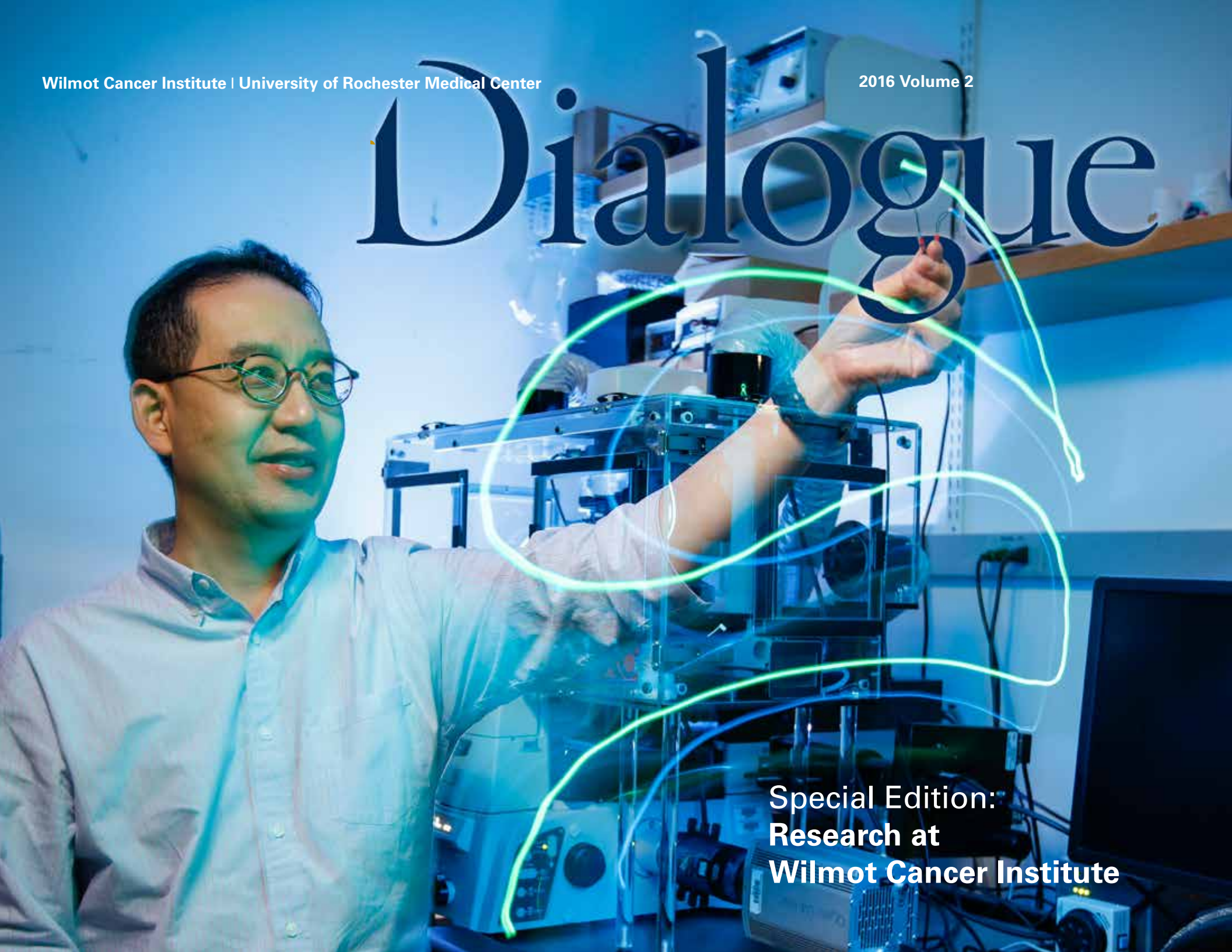
Wilmot Cancer Institute | University of Rochester Medical Center

