

ACT AGAINST CANCER

A publication of the University of Arizona Cancer Center

SPRING 2019



Prevention
Stopping cancer
development in
its tracks



ON THE COVER

James Sligh, MD, PhD (left), and Clara Curiel, MD, use photodynamic therapy to treat “precancerous” skin cells, which are targeted for destruction by a specific wavelength of light.

Dr. Curiel is the director of the UA Cancer Center’s Cutaneous Oncology Program, the clinical director for the UA Cancer Center’s Skin Cancer Institute, and professor of medicine and vice chief of the Division of Dermatology at the University of Arizona College of Medicine – Tucson. In 2018, she was honored by the Arizona Bioindustry Association as the Arizona Bioscience Researcher of the Year for her work on both the treatment and prevention of skin cancer.

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The UA Cancer Center is one of only 49 cancer centers in the nation, and the only cancer center with headquarters in Arizona, to earn the National Cancer Institute’s Comprehensive Cancer Center designation, which demonstrates our scientific leadership, the breadth and depth of our research, and the spirit of collaboration we nurture among scientists. As a leader in the national dialogue on cancer, we are initiating rapid advances in research and patients’ health.

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A NOTE TO OUR FRIENDS AND SUPPORTERS

The mission of the University of Arizona Cancer Center is to prevent and cure cancer. In this issue of *Act Against Cancer*, we explore the first component of that goal: cancer prevention.

We're excited to introduce some of the physicians and scientists working in the Cancer Prevention and Control Program to uncover new ways to prevent cancer from developing in the first place, and to keep it from recurring in survivors. They all are driven by the vision of a future in which fewer people suffer from cancer, and more survivors enjoy longer and happier lives. This future is made possible by generous philanthropic support that funds cancer prevention research and community outreach at the UA Cancer Center.

Our researchers are busy helping to stop cancer development in its tracks by investigating interventions as diverse as a citrus extract called limonene, nonsteroidal anti-inflammatory drugs like aspirin and topical creams that disrupt cancer pathways at the cellular level. They also are delving into the immunobiology behind Gardasil 9, the new cervical cancer vaccine, with the hope of making it easier for preteens and teens to take advantage of this anti-cancer immunization.

Cancer survivors who live in fear of their diseases coming back also benefit from prevention strategies. Healthy lifestyle changes can increase quality of life and potentially decrease risk of recurrence, and we have teams whose members are looking into physical activity and a plant-based diet for ovarian cancer survivors and restorative exercise for Native-American cancer survivors. These projects pair survivors with coaches who keep them on track through their survivorship journeys.

The Cancer Prevention and Control Program is one of the UA Cancer Center's crown jewels. With your continued support, our scientists and physicians can uncover innovative new strategies for cancer prevention.

Thank you and *Bear Down!*

A handwritten signature in black ink that reads "Andrew S. Kraft, MD".

Andrew S. Kraft, MD

Sydney E. Salmon Endowed Chair

Director, University of Arizona Cancer Center

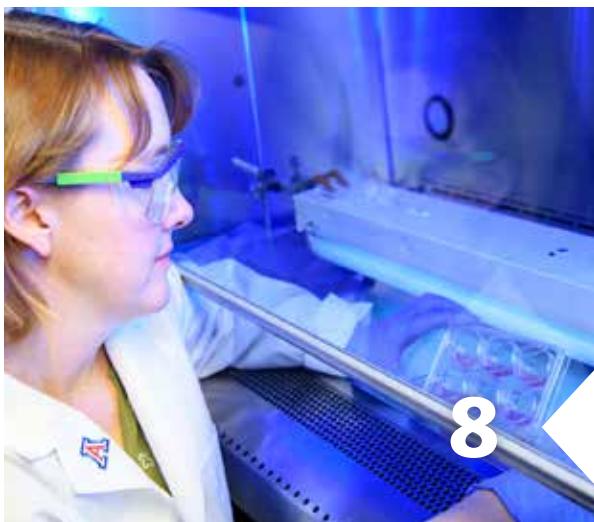
Associate Vice President, Oncology Programs, University of Arizona Health Sciences

Senior Associate Dean for Translational Research, UA College of Medicine – Tucson



“Academic medicine is what you get from a Comprehensive Cancer Center — people are really looking out for the patient.”

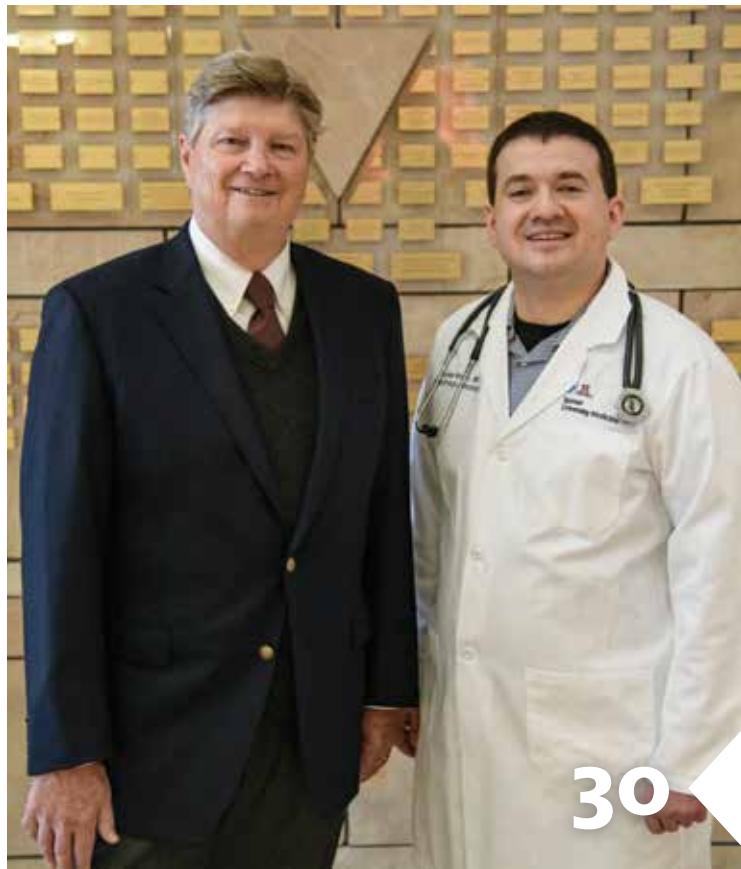
Jack Wilson, patient



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What Is Chemoprevention?

by Anna C. Christensen

Chemoprevention lacks the name recognition enjoyed by chemotherapy, but the concepts behind the names are similar.

Whereas chemotherapy is a chemical substance that can act as a therapy for a disease, chemoprevention refers to a natural, synthetic or biological agent to prevent, reverse or suppress the first steps of cancer development. There are probably some chemopreventive strategies already on your radar: aspirin to prevent colorectal cancer, tamoxifen to prevent breast cancer, the HPV vaccine to prevent cervical and anal cancers.

The University of Arizona Cancer Center is renowned for its chemoprevention research. David Alberts, MD, UA Cancer Center director emeritus, established this stellar reputation with decades of clinical and translational research. Today, these efforts are buttressed by the UA Early Phase Chemoprevention Consortium, founded in 2003. This Consortium is one of five such programs in the nation sponsored by the National Cancer Institute to help support clinical investigations into promising chemopreventive substances. Over the years, it has brought millions of research dollars to the UA Cancer Center.

