against cancer."

~ Peter Belafsky



Top left: Charlie and Alfie playing.
Above: Ralph de Vere White meets Charlie.
Left: Peter Belafsky and his daughter, Allie, with Alfie the labradoodle.

Whether in his career as a nuclear engineer or his hobby as a baker, Rick Parks practiced exacting precision – and now his life would depend on the same. Surgery to remove an aggressive throat cancer could also damage major arteries or his ability to speak, eat or control facial expressions. Rick's medical team paired robotic and traditional surgery to remove the cancer along with a unique new UC Davis research technology – a laser that may enhance surgical precision and help revolutionize cancer care. Rick emerged with minimal side effects, an excellent prognosis – and a reason to smile.

See Rick's story at healthierworld.ucdavis.edu

UC DAVIS HEALTH SYSTEM

***Synthesis* is published twice each year by the UC Davis Comprehensive Cancer Center.**

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Noriko Satake and cancer patient Dalton Wood celebrate Satake's $250,000 Scholar Hope Grant from Hyundai for her research to improve treatment for childhood cancer.

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Synthesis

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 Comprehensive 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 comprehensive cancer center.