2016 Volume 2

Dialogue



Special Edition: **Research at Wilmot Cancer Institute**

Letter from the Director

Hello Friends of Wilmot Cancer Institute,

Jonathan W. Friedberg, M.D., M.M.Sc.
Director, Wilmot Cancer Institute

On the Cover
Wilmot scientist Minsoo Kim, Ph.D., is studying the role that light can play in improving immunotherapy.

photo: Matt Wittmeyer

What an exciting time it is to be caring for patients with cancer! Every week, I see patients who five years ago would not be alive and are now not only living but thriving on novel nontoxic treatments. There is one singular reason for this success: our national investment in cancer research. We are now seeing the payoff from the War on Cancer declared more than 40 years ago.

At Wilmot, we remain committed to discovery. I believe it is the most important thing we do. We are the only academic cancer institute in the region, and this research focus allows our patients from Rochester, from Geneva, from Elmira, from Batavia, and across our entire network access to specialists in rare and complex cancers, cutting-edge clinical trials, and an environment where we are always looking forward to improved understanding of cancer, and more effective, better tolerated therapy.

Cancer research is a complex and expensive enterprise. Collaborations between scientists maximize the impact of our work. At Wilmot, we follow the model created by the National Cancer Institute, and are creating several large research teams focused on common themes.

In this issue of *Dialogue,* we highlight and celebrate the power of these partnerships across disciplines.

In geriatric oncology, for example, we are bringing together molecular biologists, geriatricians, oncologists and behavioral scientists to improve outcomes for older adults with cancer.

Scientists in chemistry, biomedical engineering and hematology/oncology are collaborating to develop a new drug delivery system using nanoparticles to improve the treatment of acute myeloid leukemia, one of the deadliest types of blood cancers.

Researchers from our Cancer Control and Survivorship team and our Center for Community Health are working throughout the region with individuals and organizations to meet the needs of an increasingly diverse population.

The depth and breadth of this research makes us unique in upstate New York, and it is only possible because of our commitment to advancing the understanding and treatment of cancer. You have invested significantly in our research program, funding seed grants to help our investigators launch new projects. Many of you have also agreed to participate in our clinical trials, the ultimate contribution for which we are truly grateful.

This is only the beginning. In the coming years, with your continued support, we will grow our research program – building more diverse teams, forming new partnerships and strategically recruiting nationally renowned faculty.

The return on your investment, only partly captured in these pages, is substantial. It means job creation, new discoveries and better care. Ultimately, it means progress toward cures. And that is why I'm so excited to come to work every day.

My best wishes for a healthy 2017.

Jonathan W. Friedberg, M.D., M.M.Sc.

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Wilmot Cancer Institute is a component of Strong Memorial Hospital.

Dialogue

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Thanks to immunotherapy, Denny Stratton's aggressive skin cancer is stable. Stratton, in the green shirt, meets weekly with friends for breakfast at Morningstar Restaurant in Rochester.

No Longer Science Fiction, Immunotherapy Offers Second Chances to Patients, New Opportunities for Research

Denny Stratton spent 45 years working outdoors, climbing utility poles and making repairs for the Rochester Telephone Co. In 2014, a mass the size of a baseball swelled near his elbow, on the same arm that used to hang out the open window of his utility truck.

Alarmed, the fair-skinned Irish-American saw a dermatologist and then an orthopedic oncologist, Wakenda Tyler, M.D. A biopsy confirmed that he had Merkel cell carcinoma, a rare, aggressive skin cancer. After surgery and 26 radiation treatments, he was ready to move on, cancer-free. But early this year a routine scan showed the cancer had returned, this time with tumors on his pancreas and prostate gland.

His care team at the Wilmot Cancer Institute cautioned Stratton that metastatic cancer cannot be cured but they also suggested a promising way to extend his life: Immunotherapy.