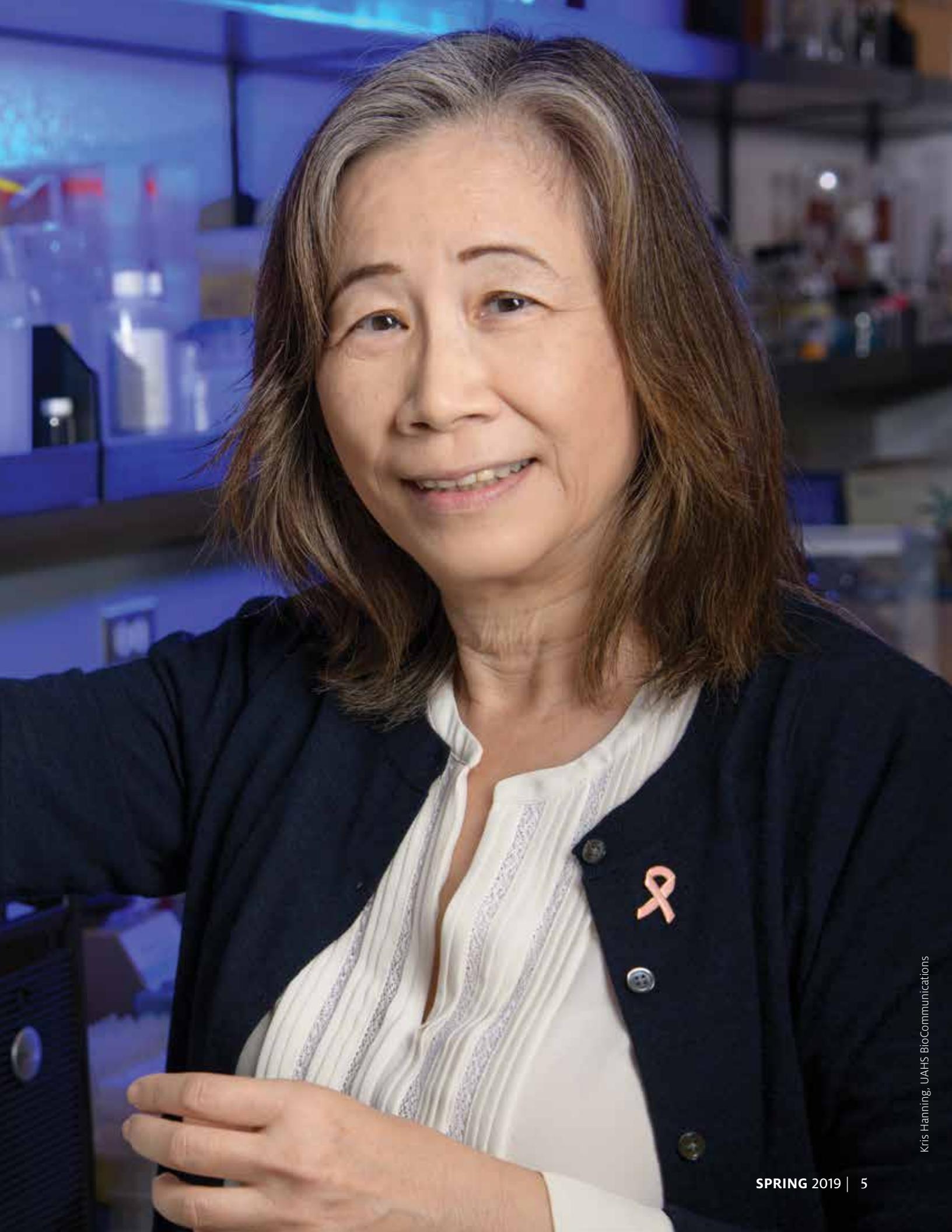
Directing these complex, yet crucial, explorations today is Sherry Chow, PhD, co-leader of the UA Cancer Center's Cancer Prevention and Control Program. Additional collaborative teams of UA Cancer Center investigators have been funded through other sources to conduct clinical and translational chemoprevention research.

"It's a very challenging task to develop a drug that can prevent cancer," Dr. Chow says. "It can take years."

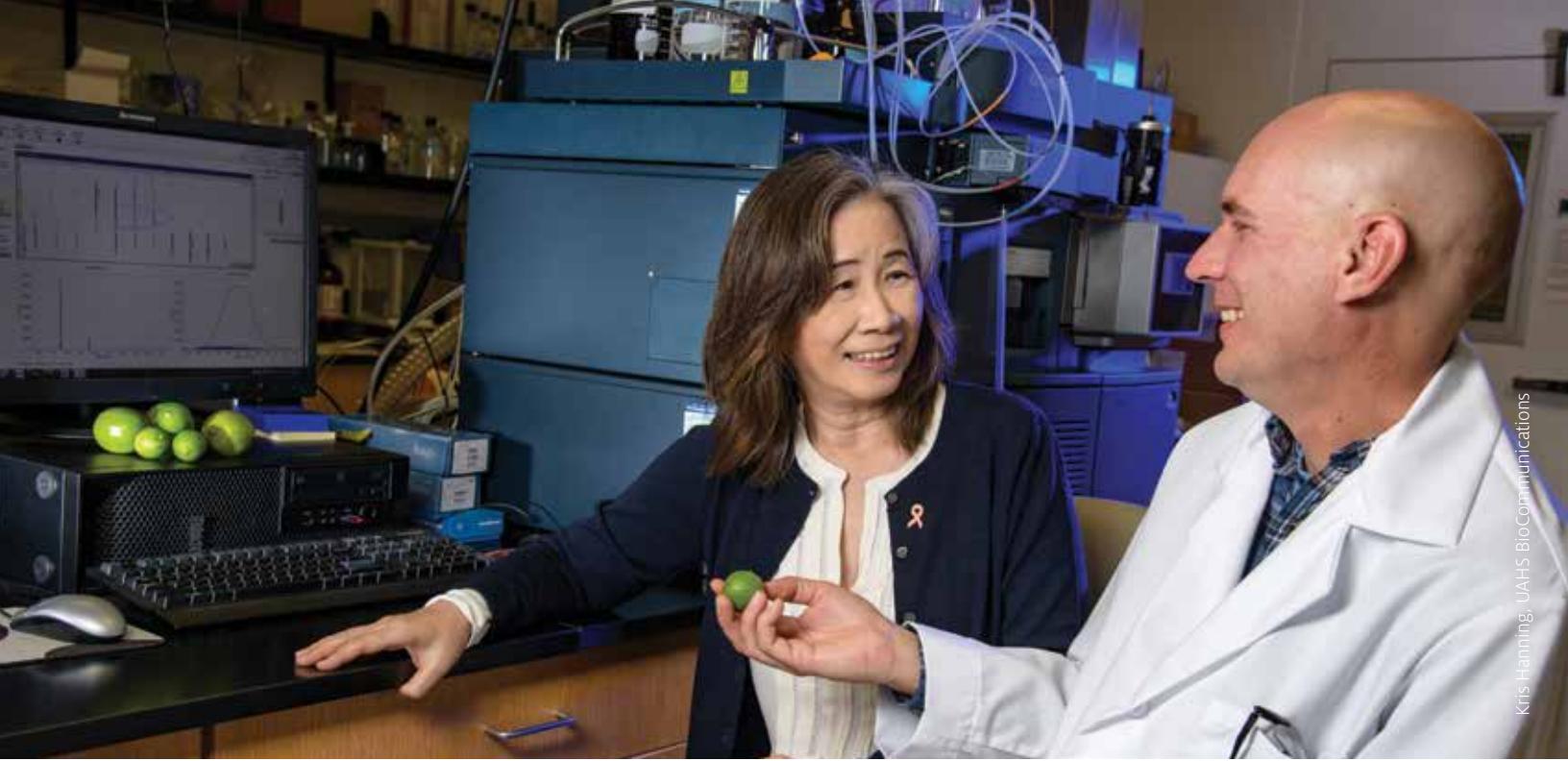
Because the journey from normal tissue to invasive cancer can be stretched out over many years, it is difficult to follow a potential chemopreventive substance over time to assess how well it works.



Sherry Chow, PhD, devotes her career to chemoprevention, a field that needs more attention.



Kris Hamming, UAHS BioCommunications



Kris Hannig, UAHS BioCommunications

Sherry Chow, PhD (left), and Wade Chew, manager of the Analytical Chemistry Shared Resource, discuss laboratory assays to support cancer prevention clinical trials.

"Definitive cancer prevention clinical trials are expensive and require long-term follow-up," Dr. Chow says. "Compelling scientific and clinical evidence from rigorously designed early-phase clinical trials is critically needed prior to advancing an agent or agent combinations into large, definitive Phase III trials."

To gather this necessary evidence, the UA Chemoprevention Consortium has conducted 17 early-phase cancer-prevention clinical trials. Investigators have examined agents running the gamut from pharmaceuticals, nutraceuticals and vaccines, which were evaluated for their ability to prevent HPV-associated cancers and cancers of the lung, breast, prostate, skin and esophagus. Funding comes from a variety of sources, including from private donors whose support is vital to accelerating cancer-prevention research.

Dr. Chow especially is interested in digging into our diets for cancer-prevention clues. We know healthful diets are associated with reduced cancer risk, but we don't know if we can isolate vitamins, minerals or other compounds from foods to prevent cancer. Early clinical trials into agents such as vitamin E and beta-carotene had mixed or even negative results — revealing just how difficult it is to untangle the intricacies of dietary patterns.

"A lot of those studies were based on observational data, but most people believe association studies don't provide rigorous scientific evidence," Dr. Chow says. "I think there's still hope. We

need to conduct prospective intervention trials to define the role of a dietary compound for cancer prevention."

Foods are packed with thousands of chemicals, which can be present at varying concentrations and can be combined in different ways. The goal is to find the right doses and combinations that will converge to provide an extra level of cancer protection.

"Hopefully we'll find a group of food — cruciferous vegetables, for example — that can be used to prevent cancer," Dr. Chow says. "More studies definitely will be needed to confirm that."

When life gives you lemons

Along with other UA Cancer Center researchers, Dr. Chow is involved in several projects investigating breast cancer prevention — including one study that seeks to unravel the potential anti-cancer properties of limonene, a component of an essential oil in citrus fruits.

"When you peel oranges or lemons, you get this oily feeling on your fingers," Dr. Chow says. "That's limonene."

So far, scientists have had the most success preventing breast cancer with tamoxifen and raloxifene, powerful drugs that block estrogen receptors. But they can be pricey and come with side effects, making them worthwhile only for people at an especially

high risk for breast cancer. But can those not at high risk protect their health with other substances — which preferably are safe and inexpensive?

Dr. Chow hopes limonene checks those boxes.

"Preclinical research has shown limonene has potential activity to prevent breast cancer," Dr. Chow says. She has taken these early discoveries into human trials. "Our studies show that limonene distributes to the breast tissue and favorably changes the plasma metabolite levels associated with breast cancer risk. We're excited about the findings."

These trials were small, and did not compare women taking limonene to women who were not.

"Everybody received limonene, so we don't really know whether these results were the true effect of limonene," Dr. Chow says. "We would like to conduct follow-up studies to further understand the role of limonene in breast cancer prevention. We need to compare people taking limonene to a placebo-controlled arm to understand whether it's really working."

