

ACT AGAINST CANCER

A publication of the University of Arizona Cancer Center | SPRING 2018


IMMUNOTHERAPY
the new
frontier
of cancer
treatment



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Cancer Center



UACC is the only cancer center with headquarters in Arizona, and currently is one of only 49 in the nation, 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, UACC is initiating rapid advances in research and patients' health.

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A NOTE TO OUR FRIENDS AND SUPPORTERS

In this issue of *Act Against Cancer*, we explore what many consider to be the next frontier in the fight against cancer: immunotherapy. While researchers have been investigating the power of the immune system to fight cancer for several decades, these past few years have seen the approval of a number of promising new drugs that are expanding our ability to treat patients who otherwise would be out of options.

Immunotherapy research is fast becoming an international sensation. The *New York Times* has explored this topic extensively, writing that immunotherapy “has brought new optimism to cancer doctors — a sense that they have begun tapping into a force of nature the medical equivalent of splitting the atom.” (See “*Harnessing the Immune System to Fight Cancer*,” published on July 30, 2016.)

Today, we are using immunotherapy drugs to treat patients at the University of Arizona Cancer Center, and our scientists are gaining a deeper understanding at the bench to discover the novel drugs of tomorrow.

It is our goal to develop research and drug discovery programs at the University of Arizona and become a global leader in immunotherapy research, drug development and care. Our staff already boasts a number of experts in the field, and you will hear from them in the pages that follow.

Now we need your help to expand our initial efforts and build a world-class immunotherapy program at the University of Arizona. We are going to recruit more scientists and physicians who specialize in immunotherapy and we need to give them the latest equipment and best lab space to do their work.

Your support will be instrumental in this endeavor, and I graciously ask you to join us in our efforts.

Thank you and Bear Down,

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

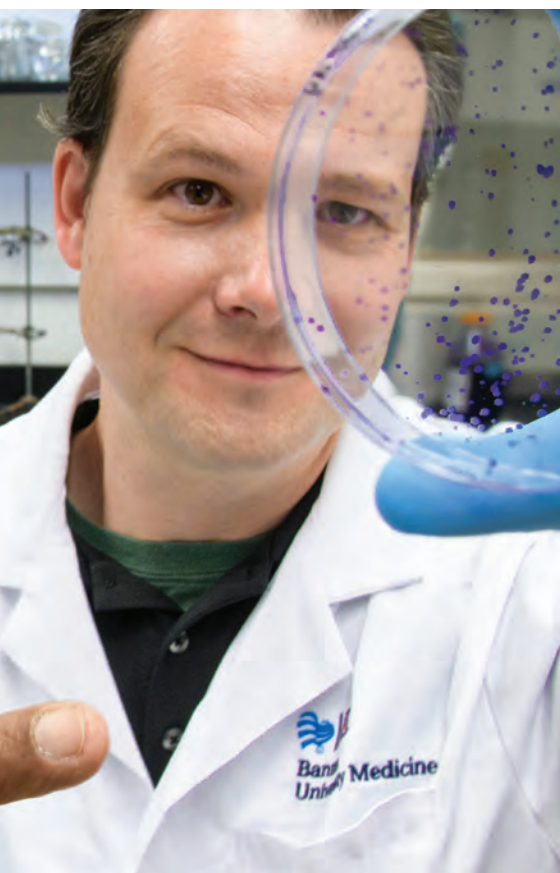


THE UNIVERSITY OF ARIZONA
Cancer Center

*“Using our immune system to
kill cancer and prevent it from
returning is the future of oncology.”*

– Lisa Kopp, DO, MPH





ACT AGAINST CANCER | SPRING 2018

.....
Message from the Director **1**

Immunotherapy: Harnessing the Power of the Immune System **5**

PATIENT PROFILE

Martha Bishop **10**

Bone Marrow Transplants: Successful Immunotherapy for Five Decades **12**

.....
From the Bench to the Bedside: To Develop New Immunotherapies, Collaboration Is Key **15**

Sprinting Toward the Finish Line: Cancer Clinical Trials **20**

Too Much of a Good Thing: Managing Immunotherapy Side Effects **27**

PHILANTHROPY

Making a Meaningful Difference: Equipping Today's Learners for Tomorrow's Discoveries **30**

Immunotherapy

Protul Shrikant, PhD,
professor of immunobiology
at the UA College of Medicine – Tucson

Anna C. Christensen, UACC

HARNESSING THE POWER OF THE IMMUNE SYSTEM

Designer antibodies, like checkpoint inhibitors, have revolutionized cancer treatment

by Anna C. Christensen

Your immune system never sleeps. Every moment of the day, immune cells monitor your body for disease, calling for backup when they detect a threat. It's a system that works elegantly — most of the time. It's not foolproof; if it were, we'd never get cancer in the first place.

"The immune system is supposed to fight tumors, but it doesn't do it very effectively," says Daruka Mahadevan, MD, PhD, director of the UA Cancer Center Early Phase Clinical Trials Program.

If the immune system can't suppress their development early, abnormal cells can blossom into cancers, and cancers can spread throughout our bodies, eventually taking our lives.

"So many of my patients feel like cancer is a betrayal of their own immune system's ability to survey and protect them," says Julie Bauman, MD, MPH, UA Cancer Center division chief of hematology and oncology.

When tumors evade detection by the immune system, we turn to chemotherapy and radiation, which don't exclusively target cancer cells and are notorious for the collateral damage rained upon healthy cells, often causing side effects like nausea and hair loss.

But what if we didn't have to subject normal cells to the friendly fire sprayed haphazardly by chemo and radiation? Many cancer researchers are optimistic about immunotherapy, a treatment that harnesses the power of the immune system, teaching it to recognize — and destroy — cancer cells.

"It's not the drugs that are killing the cancer," says Emmanuel Katsanis, MD, division chief of pediatric hematology and oncology. "It's the patient's immune system, which has been activated to fight and kill cancer by itself."

"I am amazed," says Protul Shrikant, PhD, professor of immunobiology at the UA College of Medicine – Tucson. "An educated immune cell, like a guided missile, can specifically recognize and destroy the tumor target, sparing normal tissues."

"It really appeals to people, the idea that their own immune system could do the job," says Dr. Bauman. "There's this notion that we're restoring a natural process in the body, the ability to harness its wisdom to attack cancer."

"The development of immunotherapy has revolutionized the way we treat cancer," says Clara Curiel, MD, leader of the UA Cancer Center's cutaneous oncology team. "It's a paradigm shift."

T cells: A crash course in immunity

The immune system evolved to distinguish between foreign invaders, like viruses and bacteria, and friendly faces, namely a person's own "self" cells. The ability to recognize this difference is essential to keeping the system in balance.

A crucial component of the immune army, T cells cruise the bloodstream, on the lookout for "bad guys." T cells can call in reinforcements by special-ordering customized proteins called antibodies, which are able to lock onto these "enemy" cells and tag them for destruction.

When T cells see a “non-self” invader, such as a virus, they mount an attack. But when they see a “self” cell, they need to know to leave it alone — otherwise, the immune system would be attacking its own body, a misfire that can lead to autoimmune diseases like rheumatoid arthritis and lupus. When all goes according to plan, the immune system’s foot soldiers patrol the body for enemies while leaving innocent civilians alone.

“Immune responses evolved to maintain a sense of self and distortion of self,” says Dr. Shrikant. “Mutations in normal cells are distortions that pose a threat, as in the case with most cancers. The capacity of immune cells to recognize these distortions of self is important.”

But recognizing a cancer cell isn’t as easy as it may seem.

“Cancer cells arise from our own cells, so they have a lot in common with our normal cells,” explains Dr. Bauman. “We have to exploit the things that are different about cancer and teach the immune system to recognize cancer as the enemy. Exploiting that difference is tricky.”

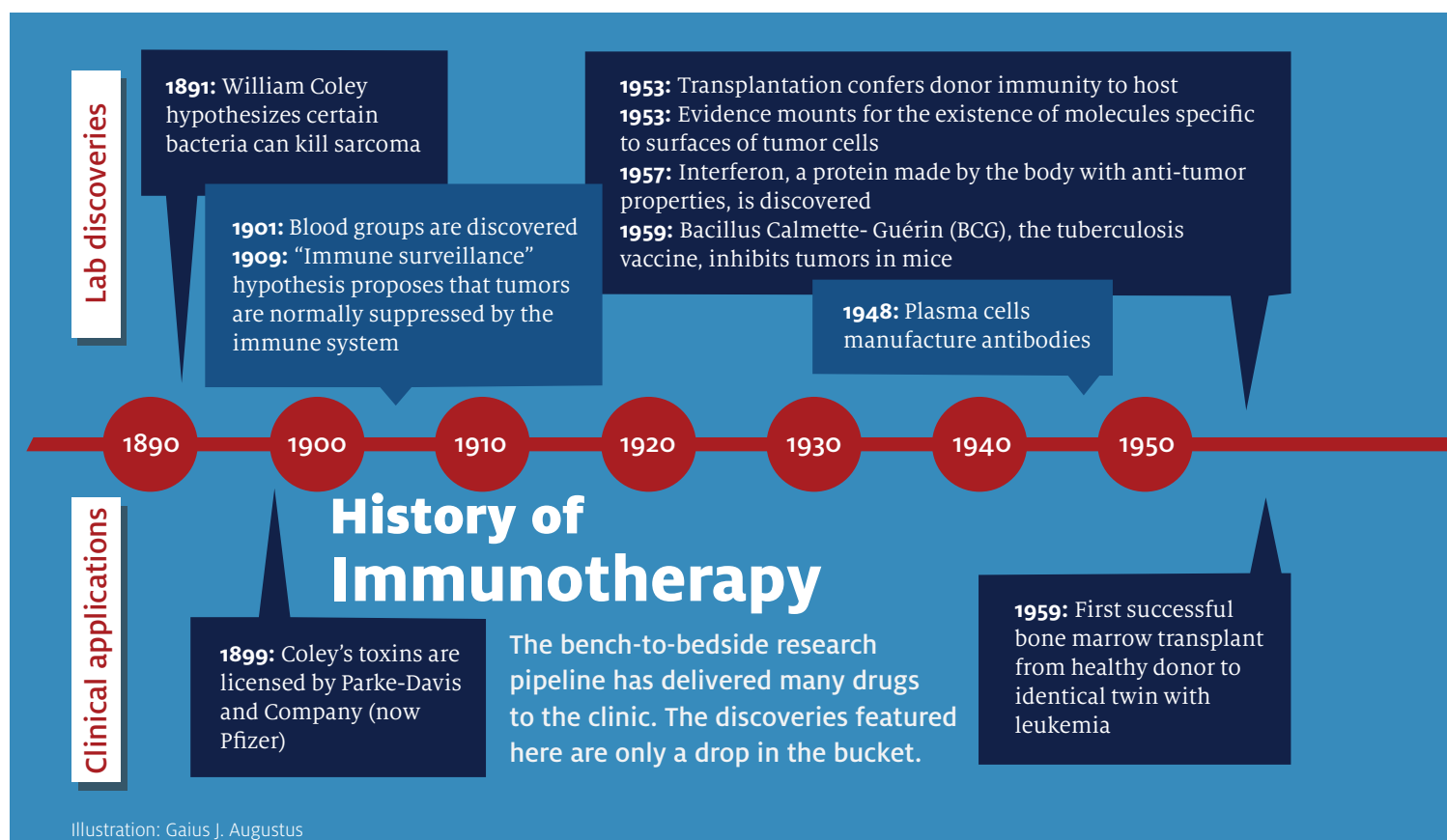
Cutting brakes and deploying supersoldiers: Boosting the immune response