They recommended that Stratton consider taking the same drug that wiped out former President Jimmy Carter's metastatic melanoma. Known as Keytruda (pembrolizumab), the drug is in a class of groundbreaking medications that harness a patient's own immune system to attack malignancies. Keytruda is used to treat melanoma and Merkel cell, lung cancer, and head-and-neck tumors.

And just like President Carter, Stratton is reaping the benefits. After four infusions, his pancreas tumor disappeared completely and only a speck remained on the prostate gland. Stratton continues to take the drug and experiences almost no side effects.

"Me and Jimmy Carter – hopefully we'll live long!" says Stratton, 77, of Penfield, N.Y. "And most importantly, this drug is helping a lot of other people, too."

Excitement around immunotherapy exists for many reasons – not the least of which is that patients like Stratton, who respond well to the treatment, are able to live fully. A retiree and former Marine, he visits Wilmot every three weeks for treatment. He also hunts and goes fishing, meets his buddies for breakfast twice a week, and spends time with his children and grandchildren. He and his wife plan to drive their RV to Florida for the winter, and his Wilmot physicians have arranged for him to receive Keytruda infusions while there.

"I know how lucky I am," Stratton says.

'Everything is Changing Now'

Immunotherapy has been around for more than 100 years. The approach aims to boost, restore, or improve the body's natural defenses to fight cancer.

It was pioneered by William Bradley Coley, M.D., who used cocktails of toxic bacteria to stimulate the immune systems of his patients in 1891. Coley's procedure, however, eventually took a back seat to advances in surgery, radiation, and chemotherapy. But scientists continued to study the immune system's response to cancer, and several drug makers showed a renewed interest in Coley's toxins during the 1990s. In the 21st century, immunotherapy was still on the radar but many scientists shifted their attention to targeted therapies that attack very specific mutations on cancer cells.

Most recently, scientists exploring immunotherapy began experiencing several new eureka moments, according to Hucky Land, Ph.D., Wilmot Cancer Institute's director of research. The immune system usually has the ability to balance its reaction to foreign invaders while also

Matt Wittmeyer

remaining tolerant enough that it doesn't become hyper-stimulated. For the first time, Land says, scientists started to understand how to manipulate immune cells to kill cancer while preserving the healthy balance.