An ounce of prevention

Everyone wants a cure for cancer, but finding effective ways to prevent tumors from forming in the first place is one of the UA Cancer Center's most important missions. The UA Chemoprevention Consortium's goal is to translate cutting-edge science into clinical breakthroughs.

"Chemoprevention is a field that needs more attention," Dr. Chow says. "We still have a lot of work to do to develop an agent that can be well-tolerated, has a good safety profile and has a broad spectrum of activity, hopefully covering different types of cancer."

Dr. Chow and her colleagues in the UA Chemoprevention Consortium are driven by a desire to lessen the tough toll cancer takes on patients around the world.

"I'm hoping that before I retire, I find something that can reduce cancer burden," Dr. Chow says. ▲

Your support for clinical trials at the UA Cancer Center helps us push vital research forward. To learn more, please visit uacc.arizona.edu.

THE DEAL WITH PLACEBOS

You probably have heard of the "placebo effect" — the improvement of symptoms one might experience simply because they believe something will help them.

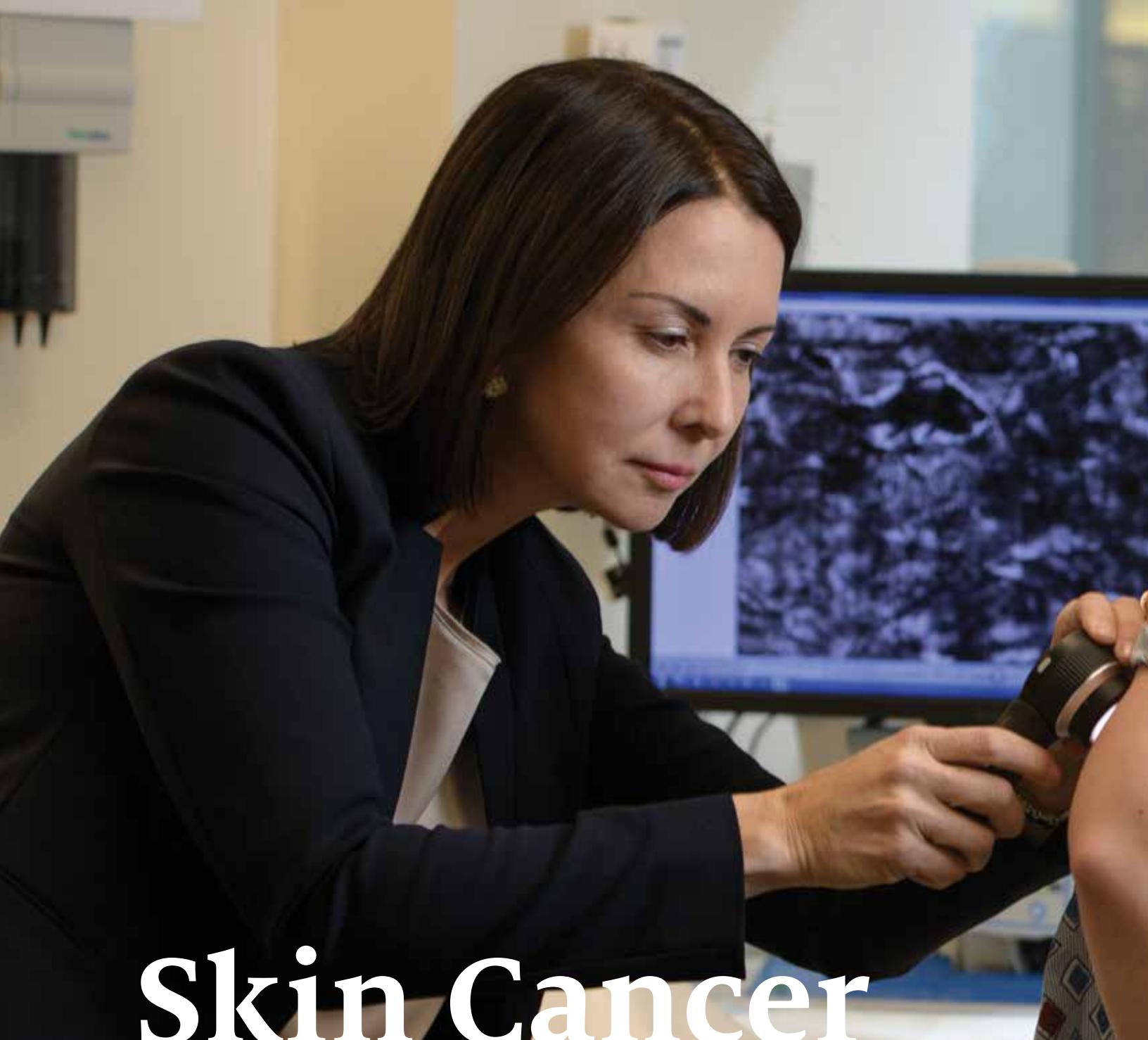
One famous example took place during World War II, when medics ran out of morphine and substituted syringes filled with saline. Believing they were receiving a powerful painkiller, many wounded soldiers felt relief. Though it was inert, the saline gave them a "boost."

While such deception is not considered ethical these days, placebos still have a place in medicine. Placebo-controlled trials, in which an experimental agent is compared to a placebo, provide scientists strong evidence for the agent's effectiveness. When patients don't know if they're receiving the drug or the placebo, they receive the placebo effect's boost, and investigators can see if the drug provides benefits beyond that boost.

Most clinical trials do not use placebos. For example, cancer patients always receive a biologically active treatment — the experimental treatment, standard care or a combination of the two. They don't forgo treatment in favor of a handful of sugar pills. Rather, researchers compare the new treatment to what patients normally receive.

Placebos are common in prevention trials, however — especially when no standard strategy for preventing a type of cancer exists.

For example, when a UA Cancer Center team tested the effect of selenium on cancer risk, volunteers received capsules of brewer's yeast that may or may not have been fermented in selenium — but they all looked alike, with the same pungent aroma. No one knew if they were taking the selenium supplements or the placebo, allowing researchers to control for the placebo effect when tracking volunteers' cancer rates over time.



Skin Cancer Chemoprevention

Slowing, stopping or reversing
a skin cell's journey to cancer

by Anna C. Christensen



Kris Hanning, UAHS BioCommunications

Clara Curiel, MD, is passionate about preventing, detecting and treating skin cancer.

In every corner of our state, the sun beats down on towering saguaros, gangly roadrunners and dry river beds. The sun's ultraviolet (UV) rays are the primary cause of skin cancer, and although they are hard to avoid in Arizona, many steps can be taken to reduce skin-cancer risk.

Skin cancer falls into two main categories, depending on which skin cells are affected. The most common types of skin cancers, basal cell carcinoma and squamous cell carcinoma, originate from cells called keratinocytes. These cells produce

keratin, the hard substance that allows your skin to act as a barrier between you and the outside world. The other type is melanoma, which originates from cells called melanocytes. These cells produce melanin, the pigment that colors your skin and protects it from UV radiation. Melanoma is rare but more likely to blaze a deadly path from its site of origin to other parts of the body.

Some of the nation's best skin-cancer research takes place here at the University of Arizona Cancer Center, which

houses the Skin Cancer Institute (SCI), a locus of patient care, research, and community outreach and education. One of the SCI's biggest research foci is chemoprevention, the use of substances that can slow, stop or reverse the progression to skin cancer. The SCI team has been extremely successful in securing multiple National Institutes of Health grants over the years, including the Chemoprevention of Skin Cancer Program Project Grant, as well as additional research funding through the UA Chemoprevention Consortium.

When you think of skin-cancer prevention, you might envision yourself wearing a big floppy hat or slathering on sunscreen. But skin-cancer chemoprevention is a little bit different.

"Sunscreens include physical blocks," says Clara Curiel, MD, clinical director of the SCI and leader of the UA Cancer Center cutaneous oncology team. "All they do is reflect, scatter and block the sun's rays before they penetrate the skin — they don't directly interact with the skin cells; they function as a filter."

"The goal of sunscreen is to prevent the initial UV damage," adds Sally Dickinson, PhD, assistant professor of pharmacology at the UA Cancer Center and co-investigator on the Chemoprevention of Skin Cancer Program Project Grant. "In contrast, chemopreventive agents go to a damaged area of the skin and prevent it from progressing to cancer."

Healing sun-damaged skin

Chemoprevention strategies can be employed at many points in time, starting when skin already has been damaged by UV radiation. Unfortunately, few products on the market fit this bill. But retinoids, derivatives of vitamin A that can be found in some over-the-counter skin creams, are one standout.

"Retinoids are known to slow down the progression of skin cancer," Dr. Curiel says. "They help the keratinocytes recuperate from the damage caused by sun exposure. They also help with texture and pigmentation changes that happen with sun exposure, so you get that added benefit."

Given how common skin cancer is, being able to lower your risk with an ointment or a daily pill would be a boon. But the catch is that any preventive measure must have an exemplary safety profile.

"Patients diagnosed with cancer frequently undergo a potentially toxic treatment, because the trade-off is justifiable," Dr. Curiel says. "With chemoprevention, safety is a big deal. Not only should the candidate drug be effective, it should also demonstrate an acceptable safety profile since individuals are typically healthy and expected to be in treatment for an extended period for chemoprevention to be effective."