If the immune system can’t detect the subtle differences between a cancer cell and a normal cell, it can’t manufacture the antibodies that are crucial in protecting us from cancer. Luckily, science can give the immune system a boost.

“We’ve learned how to turn antibodies that we engineer in the laboratory into proteins that fight cancer,” says Dr. Bauman. Scientists customize these so-called monoclonal antibodies to lock onto a specific cancer molecule, and physicians deploy these super-soldiers into the body.

One subtype of monoclonal antibody, called a checkpoint inhibitor, can tinker with a specific component of a T cell, which is akin to a “brake.”

Dr. Shrikant likens the immune process to driving a sports car. “A Ferrari owner needs to appreciate and understand the use of the accelerator and the brake to enjoy the car over the long haul,” he explains. “Otherwise, the Ferrari would be wrapped around a tree and produce injuries.”



While a normally functioning immune system needs those brakes to protect self cells from immune attack, some cancers can slam on the brakes to suppress the immune response. Checkpoint inhibitors cut that brake, a boon in an environment in which cancer cells, rather than autoimmune diseases, pose the most serious threat.

What's more, educating the immune system to recognize cancer cells can lead to long-lasting immune responses well after a patient completes treatment.

"When you prime the immune system to recognize a target, it stays as a memory in your immune system," explains Dr. Curiel. If, after treatment, a tumor cell starts replicating again, the immune system "will remember that it is a 'foreign' target and will attempt to eliminate it. Priming the immune system in combination with drugs that enhance the effect of T cells or decrease the immune escape mechanisms can lead to long-lasting responses."

Possible side effects of using checkpoint inhibitors to take the brakes off of T cells, however, involve triggering autoimmune reactions in which immune cells attack healthy cells.

"If you were to disable all brakes in your Ferrari, your Ferrari would be out of control," explains Dr. Shrikant. "When we unleash the capacity of the immune responses in an unregulated fashion, we may cause exuberant immunologic reactions that destroy healthy self cells."

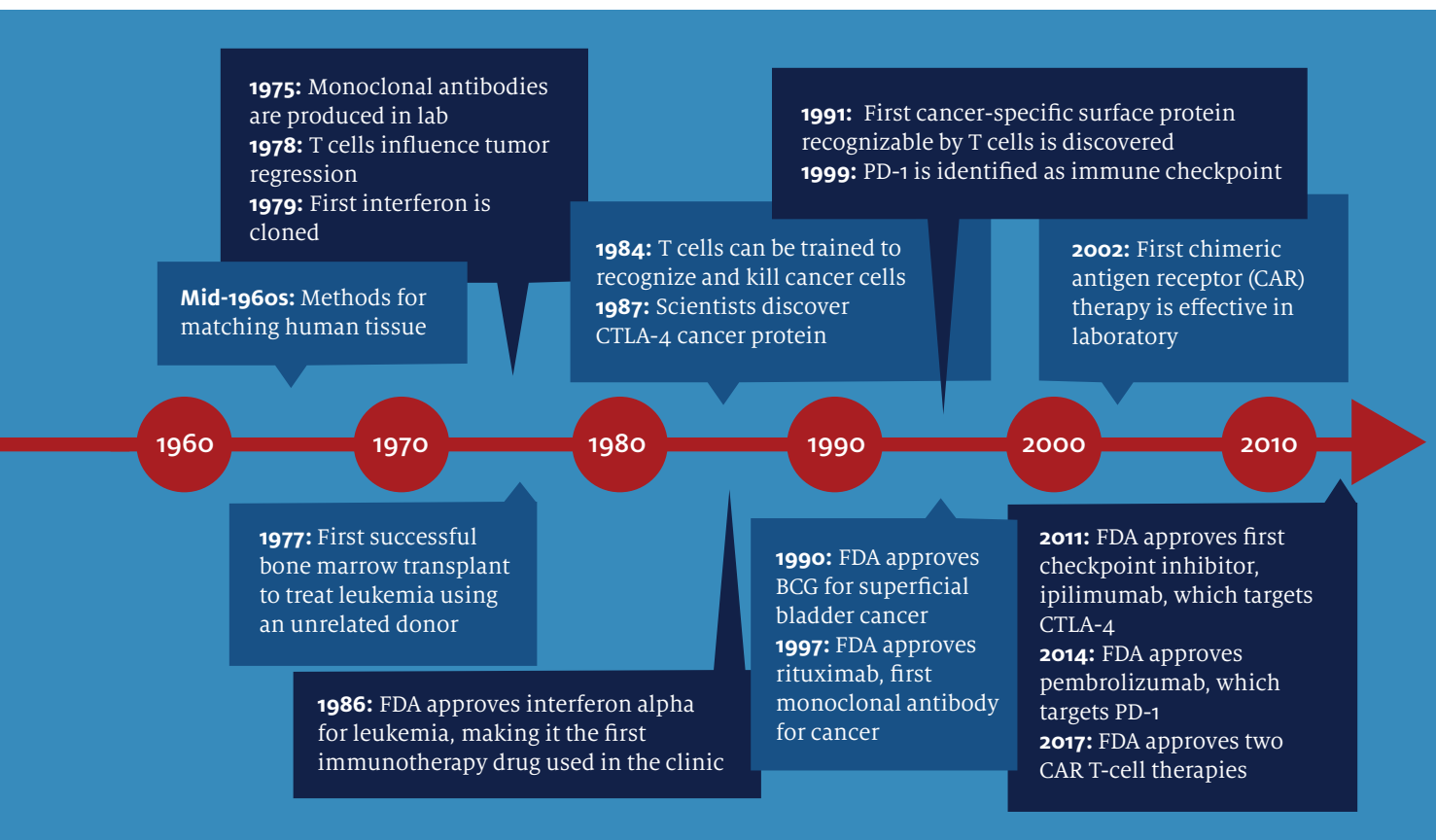
Immunotherapy joins forces with other treatments

Despite all the promise immunotherapy holds, most patients don't experience the dramatic results that make headlines.

"It really depends on the disease and the drug, but I would say that 30 percent of the time, we see some efficacy," estimates Hani Babiker, MD, associate director of the UA Cancer Center Early Phase Clinical Trials Program.

For her head-and-neck cancer patients, Dr. Bauman clocks immunotherapy's efficacy at around 15 percent.

"I've seen patients achieve deep remission that we never thought possible," says Dr. Bauman. "I wish this worked for everyone, because if 15 percent of people have meaningful responses to immunotherapy, that means 85 percent come to the table with that level of hope and are disappointed."





Kris Hanning, UAHHS BioCommunications

Julie Bauman, MD, MPH, screens a patient for head-and-neck cancer.

To realize immunotherapy's potential, it needs to work for more patients.

"I don't know whose T cells will be awakened in the right way and attack the cancer, and whose T cells will be awakened in the wrong way and attack the patient," says Dr. Bauman. "My hope is that I learn how to unlock the right T cells at the right time for the right cancer."

While it's tempting to imagine a future in which immunotherapy alone can vaporize tumors for good,

chemotherapy and radiation aren't going away any time soon, and in fact might increase the effectiveness of immunotherapy — leading to longer survival and less disappointment.

"I believe we can improve response rates to 70 to 80 percent with these rational combinations," Dr. Mahadevan tells us. "A tumor that is resistant to one immune checkpoint therapy may be really sensitive [to] a combo."

"I'm treating high-risk patients with a combination of chemotherapy, radiation and immunotherapy. And they really do work hand in hand," Dr. Bauman says.

Radiation and chemotherapy directly kill tumor cells in a process that can release cellular debris into the body.

“Radiation breaks a cancer cell open and exposes all of its hidden guts to the immune system,” explains Dr. Bauman. “Chemotherapy directly poisons the cancer cell. It dies an immunogenic cell death, and also shows more of its abnormal contents.”

When immune cells are activated by immunotherapy drugs, this debris can help train the newly empowered immune system to recognize the enemy.

“An army of T cells is waiting to recognize some part of that cancer cell as foreign and, therefore, worthy of attack,” Dr. Bauman says. “Immunotherapy is there to prime that response and help those T cells become more active.”