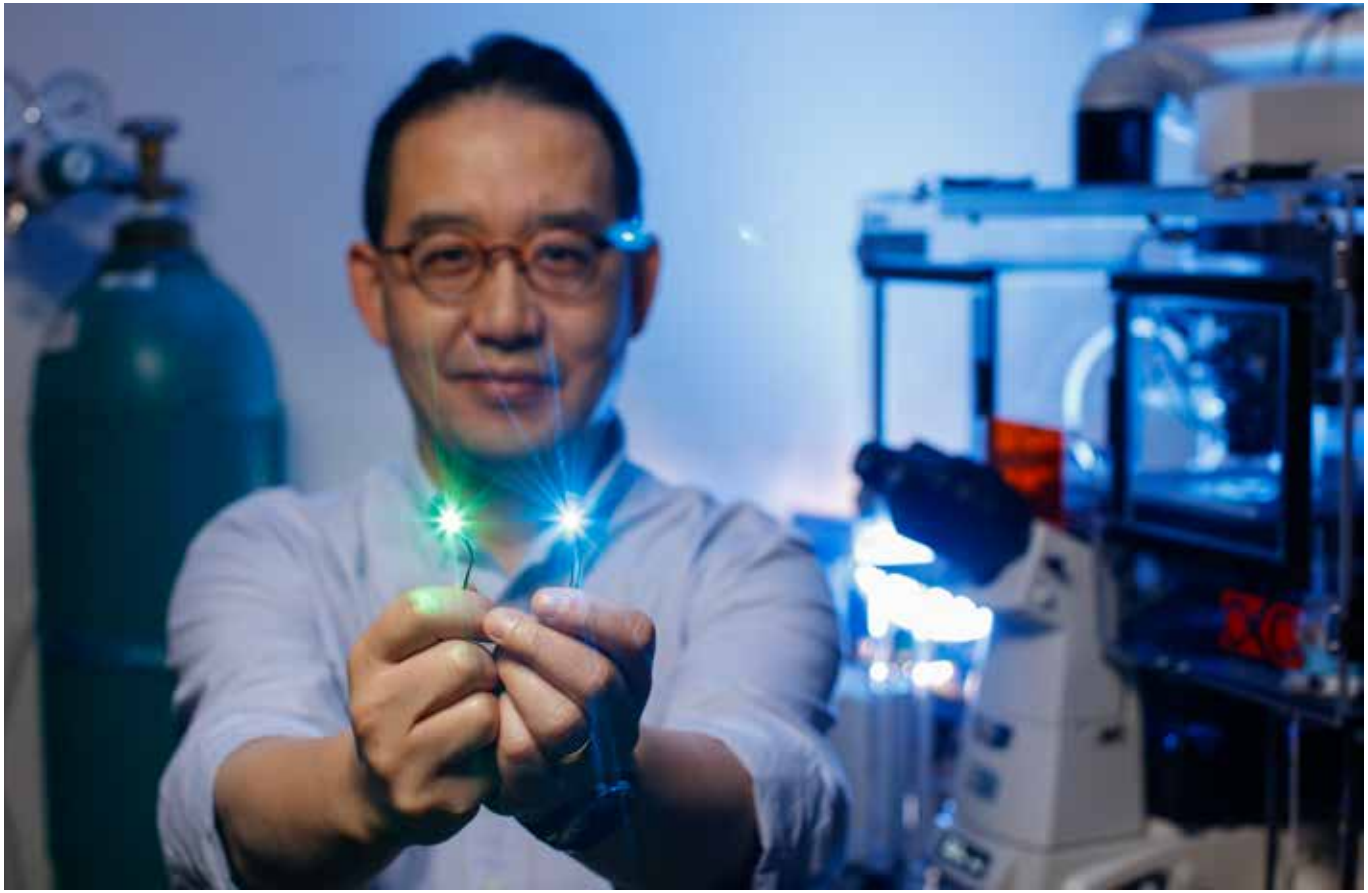
"That's why this moment is so important," Land says. "We're learning how to use immunotherapy appropriately to fight cancer."

Science magazine declared in 2013 that immunotherapy was the "Breakthrough of the Year," and at the 2016 American Society of Clinical Oncology annual meeting, the immunotherapy buzz was palpable among the 30,000 attendees. Pharmaceutical companies are investing heavily in the treatment as well.

Bone marrow transplants (BMTs) have ranked among the most reliable, modern forms of immunotherapy. The procedure involves implanting well-matched, healthy immune cells from a sibling or unrelated donor's immune system into eligible cancer patients, potentially offering cures or prolonged remissions. Wilmot recently celebrated its 3,000th BMT. New research, however, has uncovered even better transplant techniques that could benefit patients without 100 percent-matched donors. In fact, Wilmot is taking part in a national clinical study testing the effectiveness of immune cells from parents, siblings, children, or other donors who are at least a 50-percent match.

Other discoveries have led to additional new immunotherapies, such as Keytruda. It works by shutting down a protective mechanism on cancer cells (known as PD-L1), clearing the way for the immune system to control cancer growth and lengthen the life of the immune cells that target cancer.

CAR T-cell therapy, the most radical of the latest developments in immunotherapy, involves removing a patient's own fighter



Matt Wittmeyer

Minsoo Kim, Ph.D., holds tiny LED chips that can be activated to track down tumors and steer treatment toward its target. An electric field induces a current, sending the light signals in the right direction.

For more on CAR T-cell therapy at Wilmot, see "patient zero" story on pg. 7.

T-cells, re-engineering them in a laboratory to boost their ability to hunt down cancer, and then injecting the modified immune cells back into the patient. It's being tested in a limited number of people with lymphoma at Wilmot and at a select number of academic institutions across the country.