"What I'm hoping for Arizona is that exposure to significant sunlight becomes like smoking — people just don't do it."

Clara Curiel, MD

Stopping cancer in its tracks

Skin cells take their first step toward cancer when they are unable to repair DNA damage and genetic mutations start to accumulate.

One strategy for treating skin in this "precancerous" stage is to target sun-damaged cells for destruction, using a technique called photodynamic therapy. First, a substance called aminolevulinic acid (ALA) is applied to the skin, where it is incorporated into the nucleus and metabolized by the cell. Then the skin is exposed to a specific wavelength of light, which the ALA is specialized to absorb.

"Damaged cells replicate faster and internalize more of the ALA," Dr. Curiel says. "When you expose them to the light, cells with higher concentrations of the ALA will be more susceptible to the effect of energy released by light absorption. Almost selectively, the damaged cells are destroyed."

Dr. Dickinson hopes to find more ways to slow skin cancer progression. Along with her colleague Georg Wondrak, PhD, associate professor of pharmacology and toxicology, her lab is working on a cream featuring a compound called resatorvid, an "orphan drug" that the manufacturer dropped when it failed to pan out in trials as an infusion for blood infections. Drs. Dickinson and Wondrak have found that, when formulated for topical use, resatorvid is much safer and might

be effective in slowing down the progression of skin cancer.

"When we use it topically, we don't see any toxicity," Dr. Dickinson says. "Since we are pretty confident it's going to be safe, we hope to use it longer term in sun-damaged areas to see if it blocks the progression of cancer."

Resatorvid inhibits TLR4, or toll-like receptor 4, a surface protein on many cells. TLR4 can be "activated" by many factors, including UV light, setting off a domino effect that culminates in cell growth and division. When damaged cells are on the road toward cancer progression, however, activating TLR4 can hasten that journey — so, in theory, anything that can block TLR4 in a damaged cell can slow cancer progression.

In studies, TLR4 "went from low levels in normal skin to higher levels in squamous cell carcinoma," Dr. Dickinson says. It's possible that too much TLR4 increases inflammation, which is a factor in the development of cancer. Although inflammation is a normal part of the immune response, in which the body fights against injuries or infections, chronic inflammation can damage tissue and DNA, laying the groundwork for tumor formation.

"Resatorvid is attractive because it's small enough to get inside the cell, and actually targets TLR4 and blocks its activity," Dr. Dickinson says. "In mice, the topical application of resatorvid can block UV-induced skin cancer, so our next goal is to push it into the clinic to see if it hits the target in human skin."

Protecting the whole body

Topical creams — like ALA, and perhaps in the future resatorvid — can be applied to parts of the skin with the most UV exposure, protecting individuals from nonmelanoma skin cancers like squamous cell and basal cell carcinomas.

"Nonmelanoma skin cancers appear in the areas of most sun

damage: your face, your ears, your scalp, your neck, your hands, your arms," says Dr. Curiel. "It makes sense to deliver a chemopreventive agent through a topical product — you know where to apply it."

But melanoma, the most dangerous type of skin cancer, can arise in parts of the body that have had very little sun exposure.

"You don't know where melanoma is going to develop," Dr.

Curiel says. "The most common site for melanoma in men is on the back, and on the legs in women. You're not going to apply cream everywhere on your body to prevent a melanoma. So, the question is, is there a safe and effective drug you can deliver systemically, preferably in an oral formulation?"

A pill to reduce risk for skin cancer could deliver protection throughout the body, in a way a cream never could. In recent years, nonsteroidal anti-inflammatory drugs, or NSAIDs, have attracted attention for their possible role in skin-cancer prevention. Earlier in her career, at the Dana-Farber/

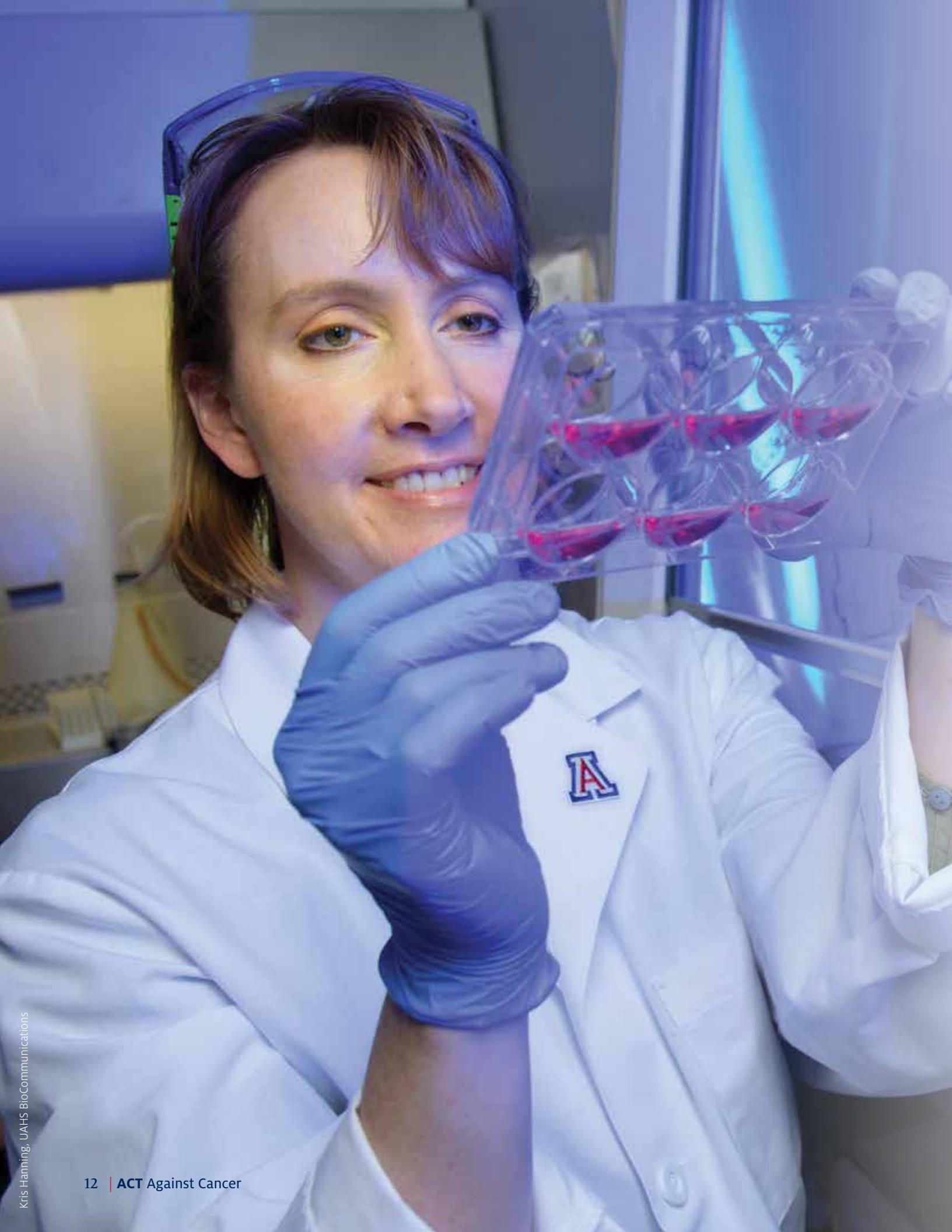
Harvard Cancer Center, Dr. Curiel pioneered a landmark study revealing this potential connection and completed the only randomized clinical trial evaluating NSAIDs in patients at risk of developing melanoma.

Because aspirin has been studied for so many other uses, many researchers have been able to make connections between aspirin and reduced skin-cancer incidence, but some studies found no association while others did. Another NSAID, celecoxib, also has seen mixed results, with a few studies finding decreases in basal cell carcinomas.

"There is still some debate," Dr. Curiel says. Robust studies must specifically be designed to assess the relationship between NSAIDs on melanoma risk. Dr. Curiel, along with Sherry Chow, PhD, co-leader of the UA Cancer Center's Cancer Prevention and Control Program, is preparing for a clinical trial



Sally Dickinson, PhD





Sally Dickinson, PhD, hopes an “orphan drug” called resatorvid can slow down the progression of skin cancer.

that will investigate the potential of two NSAIDs, aspirin and sulindac, to reduce the likelihood of melanoma in patients whose atypical moles put them at a higher risk. Studies like these are necessary to help settle the debate over NSAIDs once and for all.

Welcome to Arizona

Both Drs. Curiel and Dickinson hope more people will start to take sun safety seriously, especially in sun-drenched states like Arizona.

“I was listening to the radio this morning and they said it’s amazing how few people smoke these days,” Dr. Curiel says. “What I’m hoping for Arizona is that exposure to significant sunlight becomes like smoking — people just don’t do it.”

We can start by instilling healthful habits in children.

“Kids should be strongly encouraged to have hats on when they’re outside,” Dr. Dickinson says. “That should be a no-brainer.”

The SCI includes community outreach in its mission, providing sun-safety training for students, educators and health-care professionals. These efforts are fueled in part by donors, whose gifts to the Skin Cancer Prevention Friends (SPF) support research, community education and public sunscreen stations.