Beyond the realm of chemotherapy and radiation, Dr. Babiker elaborates on other innovative combinations. “We’re combining checkpoint inhibitors with oncolytic viruses,” he explains. “This means not only adding the checkpoint inhibitor, but adding a virus that is genetically engineered to attack the cancer.”

“It’s almost a fiction story,” says Dr. Curiel of oncolytic viruses. “We inject a virus in the tumor, the virus goes inside cancer cells, destroys the tumor and presents the immune system with the target it needs to recognize. This process allows the immune system to selectively kill additional tumor cells and decreases the chance of recurrences.”

Hope for the future

Although the idea of immunotherapy is not new, in the clinic, it is still in its infancy. Most patients don’t respond, and those who do run the risk of potentially serious side effects. But it also has been responsible for remissions that were previously unimaginable, and patients exhausted by the harsh effects of chemotherapy and radiation may find immunotherapy to be a gentler experience.

“It’s a really exciting time in drug development,” Dr. Babiker tells us. “We’re discovering a [different] modality in cancer

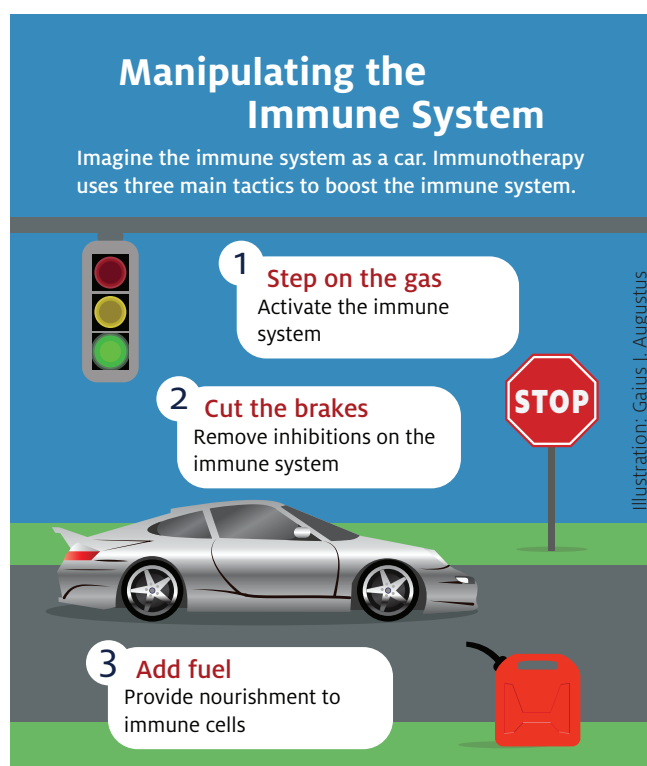
treatment, using our patients’ own immune system to target and fight the cancer.”

UA Cancer Center researchers are actively involved in laboratory research and clinical trials to delve deeper into the intricacies of the immune system, discover new immunotherapy drugs, find more effective treatment combinations and reduce side effects. Energized by the swift advances in the field over the last couple of decades, they look forward to what the near future holds.

“The future for immunotherapy is incredibly bright,” says Dr. Shrikant. “In the last 10 years we’ve come a long way.”

“My hope for the future is that cancer will not be a word we are afraid of,” says Dr. Curiel. “We have made huge progress in a very short period of time — it is encouraging, it is fascinating.”

“Twenty years ago, most oncologists would say, ‘Immunotherapy is never going to work.’ Now everybody is using it,” says Dr. Katsanis. “There’s a ways to go, but the whole field is evolving very, very quickly.”



PATIENT PROFILE



Mari Cleven

Martha Bishop

by Anna C. Christensen

Martha Bishop's cancer journey started with a mole. Something about it made her nervous, and she wanted a health professional's expertise.

Initially, her dermatologist didn't bat an eye. "It's no big deal," he told Martha, but she asked him to remove it anyway ... just in case.

Two days later, her dermatologist called with the biopsy results: "It's melanoma," he reported.

Melanoma, a type of skin cancer, is the nation's fifth-most common type of cancer. Although anyone can get it, people with fair skin and light hair are at a higher risk for melanoma. It's also most likely to strike older people, especially those between the ages of 65 and 74.

Although she has a fair complexion and reddish hair, Martha didn't otherwise fit that profile.

"I was diagnosed in 2009, right before I turned 30," Martha recalls.

Martha was one of 1,199 Arizonans to be diagnosed with melanoma that year. Of those individuals, only 26 were between the ages of 25 and 29, making her diagnosis especially shocking. Life changed for Martha and her young family, a husband and two children in preschool.

"I was a stay-at-home mom," Martha says. "My kids were 3 and 5. My goal was to survive to see them through kindergarten."

She became a patient at the University of Arizona Cancer Center. "I went through a bunch of different drugs," Martha recalls. "I did traditional chemo, I did a targeted therapy, I did two immunotherapies."

After weathering the unpleasant side effects of other treatments early in her cancer journey, Martha was introduced to the world of immunotherapy via ipilimumab, a checkpoint inhibitor that goes by the brand name Yervoy.

"It was a breeze compared to what I'd done before," says Martha. "I think that's what people need to know about immunotherapy — it's so much easier on your body than traditional chemo."

Although ipilimumab's side effects were tolerable, Martha's tumors didn't respond to the drug as well as her doctors hoped. But an opportunity to enroll in a clinical trial for a promising new treatment infused her with optimism.

"I got on a clinical trial for what's now Keytruda," she says, referring to pembrolizumab, another type of immune checkpoint inhibitor. "There was a lot of buzz about Keytruda."

Her enrollment into the trial had a rocky start.

“When I was having my pre-trial scans, they found brain tumors,” Martha recalls. “That was super scary.”

After stereotactic radiosurgery to treat her brain tumors, Martha was able to enroll in the clinical trial and begin treatment with Keytruda. “I can’t even tell you how excited we were,” she says.

At first, however, Martha’s tumors didn’t seem to be responding fast enough: “My husband and I went on vacation thinking, ‘This is our last trip together,’” she recalls.

Luckily, while Martha’s response to Keytruda was a little slower than normal, her tumors did eventually start to shrink. The turning point was when she underwent surgery to reduce her tumor load, after which Keytruda was able to finish the job.

“Since that surgery, it has been miraculous. It took a full two years for me to have no evidence of disease,” she reports. “But it was really clear that I’d made good progress.”

Similar to her experience with her first immunotherapy drug, Martha’s side effects while on Keytruda were mild.

“I had a little fatigue, but that was really only the first six months,” she recalls. And that fatigue wasn’t enough to stop her from living her life.

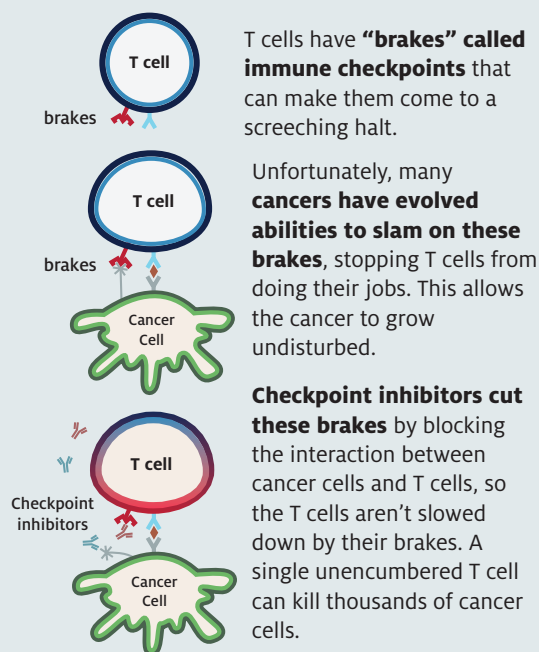
“I went back to teaching. I taught second grade. I’m teaching kindergarten now. I trained for and ran a 5K,” Martha says. “Obviously, I have to have lots and lots of energy!”

Martha has high praise for the care she received at the UA Cancer Center. She describes engaged, compassionate physicians who not only brought their expertise to the table, but also added a human touch, such as holding her hand through surgical procedures.

“It’s been amazing,” she says. “They’ve become family.”

Martha also received support from fellow patients, who acted as informal educators and mentors. She calls Bonnie Emerson, founder of her melanoma patient support group,

Checkpoint Inhibitors



Adapted from the *New York Times*

Illustration: Gaius J. Augustus

her “melanoma mama,” whose guidance at the beginning of her cancer journey endowed her with strength and hope.

Martha’s original goal, to see her children graduate from kindergarten, was met years ago, and she’s been adjusting her goals since. Her kids are now 11 and 13, and she is hopeful for the future.

“I want to see my grandbabies!” Martha exclaims, adding with a laugh that, with such young children, she doesn’t expect to welcome grandchildren into her family for many more years.

For now, she is building a life that she scarcely imagined after first receiving her diagnosis — one that includes “things I never thought I’d get the chance to experience: living life and being back in the classroom, having a career in front of me, thinking about paying for retirement,” Martha says.

Martha adds one more item to her list of unexpected milestones: “Buying eye wrinkle cream,” she says, laughing. “I worked really hard to get those wrinkles, but I don’t really want ‘em!”

Bone Marrow Transplants

**SUCCESSFUL IMMUNOTHERAPY
FOR FIVE DECADES**

by Anna C. Christensen

After reading about seemingly exotic treatments like checkpoint inhibitors, which have been approved by the U.S. Food and Drug Administration for only seven years, one might be surprised to learn that bone marrow transplants — which have been performed for decades — also fall under the “immunotherapy” umbrella.

“Anything we can use to stimulate the immune system would be considered immunotherapy,” says Emmanuel Katsanis, MD, UA Cancer Center pediatric hematology/oncology chief and director of the Blood and Marrow Transplantation Program. “Bone marrow transplantation has been around for close to 50 years. It has been a form of immunotherapy that has been very successful.”