"I've spent 20 years doing immunotherapy research and frankly, I was met with a lot of skepticism in the past," says David Linehan, M.D., clinical director at Wilmot and a surgeon who also runs a research laboratory focusing on pancreatic cancer. "Everything is changing now and we're finding a lot of enthusiasm."

Based on his own painstaking bench science, Linehan and Marcus Noel, M.D., are conducting a clinical trial to find out if chemotherapy combined with an experimental immunotherapy drug can help people with advanced pancreatic cancer, which often has a poor prognosis. The drug targets a receptor on pancreas cancer cells known as CCR2, which prevents the immune system from properly attacking the disease.

One of their patients, Jason Anderson, 41, who lives about 40 miles west of Rochester in Knowlesville, Orleans County, N.Y., had a pancreatic tumor that was surgically removed and another tumor the size of an orange on his liver, where the cancer had spread. He entered their immunotherapy study nearly a year ago, and the liver tumor shrank to the size of a peanut. Anderson continues to receive the treatment and has been stable for months.

"I was 40 years old when all of this happened and I was thinking, 'Whatever I can handle, give it to me. I've got to fight,' " says Anderson, whose passions are car shows, swap meets, and watching drag racing. He was feeling well enough last summer to travel all over western New York for his favorite events. "I'm definitely happy with the direction everything's been going. I feel good."

Oncologists are energized by seeing extremely sick patients go into complete or partial remissions.

"It's a very exciting time in cancer research, both in terms of what's hot now and what's next," says Wilmot's director, Jonathan Friedberg, M.D., M.M.Sc., who is spearheading the CAR T-cell study in upstate New York. "And with the support of the National Cancer Institute and the federal Cancer Moonshot program, we are encouraged that scientists at Wilmot and elsewhere are leveraging new discoveries and working together to bring these therapies to many more patients."

Challenges Remain

Stimulating the immune system to fight cancer has a lot of merit and seems logical. In fact, a healthy immune system quashes cancer cells that emerge regularly in most people before the cancer proliferates and does harm.

But when cancer takes hold and treatment is required, the response to immunotherapy is far from perfect despite many inspiring patient stories.

Individuals with melanoma have some of the best outcomes, although immunotherapy only works well in 25 to 40 percent of those cases, estimates John Frelinger, Ph.D., a professor of Microbiology and Immunology at the University of Rochester and a Wilmot investigator. He and Minsoo Kim, Ph.D., also a professor of Microbiology and Immunology, are working toward improving the odds to something above 50 percent.

They believe that three underlying issues challenge immunotherapy:

- Cancer cells are smart and evasive. They can hide from the immune system's T-cells, which normally are good at fighting disease.
- Aggressive tumors suppress the immune system, preventing super-fighting T-cells from doing their job.
- Some types of immunotherapy come with serious or life-threatening side effects, a result of the immune system being overstimulated and unable to shut itself down after treatment. Earlier this year, for example, one national CAR T-cell study was temporarily halted due to patient deaths from side effects.

Frelinger and Kim are each using different approaches to investigate ways to bypass all three obstacles.

Kim's lab is finding practical ways to use light or optics to guide T-cells toward tumors, exposing cancer when it hides and minimizing side effects.

With National Institutes of Health funding, he invented a tiny implantable LED chip that can steer genetically modified T-cells (like those used in CAR T-cell therapy) toward the cancer. A wireless signal from a small battery pack directs

John Schlia

John Frelinger, Ph.D., talks to a group of community members about immunotherapy at a monthly Science Café series at the Barnes & Noble bookstore in Pittsford, N.Y.

the LED beam to shine light onto the tumor, sending the T-cells racing in that direction.

"It's like sending light on a spy mission to track down cancer cells," Kim says. He tested his hypothesis in mice, with success.