You have a range of options when it comes to preventing skin cancer — and future scientific advancements will only expand them. You can use sunscreen, wear protective clothing and avoid the sun to prevent your skin from being damaged in the first place. Once the damage has been done, you can use chemopreventive agents to slow down cancer progression. Beyond that, you can regularly see a dermatologist, who can catch skin cancer in its earliest and most easily treated stages. By learning how to protect yourself, you can live in harmony with the environment, enjoying the natural beauty our state has to offer.

“I would love to see the Tucson International Airport have a big sign,” Dr. Curiel says. What would it say? “Welcome to Arizona. Put on Sunscreen and Wear Your Hat. Don’t Let Skin Cancer Be Your Souvenir!” ▲

Healing in Motion

Restoring Balance seeks to meet people where they are — physically, culturally and clinically.

by Anna C. Christensen

When Jason Pedwaydon lost his mother to cancer, his life took a turn.

"I was just lost," he recalls. "I didn't know what to do, so I turned to fitness and found some relief."



Steven Toya, NAU

Jason Pedwaydon

Mr. Pedwaydon hails from a family of athletes and had long been active in sports, but his grieving process prompted a shift in focus, from competition to fitness: endurance, strength, flexibility, cardiorespiratory health and body composition. The release it provided was powerful, and he also was building his own resilience — a sense of strength that would

serve him well years later when he was diagnosed with lymphoma in his early 40s.

"I had been prepping my body that whole time," Mr. Pedwaydon recalls. "My doctors were encouraging, telling me that I was sitting in a really good position because I was physically fit. That was the first spark in the fire, that there is a connection between fitness and cancer."

That initial spark launched his personal journey to learn more about the link between fitness training and cancer survivorship. He devoured any information he could find — and this quest for knowledge laid a foundation that prepared him for his life's next turn.



From left to right: Jason Pedwaydon; Brenda Charley, MS; and Saraphina Slim, Restoring Balance participant





Steven Toya, NAU

Sharon James (left), a Restoring Balance participant, works with Cody Chee, fitness technician

"Little did I know I would have the opportunity to help people going through something similar to what I went through," he says. "I was in remission for two years and that's when I came in contact with Brenda Charley."

First of its kind

A sedentary lifestyle increases risk of cancer and makes the disease more likely to come back. The flip side is that getting active might reduce cancer recurrence and improve quality of life — and make the side effects of treatment less severe. Having cancer doesn't have to stop someone from enjoying a healthy and fulfilling life, and physical activity can be a part of that.

Native Americans have the lowest five-year cancer survival rates of any U.S. population. Jennifer Bea, PhD, associate professor at the University of Arizona College of Medicine – Tucson, hopes to improve those statistics with Restoring Balance, a program tailored for a Native population that meets standards set by the American College of Sports Medicine (ACSM): 150 minutes of moderate, or 75 minutes of vigorous, aerobic activity per week, and two days per week of moderate- to high-intensity resistance exercise plus flexibility exercises for all major muscle groups. Dr. Bea, along with Dirk de Heer, PhD, MPH, and Anna Schwartz, PhD, of Northern Arizona University, operates this project through the Partnership for Native American Cancer Prevention (NACP), a collaboration between the UA Cancer Center and NAU.

"Exercise can be very restorative, helping to right the ship," Dr. Bea says. "Squeezing in physical activity can help improve survivors' quality of life while they are trying to get their life back after treatment."

"Exercise is so important to their survivorship," adds Brenda Charley, MS, a certified exercise physiologist and NAU program coordinator for Restoring Balance. "We want to make exercise a part of their treatment."

No one has studied the effect of exercise on cancer survivorship in Native populations — until now. Since receiving funding in 2014, the Restoring Balance team has been reaching cancer survivors in Northern Arizona tribal communities, while helping to fill a huge gap in medical research.

"So far, the literature mostly represents white Americans," Dr. Bea says. "We're striving for the ACSM guidelines, but also trying to adapt the Western ways to the tribal community. We're attempting to meet people where they are — physically, culturally and clinically."

The program serves tribal communities in Northern Arizona, with hopes to expand across the state. Native personal trainers work with cancer survivors at the Native Americans for Community Action Wellness Center in Flagstaff, the Hózhóógo Iiná Wellness Center in Winslow and the Leupp Chapter House on the Navajo Nation. Material has been vetted by cultural experts from 10 tribal backgrounds, who scrutinized everything from colors to symbolism to clarity. Through feedback from

participants, Restoring Balance constantly is being fine-tuned.

"We've had a few hiccups and we're learning from them," Ms. Charley says, "but I think the effect on survivors has been mainly positive. There's a lot of gratitude coming from the participants, and a lot of pride coming from the trainers."

Tradition and training

One of the most important aspects of Restoring Balance is that it is delivered to cancer survivors by Native trainers. Mr. Pedwaydon is one of those trainers. Originally from Detroit and of Chippewa, Ottawa, Delaware and Mohican heritage, marriage brought him to a remote part of the Navajo Nation called Big Mountain.

Word of mouth connected him to Ms. Charley, who recognized the talents he could bring to the table. Twice a week, Mr. Pedwaydon makes the nearly two-hour trek down to Leupp with items such as mats, weights and steps in tow. He draws from his own culture and past battle with cancer to motivate survivors.

"When we get diagnosed with this awful disease, we stand up and we fight! I tell my participants one of the ways we're going to fight is through exercise. I believe it, having gone through it," Mr. Pedwaydon says. "If you're down in the dumps — and cancer does a mind job on people like nothing I've ever seen — achieving goals helps you realize you are resilient."

Cultural understanding helps trainers form effective coaching relationships with participants.

"If you understand the lifestyle, you'll be more understanding and more patient," Ms. Charley says. "If they are traditional, ceremonies always take precedence. You have to be flexible if they don't show up to an appointment because they had a last-minute prayer done. They are trying not only to be reverent to their spiritual practices, but also to lead a healthy life."

All Restoring Balance trainers are working toward ACSM certification, with additional specialization in serving cancer survivors. Optimally, participants visit a trainer once a week, receiving a mega-dose of inspiration, along with an exercise

plan to sustain them through the week. Giving participants the tools they need to take their health into their own hands can be empowering.

"We can't do the work for them," Ms. Charley says. "We give them the program, we coach them if they're having trouble, but in the end, it's all their work."

Integrating cultures

The program's name, Restoring Balance, came out of focus groups with Navajo people.

"Balance was a concept that kept coming up," Ms. Charley says. "A lot of our participants would go to medicine men, and these medicine men would tell them something was not quite in balance."

"The way a Native understands chemotherapy is that this drug is going to come into your system to help you fight cancer, yet it causes a disruption," adds co-investigator Etta Yazzie, RN, UA Cancer Center research nurse and an infusion nurse at Arizona Oncology Associates in Flagstaff. "For a cancer survivor to get their energy back, they need to get the body moving. It is understood in Navajo that to restore balance is to restore hózhó. Your body restores hózhó with the mind, soul and spirit, and with the elements of nature, with the universe and with family."

Every participant receives a free water bottle, one of the incentive items that was inspired by the ongoing dialogue between the community and the program. Most Navajo ceremonies and traditional dances include prayers for water, which represent a celebration of life for all living things on Earth.

"In all Native cultures, water is important. It is sacred," Ms. Yazzie says. "Most healing ceremonies use water. Water has life in itself and allows the songs and prayers to come to it. When you drink it, that healing and spiritual meaning can flow through your veins and open up channels so you can be reconnected to the spiritual and healing energies."

Restoring Balance needs to be flexible enough to include both the exercise regimen and important ceremonies. That includes

making sure schedules don't adhere too strictly to the Western calendar.

"The Navajo and the Hopi understand and go by the moon cycle," Ms. Yazzie explains. "Each moon cycle has a purpose. When the moon changes, ceremonial dances or healing ceremonies are set to take place. The schedule has to allow for that."

Mr. Pedwaydon adjusts terminology, citing an exercise called "hot foot," which involves standing on one foot and jumping front, back, left and right. He invokes the concept of the medicine wheel, a circle divided into quadrants representing the four directions — east, south, west and north.

"The medicine wheel is a symbol that's pretty universal throughout Indian Country," he explains. "Instead of calling it hot foot, I say, 'We're going to jump in the four directions.' If you can implement little things like that to help make it relatable to our cultures, that helps encourage them."

Exercises also need to respect cultural norms regarding personal space and modesty. Ideas about "crossing over," considered a rude intrusion into one's aura, may influence how trainers interact with participants. One exercise, which originally had participants lifting their legs into the air from a position on the floor, was considered immodest by many women, and was reformulated for a sitting position.

Beyond the gym

Restoring Balance meets people where they are not just by working to ensure the program is culturally adapted, but also by reaching out to residents of rural communities. Travel can be difficult when someone is recovering from cancer treatments — especially for people from small communities outside the orbit of Tucson and Phoenix.

"If you've just been through treatments, distance becomes an even bigger issue," Dr. Bea says. "You need to be able to meter out your energy for the fundamental activities of living."

Nature is an option too often overlooked by Western exercise regimens that assume access to — and a preference for — gym equipment.

"A lot of rural Native people don't go to gyms," Ms. Yazzie says, recalling feedback from focus groups. "We talked about

getting treadmills, and they said, 'You may buy the treadmill, but it'll just be sitting there. We're used to walking on the earth. We're used to working with livestock. Maybe the young people will use it, but older people would probably just look at it and take a walk.' So, we had to cross that out."