Dr. Katsanis shifts between the laboratory, where he focuses on tumor and transplant immunology, and the clinic, where he specializes in bone marrow transplants. Bone marrow transplants involve stem cells, which differentiate into many types of blood cells, including immune cells. An infusion of stem cells helps a patient build an immune army that can battle blood cancers like leukemia and lymphoma.

Although a patient can sometimes find a fully compatible bone marrow donor in a sibling, Dr. Katsanis has helped

pioneer novel approaches for “haploidentical,” or half-match, transplants. This strategy has expanded the pool of potential bone marrow donors and increased survival for people of color, who typically have more difficulty finding matches in donor databases.

A half-match transplant is “oftentimes parent into a child, or a child into a parent, or a sibling,” says Dr. Katsanis. “Fifty percent of siblings are half-match, and 25 percent are full match, so within the family you can always find a donor.”

The problem with receiving a half-match transplant, rather than a full match, is that the patient is in danger of developing “graft-versus-host” disease, in which the donated cells attack the patient’s healthy cells as “foreign.” To reduce this risk, and to boost the donated cells’ ability to attack leukemia, Dr. Katsanis has taken his lab research into the clinic, where he is testing a new drug regimen for patients receiving half-match bone marrow transplants. (See “*Sprinting Toward the Finish Line*” on pg. 20.)

Dr. Katsanis is also using newer immunotherapies in the clinic. Before receiving a bone marrow transplant, a leukemia patient first must undergo treatment, like chemotherapy, and enter remission.



Emmanuel Katsanis, MD, specializes in performing bone marrow transplants in pediatric patients.

"After transplantation, the new immune system attacks the leukemia to kill any leukemia left behind," explains Dr. Katsanis.

But what if a patient fails treatment, and their leukemia can't be put into remission? Dr. Katsanis and his colleagues are using a monoclonal antibody called blinatumomab to put their patients in remission, setting the stage for a

successful transplant. He recently published an article about five pediatric patients treated with this immunotherapy drug followed by successful bone marrow transplantation.

"These were very high-risk patients who were not able to achieve remission," says Dr. Katsanis. But, with this drug, "all of them were successful. Blinatumomab has been a lifesaver for a lot of patients."

FROM THE BENCH TO THE BEDSIDE



To Develop New Immunotherapies, Collaboration Is Key

By Gaius J. Augustus



Daruka Mahadevan, MD, PhD, and Eric Weterings, PhD,
examine a petri dish in a UA Cancer Center laboratory.

Kris Hanning, UAHS BioCommunications

With more than 200 clinical trials being conducted at the University of Arizona Cancer Center, Clinical Trials Office Director Daniel Persky, MD, is a busy man. Among these trials are a growing number of studies evaluating the effectiveness of immunotherapy, a type of treatment generating a lot of excitement among physicians running clinical trials.

“The hopes of immunotherapy are extremely bright right now,” says Dr. Persky. “In many patients whose disease would have been judged to be fairly hopeless, there are no signs of the disease coming back after a year or so.”

Where are these new treatment options coming from? They don’t appear out of thin air. Over the course of many decades, they are slowly developed through a process called “bench to bedside,” where findings from the laboratory (“bench”) can develop into treatments in the clinic or hospital (“bedside”). This process starts with basic scientists like immunologists, who specialize in investigating how the body’s immune system protects us from threats — and why it sometimes is unable to do so.

Michael Kuhns, PhD, an associate professor of immunobiology at the UA College of Medicine – Tucson, explains that basic science is “like understanding how a machine or a car works. If you understand how the gears work together, you might be able to modify the function or engineer new designs.”

A firm grasp of how the immune system naturally responds to threats can identify weapons we can add to our therapeutic arsenal. When a potential opportunity for therapy, such as a drug target, is revealed by experiments, testing in cell cultures and mice is used to identify treatment options. If a potential treatment shows promise, scientists work with physicians to create a clinical trial to bring it to patients in the clinic.

Thanks to its reach into both academia and the clinic, the University of Arizona is uniquely poised to bring brilliant minds from multiple disciplines together into fruitful collaborations. Julie Bauman, MD, MPH, UA Cancer Center division chief of hematology and oncology, understands that a strong relationship between the lab and the clinic is necessary for the development of new cancer treatments.

"There are so many exciting directions to go in cancer research," says Dr. Bauman. "We simply can't follow every pathway, and we can't conduct every clinical trial. To prioritize, we must have close partnerships between the laboratory and the clinic."

'The Bench': Understanding the immune system

Scientists often begin by trying to understand how things work in the body under normal circumstances and how those mechanisms break down in the face of diseases such as cancer.

"If we want to understand the molecular basis for a disease or how to fight a disease, we have to do basic research to understand how that disease comes about, or how the body can naturally take care of that disease," explains Dr. Kuhns.

Dr. Kuhns' research focuses on understanding and manipulating the "conversations" between T cells and the rest of the immune system. T cells are able to respond to threats and coordinate attacks, and Dr. Kuhns says manipulating these messages can change the behavior of a T cell.

Dr. Kuhns reports that his team already has achieved success in a basic lab setting. "I can redirect T cells to kill targets," he says. "One day, that could have immunotherapeutic applications."

Thalachallour Mohanakumar, PhD ("Dr. Kumar"), research professor at the UA College of Medicine – Phoenix, has been working in the field of immunology for 40 years, focusing on transplantation. Dr. Kumar explains that when a transplanted organ is stressed, it releases small molecules into the bloodstream. His lab is interested in learning more about the immune response evoked by these molecules, which will add to our expanding body of knowledge around the immune system.

Dr. Kumar acknowledges that the progress we've made in fighting cancer is possible because of a growing understanding of how the immune system works.

"The immune system is much more complicated than we initially thought," Dr. Kumar explains. "Continued understanding of the immune mechanism is important,

not only for cancer, but also for autoimmune disease and transplantation."

'Bench to Bedside': Getting basic research into the clinic

The research done by Protul Shrikant, PhD, professor of immunobiology at the UA College of Medicine – Tucson, is a great example of how the knowledge we gain from basic immunology is essential to cancer treatment. "In fact," he explains, "immunotherapy treatment must be based on a fundamental understanding of immunology."

Dr. Shrikant's basic research focuses on how T cells recognize and destroy cancer cells. The insights gained into the immune system at the basic level are then brought to clinicians.

"Our laboratory studies span from detailed understanding of fundamental immunology, to validating in animal models, to early-phase clinical trials," Dr. Shrikant says of the ongoing work in his laboratory.

Daruka Mahadevan, MD, PhD, is the director of the UA Cancer Center Early Phase Clinical Trials Program, and specializes in the development of drugs for lymphomas, including peripheral T-cell non-Hodgkin lymphoma (PTCL), a cancer of the T cells.

"PTCL is an aggressive form of lymphoma, and we don't have any good treatments," Dr. Mahadevan says. Because immunotherapy harnesses the power of T cells, T-cell lymphoma is an especially challenging target. "The very cells that we are trying to activate are the cells that are abnormal," he explains.

Dr. Mahadevan has identified a combination treatment that is effective against PTCL tumors growing in lab mice. While the immune system is suppressed in these lymphomas, his team has been able to wake the immune system back up by blocking the ability of cancer cells to divide, significantly improving the survival of these mice. He now is working with drug companies and the National Institutes of Health in hopes of finding a combination that works in patients.

"Between 25 and 30 percent of patients respond to checkpoint inhibitors, but about 70 percent don't respond," says Dr. Mahadevan. He believes the answer to treating this 70 percent



Kris Hanning, UAHS BioCommunications

Members of the Kuhns Lab study the "conversations" between T cells and the rest of the immune system. From left to right: Heather Parrish, PhD; Michael Kuhns, PhD; Katrina Lichauco and Mark Lee.

lies in finding combinations of treatments, such as checkpoint inhibitors, which activate T cells, and targeted drugs, which attack cancer cells with less harm to normal cells.

Going backward: Bedside to bench

The journey from bench to bedside is not one way, and the University of Arizona offers a crossroads for a variety of scientists and physicians with diverse expertise to share insights and produce unique therapies. Dr. Shrikant relies on

his relationships with clinicians to guide his lab's research, often using observations from the clinic to decide what to study in the lab.

"We go back from the bedside to the bench," says Dr. Shrikant. "My clinical colleagues constantly educate me as to what are the right questions to ask and how to pose them. The information gained by testing a well-considered hypothesis can meet an unmet need in the clinic and change the standard of care, which is extremely satisfying."

Drawing from more than 20 years of research into fundamental cancer immunology, Dr. Shrikant enjoys making a difference in patients' lives.

"I am constantly developing my abilities to move between basic science and the clinic in a seamless manner so as to make an impact on cancer," Dr. Shrikant says.

"If you want to know what the potential clinical problems are, you need to work with clinical people," says Dr. Kumar. "It's important for the clinical people to come and tell us, 'These are the problems, and we need to solve this.'"

Dr. Mahadevan agrees.

"I enjoy being in the lab and in the clinic," says Dr. Mahadevan. "I'm able to bring questions from the clinic into the lab — and, hopefully, from the lab back into the clinic at some point."

Dr. Mahadevan doesn't believe in keeping scientists at the bench separated from physicians in the clinic.

"Every single person in my lab has shadowed me in the clinic or in the hospital," Dr. Mahadevan says. "They're not just thinking about cells and mice. They're also thinking about the patient."

Collaboration at the UA Cancer Center

If there are any downsides to the research being produced by scientists around the world, it's that it's yielding an embarrassment of riches. Physicians running clinical trials might be overwhelmed with options.

"We're struggling with how to deal with this pharmacologic buffet," says Dr. Persky, the Clinical Trials Office's director. "There are so many different drugs against many targets. Judging which combination to give becomes harder to figure out."

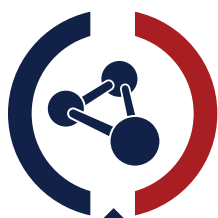


"We have more data than we know what to do with," adds Dr. Bauman.