Other applications are possible. For example, the light can be activated or inactivated in a millisecond with a safety switch that he also invented. If the immune system gets too revved up, the light source can induce T-cell suicide to slow it down.

Another drawback to immunotherapy is that doctors have no way of knowing if it's working until several weeks later when a patient gets an imaging scan. By tracking the T-cells and the tumors with light, doctors would be able to see in real time whether the immunotherapy reaches its target, Kim says.

"This approach is also appealing because light is non-toxic, inexpensive, and it can be personalized for an individual patient's needs," he says. One patient might need light therapy to guide the immunotherapy to the cancer, whereas another might need it solely to minimize side effects.

Light therapy in medicine is still a bit of a fantasy, but Kim likes to picture the future: "Imagine that a patient could walk into a chamber and colored lights would scan the body and direct healthy T-cells to kill whatever ails you," he says. "That would be really cool."

A Throwback to the Past

Like Kim, Frelinger's goal also involves unleashing T-cells as serial killers for cancer in a controlled manner. But instead of using optics, Frelinger's weapons are recombinant proteins – molecules engineered in his laboratory to perform specific duties.

His work is best described using the analogy of Pac-Man, the popular 1980s arcade game. In Frelinger's world, Pac-Man stands for protease-activated cytokines. Cytokines are proteins that act on immune cells, causing them to expand in number and also making them more effective at killing tumor cells. Proteases "chop up" other proteins (chewing them like Pac-Man) and are over-expressed by cancer cells as they invade surrounding normal tissues.

Frelinger and other scientists have known for years that a cytokine called interleukin-2 (IL-2), a growth factor that spurs T-cells into action, can prompt tumor killing. Indeed, some patients receiving IL-2 therapy experience long-lasting remissions and apparent cures. But IL-2 treatment often comes with dangerous side effects; IL-2 stimulates legions of immune cells at once, which can cause a "cytokine storm," producing a violent immune-system reaction.

To circumvent the storm, Frelinger engineered proteins that contain a form of IL-2 that remains inactive until it reaches the tumor. Once at the site of the cancer, overactive proteases then "chop up" the recombinant protein, releasing IL-2 precisely where it's needed, he says.

This stimulates the killer T-cells in the tumor without triggering a dangerous immune-system reaction in the rest of the body. Frelinger's approach has been supported by the NIH. He and a postdoctoral fellow in his lab, Denise Skrombolas, Ph.D., are now working on expanding the potential of Pac-Man, testing it with different cytokines and investigating whether it can work in tandem with other immunotherapies.

Scientists utter the word "revolutionary" to describe today's immunotherapy research – in part because they believe immunotherapy has the potential to cure some cancers.

"It's a 30-year, overnight success," Frelinger jokes, thinking back on decades of study that led to major progress in modern times.

And yet many steps remain before immunotherapy will be routinely offered alone or in combination with other treatments. The next big initiative, according to Wilmot investigators, is to outsmart relapsing cancer cells that sometimes linger in the body despite their best efforts to uproot the disease.

"This is a golden age," Frelinger says. "People use the term 'tipping point' because scientists really believe immunotherapy can work, even those who are outside of the field of immunology. I'm keen on the future." WCI

"patient zero"

A Tale of Risk and Hope with Immunotherapy

A doctor from rural Elmira, N.Y., was Wilmot's "patient zero" for a treatment that has been hailed as one of the most remarkable new approaches ever used against cancer.

Ed Foster, 64, arrived at Wilmot last February very sick after his advanced diffuse large B-cell lymphoma did not respond to two courses of standard chemotherapy. About 66 percent of patients with this type of blood cancer are essentially cured with chemotherapy, but for the remaining one-third, the prognosis is poor.

"It's odd to be on the other end," Foster said last winter, choking back tears, as he thought about all of the patients he had treated over the years in his small town. "My reaction to cancer has largely been denial, and that somehow I'm just going to get through this."