"Communing with nature can be an important piece of recovery," adds Dr. Bea. "A lot of folks like to walk or run — that's a long-standing tradition, to rise before the sun and walk or run."

In addition to understanding the culture, trainers need to understand cancer care.

"If somebody has radiation or chemotherapy on Monday, how are they going to feel the next day? How do you coach them so that they can get back to exercising by Thursday or Friday?" Ms. Charley asks. "It takes a special person to understand the way those things work."

Sowing success

Dr. Bea is excited that Restoring Balance won't just help cancer survivors in the short term — the NACP's overarching goal is to recruit more Natives into biomedical research and health-care professions, equipping them to lead their own research projects and develop a more culturally competent workforce.

"Instead of us running everything as university employees, we are empowering the community trainers and federally recognized centers to deliver the exercise program and to really own the research," Dr. Bea says. "It sets them up for running their own research projects in the future."

Involving people from the community is crucial to the program's success.

"Etta is Navajo, Brenda is Navajo. You have to have folks who are part of the community," Dr. Bea says. "If you're going to show up at a ceremony, you may need to be Native. You need to understand what might be open, what might be closed and when you need to bring gifts. Those are important things about respecting the culture, which no outsider can do as effectively as a Native person."

And by helping trainers obtain ACSM certification, everyone in the community benefits. ACSM-certified trainers with specialization in cancer exercise are rare in Arizona, especially



Kris Hanning, UAHS BioCommunications

From left to right: Ravina Thuraisingam, UA College of Medicine student, Jennifer Bea, PhD, and Vinson Lee, MS

in rural communities.

"We are taking people from each of the communities and making sure they have the expertise," Ms. Charley says. "When the research project leaves, that expertise stays in the community."

Restoring Balance has attracted fitness enthusiasts who want to serve their people.

"I love to exercise, I love fitness and health, and I get to work on that every single day," Ms. Charley says. "I've always wanted to get into research, but I didn't know how, especially in a small town like Flagstaff."

"I have the opportunity to do something I love — fitness — to help fight something that I despise — cancer," adds Mr. Pedwaydon. "This is tailor-made for me."

Being able to follow these passions while staying in their communities helps bring a sense of wholeness to their lives.

"It's good for Indians to occupy their native lands. It's difficult and it poses its challenges, but it's very rewarding, unlike anything that you can find, feel or obtain in the city," Mr. Pedwaydon says. "It's really a blessing to have such an opportunity. All aspects of it are a win-win-win-win all the way around."

"I'm so grateful that I get to take care of my family, I get to take care of my community, and I still get to have a good job," Ms. Charley adds. "It's a really awesome balance." ▲

Restoring Balance is supported in part by the National Institutes of Health NCI grant U54 CA143925-06 and is approved by oversight committees at the University of Arizona, Northern Arizona University and the Navajo Nation Human Research Review Board (NNHRRB No. NNR14.192).

A Shot at Prevention

By learning about their immune response, we could defend more children against a cancer-causing virus.

by Anna C. Christensen

Vaccines have helped transform our relationship with infectious diseases. In parts of the world with widespread vaccination, fatal illnesses like measles and whooping cough no longer inspire fear. Rather than fretting over microbes, most of us reading this magazine are more concerned about chronic diseases like diabetes, heart disease and cancer.

A handful of cancers, however, are vaccine preventable — including cervical cancer and anal cancer, which almost are exclusively caused by human papillomavirus, aka HPV. This common virus also can cause head-and-neck, vaginal, vulvar and penile cancers. Overall, HPV is responsible for about 1 out of 20 cancers worldwide.

Fortunately, preteens and teens can be protected by the HPV vaccine. Since its debut in 2006, HPV infections have declined, and HPV-associated cancer rates are projected to nosedive as well. Previous versions protected against two cancer-causing strains of HPV, but the latest HPV vaccine, Gardasil 9, protects against seven cancer-causing strains.

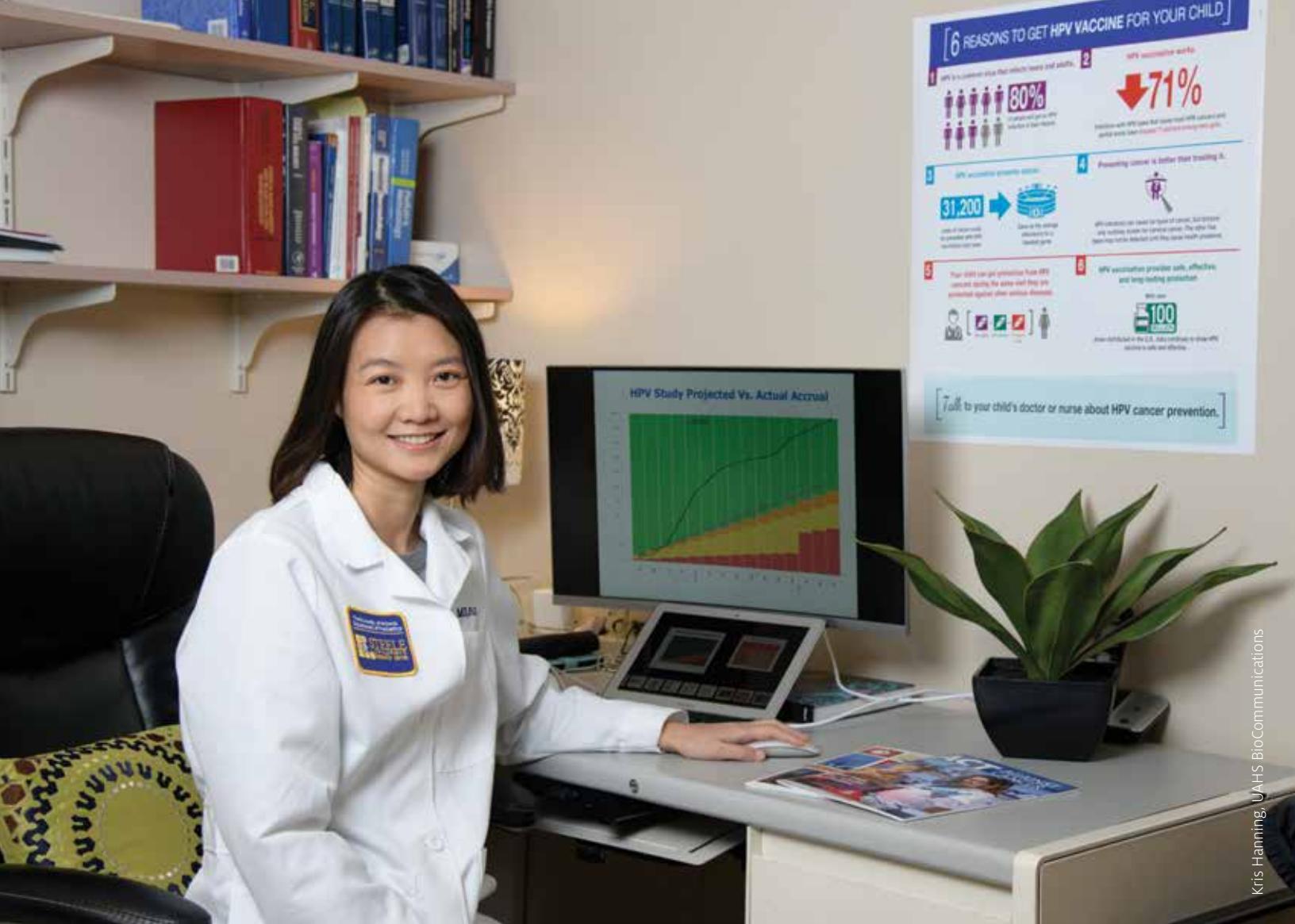
Unfortunately, in 2017, only 49 percent of 13- to 17-year-olds were up to date on their HPV vaccinations, falling short of the Department of Health and Human Services' goal to achieve an 80-percent vaccination rate by 2020. Many barriers stand in the way of that goal. One is that the vaccination series requires kids to receive multiple shots over the course of six months.

“Hopefully in the future, we'll decrease HPV-related cancers and diseases in women and men.”

Yi Zeng, MD, PhD

Yi Zeng, MD, PhD, hopes more preteens and teens will receive the HPV vaccine.





Yi Zeng, MD, PhD

"It's the logistics," says Yi Zeng, MD, PhD, associate professor of pediatrics at the University of Arizona College of Medicine – Tucson. "Preteen and teenage girls and boys are busy. Requiring them to take time off from school and their other activities to come to the doctor's office is a challenge."

When the vaccine first was approved, recipients typically were given a first shot, a second shot two months later and a third shot four months after that.

"Most kids don't get the three doses," Dr. Zeng says. "Three vaccines within a six-month period is a lot to ask of a teenager and their parents."

Fortunately, as we learn more about the vaccine, recommendations are changing. We now know that younger recipients — those between 9 and 14 years of age, whose

immune responses to HPV vaccines are stronger — receive protection from just two doses. (Older recipients still get three doses.) Two shots instead of three save a trip to the doctor — thus saving the time parents have to take off from work and allowing kids to avoid the extra sting of a needle.

But some studies, looking at earlier versions of the vaccine, have hinted that one dose might be all it takes to give a young person lasting protection. So, what about Gardasil 9? That's the question Dr. Zeng is hoping to answer. With support from the National Cancer Institute, she is at the helm of a clinical trial taking place at the UA Cancer Center and UCLA. The trial has enrolled nearly 200 preteens, ages 9 to 11, and is tracking their immune response to a single dose of Gardasil 9.