Fortunately, scientists at the University of Arizona and physician-scientists at the UA Cancer Center have built a strong relationship that is poised to push forward our understanding of the immune system and how we can improve its ability to detect and kill cancer cells. Partnerships like those seen at the University of Arizona have made the journey from the bench to the bedside faster.

Mark Lee, left, and Katrina Lichauco are graduate students in the Kuhns Lab.

Bench to Bedside



Basic Science

New cancer treatments arise from a strong partnership between the laboratory and the clinic.

Each link in this chain addresses different but important questions, accelerating the development of new drugs.

Basic scientists discover how our bodies work and make fundamental insights that can lead to future therapies.

Basic scientists ask questions such as:

How does the immune system fight off diseases?

Why does it not detect cancer?

How can we help it recognize and attack cancer cells?



Translational Science

Scientists who make translational discoveries are focused on finding potential treatment options and testing them in human cells or animals.

Translational scientists ask questions such as:

Which therapy is most effective?

Is therapy effective in human cell lines?

Is therapy effective in animals like mice?



Clinical Trials

Clinical trials apply knowledge from the laboratory to assess treatment efficacy in cancer patients.

Clinical trials investigators ask questions such as:

Is therapy effective in patients?

What is the best drug dosage?

What are the best drug combinations?

Illustration: Gaius J. Augustus

"The pace of development has quickened significantly," says Dr. Persky. "It takes less time to go from bench to bedside than ever before."

"The field is moving so quickly," says Dr. Bauman. "We're making meaningful advances at a fast pace."

The potential for the UA Cancer Center to continue its contributions to the discovery of more effective cancer treatments is strong.

"There's incredibly good science on campus, and there are a lot of clinics," says Dr. Shrikant. He is working to continue

improving collaboration in order to develop more effective single and combination therapies.

Scientists in the lab may be driven by curiosity about how the immune system works, but seeing their discoveries lead to the development of better drugs is immensely rewarding.

"When I was younger it was the sheer joy of kicking over rocks to see what's underneath," recalls Dr. Kuhns. "As we become more experienced, we want to see a tangible application to the work we're doing."

Adds Dr. Shrikant, "Seeing your ideas work in real life is empowering."



From left to right: Benjamin Lee, MD;
John Michalak, MD; and Grant Pollock, MD;
perform robotic surgery.

Sprinting Toward *the* **Finish Line** **CANCER CLINICAL TRIALS**



Kris Hanning, UAHHS BioCommunications



Gloria* was in her 80s with a rare variant of pancreatic cancer, a disease that generally is considered to be incurable. She went through multiple rounds of treatment, but they failed to tame her tumor. Nausea, vomiting and severe abdominal pain plagued Gloria's daily life, and she was losing weight. Done with standard treatments, she went to the University of Arizona Cancer Center to discuss her only remaining options: hospice ... or a clinical trial.

Luckily, Gloria was eligible to enroll in a "first-in-human" clinical trial, a type of study in which patients are the first to receive investigational drugs. Daruka Mahadevan, MD, PhD, director of the UA Cancer Center Early Phase Clinical Trials Program, gave Gloria a type of immunotherapy drug called a checkpoint inhibitor, which wasn't a standard treatment for pancreatic cancer.

"A year later, she's had a response of close to 90 percent," Dr. Mahadevan reports.

"She gained weight and she's living her life normally," continues Hani Babiker, MD, associate director of the Early Phase Clinical Trials Program. "She's definitely not going to hospice."

** Patient's name has been changed to protect her privacy.*

Gloria's dramatic experience isn't typical. She had a rare subtype of pancreatic cancer; most pancreatic cancers don't respond to immunotherapy. Today, about 25 to 30 percent of cancer patients overall are helped by immunotherapy — and those who respond are a source of great hope to the cancer community. Although immunotherapy is in its infancy, clinical trials are continually ushering this treatment strategy toward maturity.

"We don't yet know the best way to use immunotherapy, but we do know that using our immune system to kill cancer and prevent it from returning is the future of oncology," says Lisa Kopp, DO, MPH, associate professor of pediatrics at the UA College of Medicine – Tucson. "The only way to increase the cure rate of cancer is through conducting clinical trials."

In the race to bring cancer treatments from the bench to the bedside, clinical trials represent the final hurdles. After a new drug shows promise in the laboratory, it begins the last leg of the race in hospitals and clinics. A successful drug advances through multiple phases of clinical trials and, with approval from the U.S. Food and Drug Administration, triumphantly crosses the finish line.

Randomized clinical trials are known as the "gold standard" of medical research. Patients are randomly placed into one of two groups — like flipping a coin — so the drug under investigation can be compared to standard treatments. At the UA Cancer Center, many immunotherapy drugs are being studied in clinical trials, which physician-scientists sometimes design and conduct on their own, but usually participate in as part of a larger effort taking place at multiple sites around the country — or world.

Finding the best combinations

To recruit patients, see them through the trial process, collect data, and adhere to stringent legal and ethical regulations, the UA Cancer Center needs a well-coordinated team. Enter the Clinical Trials Office.

"Our mission is to support physicians in running clinical trials and make sure they are done in a safe manner," says Clinical

Trials Office Director Daniel Persky, MD. "Medicine and cancer trials are a team sport. It takes all the team members being at their best."

Immunotherapy features prominently in Dr. Persky's clinical trials.

"We have a lot of trials with monoclonal antibodies, sometimes by themselves, sometimes in combinations with traditional chemotherapies, sometimes in combinations with novel drugs," he says.

While immunotherapy drugs can be used alone, investigators are especially excited about their potential when combined with other treatments.

"Historically, medical oncologists would combine drugs here and there, but without any rationale behind it," says Dr. Mahadevan. But to treat the majority of patients who don't respond to immunotherapy, "We need to find combinations. These therapies can be synergistic when given that way."

Julie Bauman, MD, MPH, UA Cancer Center division chief of hematology and oncology, is hoping to increase response rates by combining immunotherapy with other treatments.

"I have clinical trials looking at checkpoint inhibitors when added to chemotherapy and radiation," says Dr. Bauman. "I am taking FDA-approved drugs but adding them to therapy that is not as effective as we wish it were."

Dr. Bauman is also leading a trial that combines a newer monoclonal antibody — ficlatuzumab — with an older one — cetuximab — to see if it will help patients whose cancers have not responded to other treatments, including other immunotherapies.

"These are patients who have no therapeutic options remaining," says Dr. Bauman.

Surgery, too, can be paired with immunotherapy. Sometimes, a tumor cannot be completely cleared away by the newly activated immune system, but enough of it could have shrunk or disappeared that a previously inoperable cancer now could be surgically removed.

Benjamin Lee, MD, division chief of urology at the UA College of Medicine – Tucson’s Department of Surgery, specializes in prostate and kidney cancers, and is enrolling kidney cancer patients into a trial in which a checkpoint inhibitor called nivolumab is used in combination with robotic surgery. This type of surgery can save 50 to 75 percent of the kidney, and the hope is that nivolumab will set the stage for even better surgical outcomes.

“This clinical trial gives us an opportunity to shrink the size of a kidney cancer and save more kidney function,” explains Dr. Lee.

Beyond the realm of chemotherapy, radiation and surgery, some trials are looking toward therapies of the future, combining immunotherapy with even more cutting-edge treatments. One such trial pairs a checkpoint inhibitor with a cancer-killing virus.

“The virus is engineered to infect tumors,” says Dr. Mahadevan, who is conducting the trial at the UA Cancer Center. As the viral infection attracts the immune system to the tumor, the checkpoint inhibitor activates those immune cells, supercharging them to kill the tumor to which they have been summoned.

Treating children

Most clinical trials are only open to adults — which makes sense, since cancer usually strikes people in their 60s and 70s.

“Only 1 percent of all cancers are seen in kids,” says Emmanuel Katsanis, MD, division chief of pediatric hematology and oncology.

But that 1 percent needs help, which is why the Clinical Trials Office has a team devoted to pediatric cancers.

Dr. Katsanis is recruiting both children and adults into a trial to investigate a drug regimen to use in leukemia patients receiving bone marrow transplants. These transplants, called “grafts,” can fight leukemia by introducing healthy T cells from a donor into a patient. If all goes well, the patient will experience a “graft-versus-leukemia” effect, in which the donor cells fight the cancer. A possible side effect, however,

is the “graft-versus-host” effect, in which the donor cells recognize the patient’s healthy cells as “foreign” and attack them, too. Doctors want to maximize graft-versus-leukemia effects and minimize graft-versus-host effects.

Dr. Katsanis and his team are investigating the effectiveness of replacing a standard chemotherapy drug, cyclophosphamide, with a different type of chemotherapy called bendamustine, hoping this new chemotherapy regimen will create an immune environment more hospitable to a type of T cell better equipped to help the body accept the transplant. A clinical trial is helping him test that hypothesis.

“So far, the first three patients have done well,” reports Dr. Katsanis. “Eventually, we’ll be able to totally replace cyclophosphamide and show that bendamustine in humans allows more graft-versus-leukemia.”

Additionally, Dr. Kopp is investigating a monoclonal antibody called ganitumab in combination with chemotherapy in children with metastatic Ewing sarcoma. This antibody binds to cells that produce insulin, inhibiting its production and shutting down a source of nourishment for cancer cells.

“We are hoping that this combination given as initial therapy will lead to better responses and increase the cure rate in this very hard-to-treat cancer,” says Dr. Kopp. “This is very exciting.”

Beyond treatment

Clinical trials don’t just look at cancer treatments — they can also be used to compare different techniques in patient care, which might have advantages over current techniques, potentially leading to safer, less unpleasant or more accurate medical treatment.

Clara Curiel, MD, leader of the UA Cancer Center’s cutaneous oncology team, is conducting a study to determine if skin biopsies can be used to predict the likelihood of responding to immunotherapy — including the likelihood of experiencing side effects.

“We are attempting to understand if patients could be grouped based on how their normal skin cells are modulated by these drugs,” explains Dr. Curiel. “We obtain skin biopsies

before and during treatment and look at hundreds of biomarkers to explore associations with side effects and therapeutic response.”

If successful, a simple skin biopsy could have predictive implications for many types of cancer, not just skin cancer.

“We hope to build enough of a database that we’re able to understand in advance who might develop relevant side effects,” Dr. Curiel says. “We’re the only ones trying to develop this approach using a different organ as a prognostic site.”

“And the skin is so accessible,” Dr. Curiel continues. “Skin biopsies are less invasive [than performing] a biopsy of a liver or lung.”



Clara Curiel, MD, performs a dermatological examination on a patient.

Crossing the finish line

The race toward FDA-approved drugs begins in the laboratory, where scientists decode the immune system one gene, one molecule, one experiment at a time. Then translational scientists take the baton, observing how new drugs interact with human cells or lab animals, on their own or in combination with existing drugs. Finally, clinical trial investigators run the last leg of this bench-to-bedside relay race. It’s a long, arduous process, but when they cross the finish line, the victory is shared by the entire team.

“Strong collaboration must occur between basic scientists and physicians,” says Dr. Babiker. “Collaboration is the driving force in developing drugs, through scientists at the bench working closely with investigators in the clinic.”

While crossing that finish line is the goal, clinical trial investigators at the UA Cancer Center are primarily driven by their patients and their patients’ families. Helping them during difficult times is the only gold medal they need.

“Seeing our patients cured is a tremendous reward in and of itself,” says Dr. Lee.

Dr. Kopp agrees: “The most rewarding aspect of conducting clinical trials is having the privilege of being a part of the team that, through amazing scientific research, can make a difference in families in my own community.”

Clinical trials bring together scientists and physicians, who use the clinic as the final testing ground for discoveries made in the laboratory. They are an integral part of what makes the UA Cancer Center so important to Arizona and to the cancer community worldwide. Dr. Persky believes they are an essential component of any forward-looking cancer program.

“We’re contributing to a future without cancer,” Dr. Persky says. “We may not benefit that specific patient, but we definitely benefit the patients who come after them. That’s the only way to make progress against cancer.”

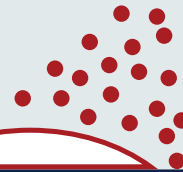
Types of Immunotherapy



Bone Marrow Transplants

Bone marrow contains stem cells from which mature cells can develop. These stem cells can turn into immune cells, helping a leukemia or lymphoma patient rebuild a healthy immune system. In 20 years, potential donors expanded from identical twins to immune-matched unrelated donors.

Year	Donor
1959	identical twin
1969	matched sibling
1977	unrelated donor



Cytokines

Some immune cells create and secrete proteins called cytokines, which can stimulate the immune system. They can also be made in the lab to help fight cancer. These were the first immunotherapy drugs used clinically.

Treatment	Approval	Cancers
interferon alpha	1986	hairy cell leukemia melanoma non-Hodgkin lymphoma
interleukin-2	1992	kidney cancer melanoma



Vaccines

Traditional vaccines prevent infection, including against two cancer-causing viruses. Other vaccines treat cancer after it has appeared, helping the immune system attack cancer cells.

Preventive	Approval
hepatitis B virus	1981
human papillomavirus	2006

Therapeutic	Approval
bladder cancer	1990
prostate cancer	2010



Monoclonal Antibodies

Monoclonal antibodies attach to cancer or immune cells. They manipulate their target cells in many ways, including blocking tumor growth or delivering another treatment directly to cancer cells. Checkpoint inhibitors are a type of monoclonal antibody.

- ☒ rituximab, first monoclonal antibody (1997)
- ☒ ipilimumab, first checkpoint inhibitor (2011)



CAR T Cells

A patient's T cells are removed from the body, "supercharged" in the lab and reinfused into the patient. These newly empowered T cells now have a chimeric antigen receptor (CAR), which allows them to recognize and kill cancer. In 2017, the FDA approved two CAR T-cell therapies.

Treatment	Cancers
tisagenlecleucel	acute lymphoblastic leukemia
axicabtagene ciloleucel	large B-cell lymphoma



Too Much of a Good Thing:

Managing Immunotherapy Side Effects

IMMUNOTHERAPY CAN BACKFIRE WHEN A SUPERCHARGED IMMUNE SYSTEM ATTACKS HEALTHY CELLS, BUT RESEARCHERS ARE HOPEFUL FOR THE FUTURE

by Anna C. Christensen

One of the most attractive features of immunotherapies like checkpoint inhibitors is that they teach immune cells to target cancer specifically, setting them apart from chemotherapy and radiation, whose attacks on tumors spill over onto healthy cells. But if immunotherapy ignores healthy cells while waging war on cancer cells, the unpleasantness associated with chemotherapy and radiation shouldn't be an issue.

"Side effects tend to be relatively minor," says Emmanuel Katsanis, MD, University of Arizona Cancer Center division chief of pediatric hematology and oncology. "Patients don't lose their hair, they don't have nausea and vomiting, they don't get mouth sores. Most of it can be done as an outpatient."

Despite immunotherapy's well-earned reputation as a kinder, gentler cancer treatment, in a small percentage of patients it can have serious side effects. Sometimes, immune cells

become hypervigilant and start attacking healthy cells, a phenomenon known as autoimmunity.

"In the same way that an activated immune system is attacking the cancer, immunotherapy may cause similar side effects, as you would see in autoimmune conditions like lupus or rheumatoid arthritis," says Dr. Katsanis.

"If you awaken the immune system to fight cancer, sometimes those armies of immune cells could attack 'self,'" says Hani Babiker, MD, associate director of the UA Cancer Center Early Phase Clinical Trials Program. Fortunately, autoimmune side effects are rare. "Not a lot of patients get side effects. I would dare say that serious side effects are less than 8 percent of patients, in some of the drugs."

Furthermore, most side effects are mild and do not interfere with a patient's day-to-day life.

Rousing the immune system: A range of side effects

Daniel Persky, MD, director of the UA Cancer Center Clinical Trials Office, says many types of immunotherapies, especially monoclonal antibodies, carry a risk of an allergy-like reaction to the infusions.

"We're very well prepared for such side effects because we've had a lot of experience dealing with these drugs," says

Dr. Persky. “We typically give medications beforehand, such as Benadryl and Tylenol. We may give a corticosteroid like prednisone to reduce the possibility of a reaction.”

Fortunately, allergic reactions to infusions usually pose no long-term problems.

“Typically, after a person has been exposed to it, the body gets used to the drug,” says Dr. Persky. “The subsequent risk of similar infusion reactions is much less.”

Beyond the initial possibility of reacting to the infusion of the drugs, side effects can accompany treatment. Rashes or itching are common, but they can be treated effectively with topical medicines like corticosteroid creams or antihistamines.

Other side effects, however, are similar to those experienced by people receiving chemotherapy, including fatigue, which is the No. 1 side effect experienced by patients using checkpoint inhibitors.

“Fatigue, the most common side effect, is not debilitating and it’s better tolerated with time,” says Daruka Mahadevan, MD, PhD, director of the UA Cancer Center Early Phase Clinical Trials Program.

Additionally, whereas chemotherapy can directly attack healthy cells in the gastrointestinal tract, so too can immunotherapy deploy over-revved immune cells to this region of the body, resulting in similar side effects, such as difficulty eating, nausea and diarrhea.

Fortunately, severe side effects from immunotherapy are rare.

“In my practice, the side effects we see with immunotherapy are much less than what we see with chemotherapy,” says Dr. Babiker.

The most serious side effects are linked to uncontrolled inflammation — conditions that end in the suffix *-itis*, like pneumonitis, colitis or hepatitis. Although inflammation is a normal part of the immune response, in which the body fights against injuries, infections or cancers, there can be too much of a good thing. Chronic inflammation can harm healthy tissue, potentially leading to major damage. Fortunately, UA Cancer Center physicians know what to look out for.

“We keep a close eye on all side effects,” says Dr. Mahadevan of his clinical trial patients. Members of his staff “contact trial patients frequently to see how they’re doing. We bring them in regularly for check-ups so we don’t miss anything.”

Ultimately, if a patient’s cancer goes into remission, these side effects might be worth it. “I’d rather have a patient who’s alive with some autoimmune symptoms than a cancer that metastasizes and kills the patient,” says Dr. Katsanis.

Fighting fire with fire: Addressing side effects with medication and education

When the immune system is hyperactive, it needs to be tamed, and UA Cancer Center physicians have the necessary tools.

“We have learned a lot about how to manage these side effects over the course of the last decade,” says Julie Bauman, MD, MPH, UA Cancer Center division chief of hematology and oncology.

The trick is to strike a balance between letting the immune system kill cancer cells, while suppressing it just enough to bring autoimmune conditions under control. A class of drugs called corticosteroids frequently is used to counter immunotherapy side effects.

Outside the field of oncology, health-care providers are gaining awareness of the unique side effects immunotherapy can trigger. If a cancer patient visits the emergency department with shortness of breath and a cough, a physician more familiar with the immune-suppressing effects of chemo, rather than the immune-enhancing effects of immunotherapy, might diagnose the patient with an infection and prescribe antibiotics — but what if the patient actually has a life-threatening case of autoimmune pneumonitis?

“When a person comes to the ER with a severe infection, the time to antibiotics is critical,” Dr. Bauman says. “Similarly, if a person comes to the ER with severe autoimmune side effects, it’s the time to steroids that really matters.”

To provide appropriate treatment, health-care providers must be able to distinguish between infections and autoimmune symptoms.

The Immune System

Many types of immune cells work together to defend against threats. Immunotherapies leverage this system to improve the body's defenses against cancer.