Whenever the immune system encounters a "bad bug" — or, in the case of the HPV vaccine, an inert protein that exactly

mimics the virus's outer shell — it responds by manufacturing customized proteins called antibodies, which lock onto a pathogen and "tag" it for destruction. As long as our blood contains sufficient numbers of these custom-made antibodies, our immune systems can protect us from these bugs if we encounter them in our daily lives. We can test a patient's immunity by looking at blood samples, which Dr. Zeng's team takes from trial participants every six months over a two-year period.

"We hope one dose gives our study participants a sustainable level of antibodies," Dr. Zeng says. "If our data support our hypothesis, in the future, kids may need only one dose of Gardasil 9."

At the outset, Dr. Zeng's team was worried it might be difficult to recruit participants to their study — and keep them coming back every six months to give blood samples.

"There were a lot of uncertainties about how we were going to retain the patients, because we plan to poke them," Dr. Zeng says with a laugh. "But it worked out very well."

One reason Dr. Zeng believes the study has been so successful in holding onto participants is its flexibility.

"How do you convince busy kids and busy parents to come to the clinic to do this?" she asks. "We offered them a very flexible schedule, like very early or very late appointments to accommodate their needs."

Although Dr. Zeng was initially only looking at girls' immune responses, her team quickly opened enrollment to boys in response to demand.

"The brothers of some of our participants asked, 'When can I get my vaccine?'" Dr. Zeng recalls. "The NCI decided to expand the study, so we were able to recruit boys of the same age group."

Study participants still get the FDA-recommended two doses of the vaccine — they just wait 24 months to receive the second shot, allowing researchers to monitor antibody levels over a two-year period, and allowing children to stay in compliance with current FDA recommendations.

The last participant is expected to complete the final study visit in February 2020. If the results show that children maintain sufficient levels of antibodies in their blood, larger studies will be designed to answer further questions about a possible one-dose regimen more definitively. If HPV protection could be obtained with just one visit to the doctor's office, children would have one less barrier standing between them and cancer prevention.

"I'm hoping more boys and girls will be immunized," Dr. Zeng says. "Hopefully in the future, we'll decrease HPV-related cancers and diseases in women and men." 

An Intervention with Heart

LLvES uses the power of personal connections to help ovarian cancer survivors forge healthier habits

by Anna C. Christensen

Tucked away on the third floor of the Pima County Health Department is a suite of offices housing University of Arizona undergraduate students and their faculty mentors. Armed with telephone headsets and an array of crafting supplies, they are at the center of one of the largest and most ambitious efforts to extend lifespans of ovarian cancer survivors.

Ovarian cancer is relatively rare, striking 1 out of 78 women. But it also is one of the deadliest cancers, with only 44 percent of patients surviving five years past their diagnosis. After their disease goes into remission, many patients worry the cancer will return.

"When treatment is over, there is a 'respite' when patients start to feel better and go back to living their lives," says Janiel Cragun, MD, assistant professor of obstetrics and gynecology at the UA College of Medicine – Tucson. "But in the back of their minds, there is the psychological concern of disease recurrence. Their No. 1 fear is that it's going to come back."

Many physicians advise patients to make positive changes in diet and exercise, as these choices lay a foundation for good health overall.

"I would like patients to keep active," says John Farley, MD, professor of obstetrics and gynecology at the UA College of Medicine – Phoenix. "The more active you are, the more likely you are to keep the cancer from coming back."

Shaping one's own survivorship through lifestyle changes is an empowering idea.

"These women have survived cancer. Being able to take control of something is important," says Tracy Crane, PhD, assistant professor at the UA College of Nursing. "Patients ask, 'I'm done with treatment — now what?'"

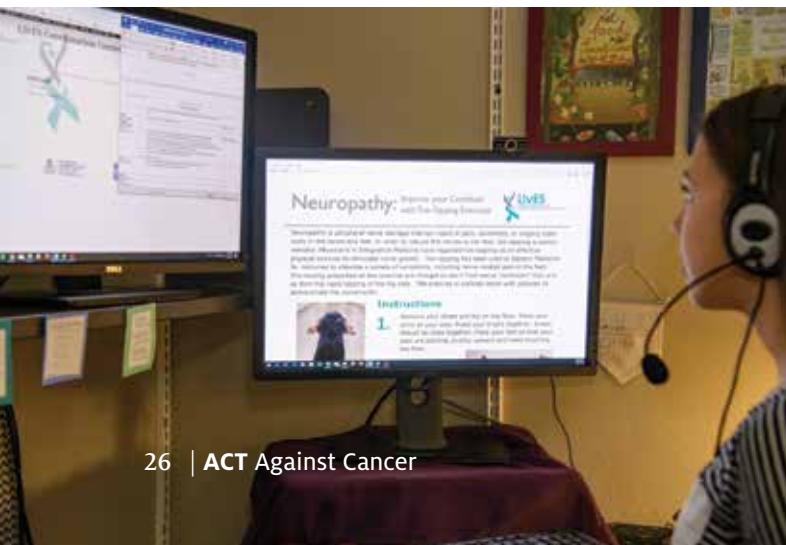
A team at the University of Arizona is answering that question in the form of a rigorous study called LLvES — Lifestyle Intervention for Ovarian Cancer Enhanced Survival, the first study to investigate if ovarian cancer survivors can enjoy a longer period of wellbeing through healthful changes in lifestyle and behavior.

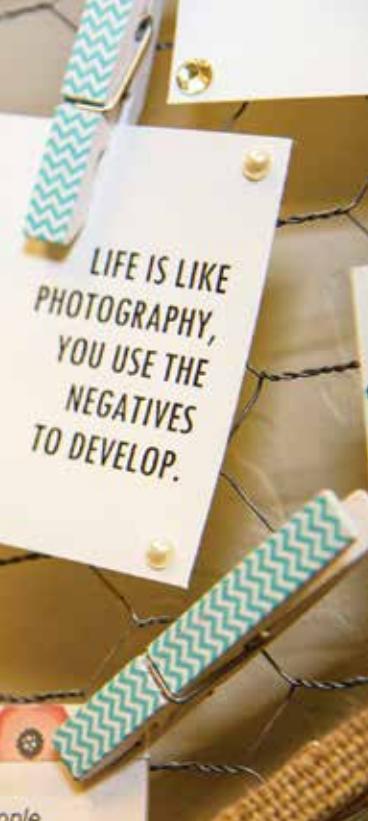
Based on previous evidence that physical activity and a plant-based diet could lower cancer risk, the team hypothesized that these lifestyle changes also could prolong survivors' respite from the disease, stretching out the time it takes for ovarian cancer to return — if it comes back at all. Participants aim for a daily intake of four servings of vegetables, two servings of fruit, 30 grams of fiber and no more than 20 percent of total calories obtained from fat.

"We had growing evidence suggesting that diet and physical activity matter, not only in terms of risk but perhaps in terms of long-term prognosis," says Cynthia Thomson, PhD, RD, who oversees LLvES nationwide and is co-leader of the Cancer Prevention and Control Program. Her team set out to test that idea.



Tracy Crane, PhD (left), and Cynthia Thomson, PhD, RD





Kris Hannning, UAHS BioCommunications and Anna C. Christensen

Laying the groundwork

LiVES initially was conceived more than a decade ago by Dr. Thomson and David Alberts, MD, now UA Cancer Center director emeritus. Dr. Crane was a graduate student when, beginning in 2008, she helped prepare LiVES for launch. Now a co-investigator, her feelings toward the project are downright maternal.

"I had all three of my babies in the time it took for us to get this study up and going," Dr. Crane recalls. "Dr. Alberts likes to joke that LiVES was my fourth baby. It's been a huge part of my life."

By June 2012, LiVES was recruiting participants from all over the nation. In August 2018, they reached their goal, recruiting a total of 1,205 participants from 300 centers in nearly every state. The team is slated to finish collecting data in August 2020, when the last participant completes the program.

"The intervention is centralized in Arizona," Dr. Thomson says. "We are responsible for training our health coaches, for evaluating them on a regular basis and for doing the quality control. We make sure this trial is conducted with the highest level of rigor and integrity."

Telephone coaching is at the heart of LiVES, and participants receive regular phone contact over a period of two years. From the program's headquarters in the Pima County Health Department, LiVES coaches have talked to all 1,205 study participants. Public health students coach the "control group," which is made up of survivors who receive 22 coaching sessions covering general health topics, such as the importance of hydration and sun safety. Dietetics students coach the "intervention group," which receives 33 coaching sessions centering around diet and physical activity goals. At the end of the study, the control group will be compared to the intervention group to see if the program made a difference, not just in terms of survival but also in quality of life.

The training process for coaches is intense. Intervention coaches undergo several months of training, learning all about ovarian cancer and the particulars of diet and

exercise. On top of everything else, coaches engage in multiple practice calls to prepare for a variety of situations. These roleplaying sessions culminate in a final phone call with Dr. Thomson.

"It was close to 30 minutes, and you're on your feet for most of the call," says intervention coach Emily Diana of that "graduation" call. "It's nerve-wracking — you want to pass and start doing what you've been training to do for so long."