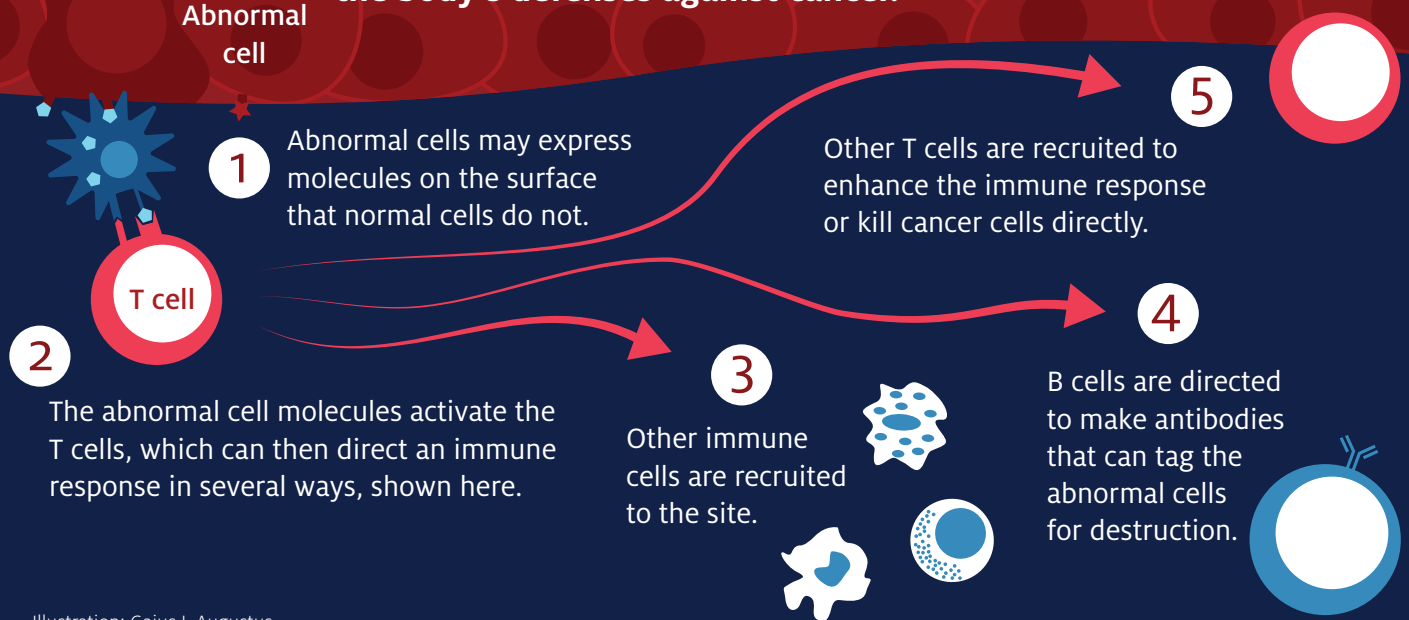


Illustration: Gaius J. Augustus

“There is a clear need to educate first responders, urgent care centers and emergency departments to recognize autoimmune responses,” says Dr. Bauman, who has helped educate other health-care providers about immunotherapy, whether addressing colleagues at conferences or talking to other physicians one on one. “If I have a patient who’s going to an ER, I call the ER physician directly and let them know what they need to be looking for, and teach them about immunotherapy,” says Dr. Bauman. “They are so appreciative, because it really is a completely new treatment.”

The road ahead: Improving the patient experience

All medical treatments have side effects, and immunotherapy is no exception. It is tempting to hope that the side effects associated with surgery, radiation and chemotherapy can be left in the past, with immunotherapy raising armies of perfectly trained immune cells to target tumors and leave innocent bystanders alone. But the power of the immune system can be a double-edged sword. Fortunately, scientists and physicians are learning how to wield it.

By continuing to unravel the mysteries of the immune system, researchers hope in the near future we will make strides in identifying appropriate biomarkers — chemicals in the body

that can be measured to give doctors information about what is going on inside, perhaps by blood tests or molecular tumor testing. These biomarkers could help us predict which patients are more likely to respond to an immunotherapy — and who might be at risk for serious side effects.

“Identifying the biomarkers for response to immunotherapy can help us select specific immunotherapeutic drugs, one over the other, to fight specific cancers,” says Dr. Babiker.

Researchers at the UA Cancer Center are investigating a new method to identify biomarkers in a simple skin biopsy, which might be used to predict which patients will have serious side effects to a drug. (See “Sprinting Toward the Finish Line” on pg. 20.) In the future, tests that uncover information about a tumor’s biomarkers or genetics could help physicians match individual patients to the safest and most effective drugs.

“We have the ability to sequence the human genome, and we have a multitude of immunotherapy candidates,” says Dr. Bauman. “When these two things come together, we will have powerful cancer therapy for every person. We can wake up their immune system to the unique antigens within their cancer. That is the holy grail.”

PHILANTHROPY

Making a Meaningful Difference



Jim Cockrum talks to Nathan Sweeney, a student in the UA Cancer Biology Graduate Interdisciplinary Program.

by Anna C. Christensen

Jim Cockrum is a lifelong learner. In college, he took an art class on a dare. Early in his career, he taught himself numerical analysis and assembly language. And throughout his adulthood, he has studied several types of meditation and dabbled in languages such as Italian and Greek. Underlying all of these disparate paths is an unquenched curiosity about the world around us — and now he and his wife are supporting the next generation of curious learners.

In 2017, Jim and Maria Cockrum established two funds. The Cockrum Research Fund is an annual gift that will help University of Arizona Cancer Center graduate students

continue their education as tuition costs rise. The James and Maria Cockrum Research Endowment will be funded by half of their estate, and is an investment in future students of the Cancer Biology Graduate Interdisciplinary Program. Thanks to Jim and Maria, our students' creativity will be channeled to advance cancer research.

"We started thinking about things that might make a meaningful difference in people's lives," Jim tells us. "We wanted to focus on the education of cancer researchers because that would provide the greatest amplification of any gift we could give."

The interdisciplinary nature of the cancer biology program was especially attractive to Jim because "it's exposing students to

more than just one way of looking at cancer. To really make a change, you need to be exposed to lots of different disciplines — to get out of a narrow track.”

Jim gained additional inspiration from his visit to Tucson to meet the graduate students who would benefit from his generosity.

“When I was talking to them, I thought, ‘They know so much, they’re so excited and they’re just going full blast!’ What a neat thing to see,” he says.

Jim describes his early education in a “one-room country school” in Missouri in which he started reading chemistry and physics books out of the pure fascination of learning how the universe works. And back home on his family’s farm, he constantly was reimagining better ways to do things.

“I used to drive my dad crazy,” he recalls. “I’d say, ‘Why do we have to do it this way?’ He’d say, ‘We’ve always done it this way.’ I was always trying to find some new and better way to do something.”

Jim believes this ability to examine a problem from multiple angles is crucial to scientific discovery.

“I think questioning is better than accepting,” he says. “The best thing to teach young people is how to think. Life changes, the environment changes, but if you can learn to think and question dogma in yourself as well as other people, you’ll never be off balance.”

The ability to think — rather than memorize and regurgitate names, dates and places — served him well at his first job at Boeing in the 1960s, when he essentially had to teach himself computer programming with very few resources.

“I’d never seen a computer,” he recalls. “They gave me a book on numerical analysis. I started getting the manuals and reading about things. You need the curiosity and confidence that you can attack something new, even though you don’t know anything about it.”

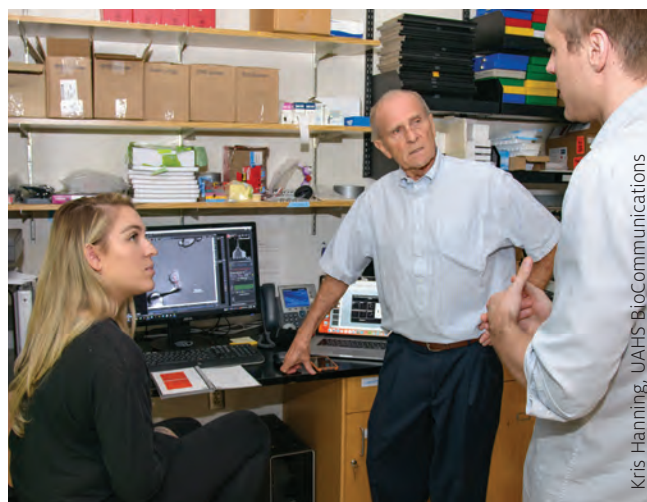
These days, Jim and Maria are retired in a Scottsdale home where they are surrounded by a large collection of modern art. His interest in art goes back to college.

“I took art on a dare,” he tells us. “Somebody bet me that I couldn’t pass an art course. I was a smartass and said I could pass anything. I discovered that I could draw, I could paint. I was hooked.”

His career took him from Missouri to the West Coast — places like Seattle, San Diego and finally the San Francisco Bay Area — where he worked for companies like Boeing, Hewlett-Packard and IBM. It was when he was based in the Bay Area that he met Maria, who also worked with computers. Together, the couple share a passion for helping students receive a well-rounded education to prepare them to join the next generation of innovators in cancer prevention, treatment and cures.

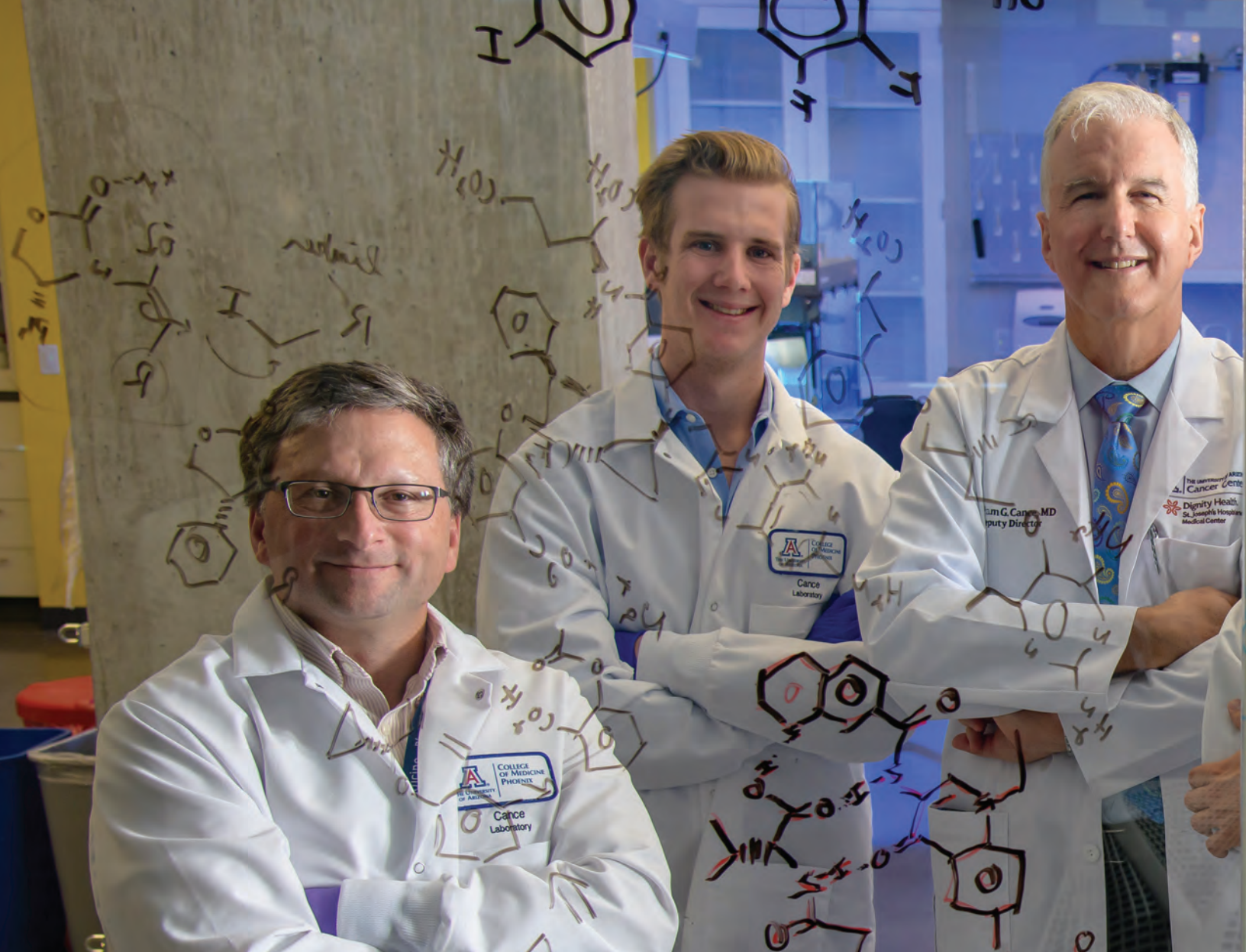
The Cockrums’ gifts to the UA Cancer Center will impact cancer research at the University of Arizona for years to come.

“We got involved to help young people do the most they can with their lives,” says Jim. “I hope I live long enough to see some really great breakthroughs happen.”



Jim Cockrum (center) meets with graduate students Julieann Puleo (left) and Adam Watson (right).

For more information on ways to support the UA Cancer Center with a gift from your estate, please contact the UA Cancer Center Development Office at give@uahs.arizona.edu or 520-626-5752 or 877-518-4638.

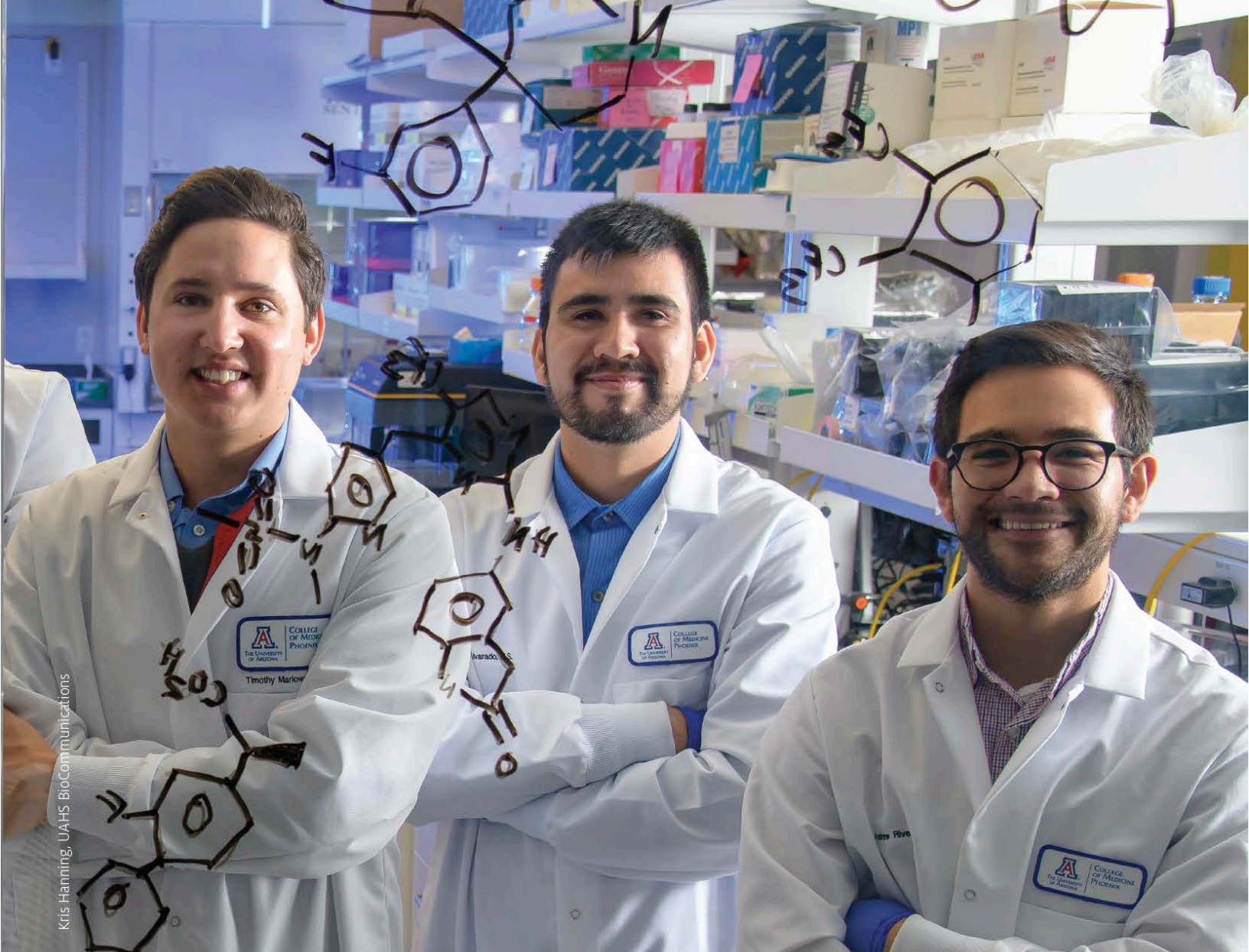


DRUG DEVELOPMENT IN DOWNTOWN PHOENIX

Developing new drugs is time-consuming and complicated work. In the copper-gilded Biomedical Sciences Partnership Building at the University of Arizona Cancer Center – Phoenix, surgical oncologist and UACC Deputy Director William Cance, MD, and Director of Drug Discovery Tim Marlowe, PhD, embrace this challenge. The members of their lab study a protein called focal adhesion kinase (FAK), which helps cancer stay alive. A drug that targets FAK could be powerful — but finding the perfect drug target is just one step of many.

Drug discovery begins when scientists look for candidates in a large library of experimental compounds. Scientists conduct further testing on promising molecules — a grueling process that can narrow thousands of compounds down to a handful.

It doesn't stop there. A promising compound's chemical structure is further altered, which could make the difference between a weak or strong response to a drug. Scientists meticulously make one change after another until a drug is worthy of a pre-clinical study in animals — which, if successful, can lead to human clinical trials. Several FAK inhibitors are already at this stage. These



Kris Hanning, UAHS BioCommunications

The Cance Lab, from left to right: Warren Weiner, PhD; Mitch Glauner; William Cance, MD; Tim Marlowe, PhD; Carlos Alvarado; Andy Rivera, MS

trials have had limited success because they target only the FAK enzyme, an approach that enables tumors to build rapid resistance to treatment. The Cance Lab is using a different tactic by targeting the molecules that FAK interacts with, allowing for the development of therapeutics that can be personalized to each tumor.

Through hard work — and repeated failures, which don't deter these tenacious researchers — scientists have progressed from identifying targets to creating therapies against them. Targeted drugs like FAK inhibitors can be combined with immunotherapy to attack tumors on two fronts: A targeted drug can initiate the battle by weakening a tumor's grip on immortality, while immunotherapy can summon the immune system to administer the coup de grâce. In fact, FAK inhibitors are now also considered to be a type of immunotherapy, as they can help the immune system recognize cancer cells.

Phoenix is a hotspot for scientific discovery, and the UA Cancer Center has put down roots there to expand its research capacity. The Biomedical Sciences Partnership Building is nestled on the same block with the UA Health Sciences Education Building and the Translational Genomics Research Institute (TGen), and is across the street from a clinical building, where UA Cancer Center oncologists see patients. Other institutions, like Arizona State University, Mayo Clinic and Honor Health, are just a few miles away.

"Our location in the heart of Phoenix gives us instant access to some of the best minds in drug discovery and cancer clinical trials in the world," says Dr. Cance.

BEAR DOWN **BEAT** **CANCER**



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