By the time they receive their degrees, the student-coaches demonstrate high-level competency in health coaching.

"It doesn't seem like it would be possible to ask busy undergraduate students to do this, but they do and they thrive," says lead coach Sarah Wright. "They grow so much, and have gone on to amazing things because they've had this early experience."

Building bonds

Intervention coaches learn a patient-centered counseling technique called "motivational interviewing."

"The patient is always in the driver's seat with motivational interviewing. We're drawing upon the individual and what they want to work on, versus the coach telling them what they're going to work on," Dr. Crane explains. "It's like when you were a kid reading 'Choose Your Own Adventure.' We're trying to get them to this one overall goal of eating healthier and exercising more, but how they get there can look different."

Coaches start out with frequent phone calls, which are important in establishing rapport and helping participants become self-sufficient early in the program. As they continue their journey into survivorship, the tone and frequency of these interactions adapt to meet the survivors' changing needs. Coaches often become a vital component of their support network.

"After you've gotten through treatment, you're not coming back to the clinic for follow up as often," says Dr. Crane. "The coaches serve as a branch of their health care team."

The emotional support coaches offer participants might be just as important as the diet and exercise information they provide. Their ability to build these bonds with participants is indispensable.

"They're amazing," says Dr. Thomson. "They form a rapport with these women that goes beyond meeting the goals of the study. It's a much broader and deeper commitment to their wellbeing."

The connection built through telephone conversations over the course of two years is buttressed by other forms of personal contact. Drawing from a full stock of craft supplies, coaches send hand-made cards to participants to acknowledge

sad news, like the recurrence of a patient's cancer, and happy news, like the birth of a grandchild or accomplishing a health goal.

"It's a way that we can physically connect with our participants," says study coordinator Meghan Skiba, MS.

"A card lets them know we hear them and we care. The whole team is supporting them through both the negative and positive experiences that come with survivorship."

"They see a different side of you, even if it's something small like your handwriting," adds bilingual intervention coach Sofia Grijalva. "It's another little connection you make. They love it."

When coaches sign up for their two-year stints with LIVES, they must prepare to take on the emotional ups and downs that come with survivorship.

"It's hard when someone you've talked to for 18 months has a recurrence. Those calls are heartbreaking, and there are often tears," Ms. Wright says. "But the vast majority of calls are positive, exciting or optimistic. That keeps you going through the calls that are more difficult."

"Every day is an emotional rollercoaster," Ms. Grijalva adds. "You never know what you're going to get, but we're there to support them. That is the most rewarding thing about this job."

If I buy people one more day that's a healthy, happy day, that would be great.

Cynthia Thomson, PhD, RD



Tabbs Mosier, UA College of Medicine - Phoenix

John Farley, MD, helped recruit ovarian cancer survivors to the LIVES trial.

Healthy, happy days

LIVES is popular with participants — and that high esteem is reflected by glowing exit interviews and a low dropout rate.

"A lot of times, when there are new drugs and you worry about side effects, patients can be a little hesitant about participating in trials," Dr. Farley says. "LIVES encourages a lot of natural things — dietary changes, exercise — which are generally appealing to patients."

At the UA Cancer Center, both Drs. Cragun and Farley recruited ovarian cancer survivors to join the study, and hope the results will equip them to give well-rounded advice to ovarian cancer patients beginning their survivorship journey.

"We're so focused on disease-free progression that we lose sight of quality of life," Dr. Cragun says. "We need to move away from the mentality of 'treat at all costs' and pay more

attention to survivorship. In the future, I hope we can extend survival without sacrificing quality of life."

When the last patient completes the study next year, the resulting data will form the backbone of the largest lifestyle intervention trial conducted with ovarian cancer survivors. Drs. Crane and Thomson both anticipate that when this trial is done the results will make national headlines.

"This is a huge trial," Dr. Crane says. "There's been nothing else like it, and I'm not sure there will ever be anything like it again."

"My whole world is about preventing disease," Dr. Thomson adds. "Even if I buy people one more day that's a healthy, happy day, that would be great." ▲



Jack Wilson, left, with Daniel Persky, MD

DONOR-PATIENT PROFILE

Jack Wilson

by Anna C. Christensen

Married since 1973, working in the same field since coming to Phoenix from New Jersey in 1975, and living in the only house he'd ever owned, Jack Wilson's life was the picture of consistency. Then, in 1997, an oncologist informed him he had mantle cell lymphoma.

In addition to being an unwanted wrench in an otherwise stable life, it was the wrong diagnosis.

"They had me teed up for chemo," Jack recalls. But a week before he was scheduled to start treatment, a "little voice" prompted him to seek a second opinion. A long-time friend, who also happened to be a top cardiologist in Scottsdale, recommended he see a specialist at the University of Arizona Cancer Center.

Jack booked an appointment with Alan List, MD, then the clinical director of the Bone Marrow Transplant Program at University Medical Center in Tucson. To Jack's relief, Dr. List advised delaying his scheduled chemotherapy treatments — and further tests revealed some additional news.

"You don't have mantle cell lymphoma," Dr. List told him. "You have chronic lymphocytic leukemia. The protocol on that is watch and wait."

Jack was relieved — instead of diving headfirst into cancer treatments and all their unpleasant side effects, the chemo his oncologist in Phoenix was rushing him toward could wait. He "fired" that doctor and has been with the UA Cancer Center ever since.

Watching and waiting paid off: It was another year and a half before he embarked on his first chemo regimen — which was successful, but not before it landed Jack in the hospital.

"My family was confident that I had the latest and greatest care."

"My red blood cell counts were plummeting," he recalls. "They had to do some rapid work in the emergency room to get me back on track. I spent several weeks in the hospital, but at the end, I was cancer-free."

Over the next two decades, whenever his cancer came back, a newly approved treatment drove it back into remission.

"Through this whole process, I had hope that technology was going to pull me through, and in fact it has," Jack says.

His first and second relapses were treated with different "cocktails," combinations of potent anti-cancer drugs that gave him years of remission. Around five years ago, when his cancer reared its head again, the FDA had just approved a pill that targets a certain protein in cancer cells.

"Today I take a pill every day, and that keeps my cancer at bay," he says of his current treatment, ibrutinib. "I've had a few minor side effects, and I have a compromised immune system — but in general, this drug has been terrific."

The UA Cancer Center cares for many appreciative patients, but some of them take that gratitude to the next level. In Jack's case, he has made philanthropic gifts to support UA Cancer Center research. These days, he has helped support projects spearheaded by Daniel Persky, MD, director of the Clinical Trials Office — who is also Jack's current oncologist.

"Jack has been an invaluable supporter of the lymphoma program, and of UA Cancer Center research in general," Dr. Persky says. These research efforts range from building robust databases to enable better cancer tracking, to examining tumor proteins in non-Hodgkin's lymphoma, to studies of aggressive lymphoma in older patients. Donors like Jack play

a vital role in fast-tracking UA Cancer Center research — especially when federal grants and other forms of funding can be difficult to obtain.

In addition, for the past several years Jack has chaired the UA Cancer Center Advisory Board, working hard to increase philanthropy and raise our profile in Phoenix and Tucson. He is also recruiting “new blood” for the board, particularly in Tucson.

“We’re looking for leaders who can open doors for us in the various communities the UA Cancer Center serves,” he says. “It’s also helpful to have grateful patients serve on the board.”

Jack is optimistic about the future of the UA Cancer Center under the university’s new leadership, from fresh faces in UA Health Sciences, including Senior Vice President Michael Dake, MD, and Senior Associate Vice President Irving Kron, MD, as well as UA President Robert C. Robbins, MD.

“I’m very excited with where we’re going now,” he says. “We’ll go a long way to accelerating our mission for the UA Cancer Center.”

A cancer patient’s journey is never easy, but Jack credits the UA Cancer Center’s care with reducing not just his own anxiety, but his family’s as well.

“Having a good cancer team really does take the stress out of a lot of this,” he says. “My family was confident that I had the latest and greatest care.”

Finally, Jack’s faith in the UA Cancer Center’s expertise was bolstered by its designation as a National Cancer Institute Comprehensive Cancer Center.

“Academic medicine is what you get from a Comprehensive Cancer Center — people are really looking out for the patient,” Jack says. “The people who have taken care of me are the top in the state. They know where the technology is, what the science is, what drugs are in the pipeline — all of that has given me hope throughout the years.” ▲

A family’s mission to keep a memory alive through research.



Joan Luft Cohen passed away after a long battle against ovarian and breast cancer 20 years ago. As the anniversary of her passing drew near, her family approached us with an idea. They wanted to remember

their wife and mother with a crowdfunding campaign that would raise funds to purchase a piece of equipment to assist the UA Cancer Center’s researchers and physicians.

In collaboration with the UA Foundation, the family launched crowdfund.arizona.edu/joanluftcohen in October to raise \$29,000. This campaign would fund the purchase of equipment called “digital PCR” (polymerase chain reaction), which can detect ovarian and other cancers sooner than traditional methods by identifying tumor cells in blood samples.

More than 50 donors have helped the family raise more than \$15,000.

To help the Cohen family meet their goal and fund important cancer detection, visit the crowdfunding page to learn more and to make your gift. Gifts of all sizes provide our researchers with vital funding to support cancer research and find better treatments.



University of Arizona undergrad Alexa Nguyen is helping the Schroeder Lab unlock breast cancer's secrets.

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