He was fortunate that his case was referred to Jonathan Friedberg, M.D., M.M.Sc,. the director of Wilmot and a lymphoma specialist, at the same time that Wilmot was selected to be the first center in upstate New York to participate in a national, phase II, immunotherapy study investigating engineered CAR T-cell therapy to treat lymphoma.

CAR (chimeric antigen receptor) T-cell therapy works by using a person's own altered T-cells to directly target tumors.

Ed Foster in his hometown of Elmira.

Because it forces the immune system into overdrive, however, the treatment comes with considerable risk. Known side effects include severe inflammation, high fevers, blood pressure irregularities, heart problems, serious infections, and neurotoxicity. And since only a few dozen patients across the country have received CAR T-cell therapy, doctors also worry about the "unknowns" that can easily arise with experimental treatments, says Patrick Reagan, M.D., the Wilmot oncologist who supervised Foster's case along with Friedberg.But Foster decided the risk was worth it.

After several days in intensive care and a complicated recovery due to neurotoxicity and frailty, Foster left Wilmot in late March full of hope and optimism. His doctors and nurses watched as he regained strength. Foster's wife, Hanna, is a nurse practitioner, and he also has three children and his 101-year-old mother living with the family.

In June when Foster returned to Wilmot for his first comprehensive tests following CAR T-cell treatment, his care team was elated. His imaging scans and blood tests were absent of cancer, and he looked fit and healthy again. "The way I'm feeling," Foster said, grinning, "I knew it was going to be good news, nothing but good news!"

Throughout the summer he tended the family garden and supervised the construction of a new backyard patio. His wife marveled at his joyfulness. He dusted off old cookbooks and would post the week's dinner menu to the family bulletin board every Sunday, and then whip up one tasty meal after another. Later he returned to work part-time.

"Very often an experimental protocol offers something you can't get otherwise. Hopefully this will inspire people to think about clinical trials."

Danielle Benoit, Ph.D., Ben Frisch, Ph.D., and Rudi Fasan, Ph.D., hold elements from each of their labs, which are collaborating to develop a new leukemia drug and a new way of delivering it with nanoparticles.

Teamwork toward a 'Perfect Bullet' for Leukemia

Imagine that a drug is "oil" and the human body is "water." A conduit would be needed to steer cancer drugs through the body to selectively target cancer cells, wherever they reside.

If a budding Wilmot Cancer Institute investigation pans out, a nanoparticle-based delivery system might be exactly what Wilmot scientists have been looking for, the trio of young researchers say.

Rudi Fasan, Ph.D., associate professor of Chemistry; Danielle Benoit, Ph.D., associate professor of Biomedical Engineering; and Ben Frisch, Ph.D., a research assistant professor of Medicine, Hematology/Oncology, are working together to improve the treatment of acute myeloid leukemia (AML), one of the deadliest types of blood cancers because it often relapses after initial therapy.

They each bring a different scientific discipline and a distinct role to the project.

Fasan develops new drugs and new methods to make them more effective. In this case, he discovered and modified a small-molecule anti-cancer drug derived from a natural plant source related to the magnolia tree. After testing several different chemical forms of the compound, he is studying the correct potency and ability to precisely destroy cancer cells.

Benoit's nano-delivery system can transcend the barriers that sometimes prevent drugs from reaching their target. Nanoparticles are microscopic materials that act as a bridge between different structures – in this case the nanoparticles are designed to encapsulate an oily drug compound and make it more compatible with the body's water. Her system also packages the drug with peptides (amino acids) that direct the treatment into the bone marrow, where leukemia takes root.

Getting to the root of the disease is important. Years ago, scientists discovered that leukemia most likely relapses because a subset of cells, known as leukemia stem cells, can dodge standard chemotherapy. Mature leukemia stem cells hide in the bone marrow in a quiet state, until they resurge. Wiping out these stem cells is the key to improving the treatment for a disease that can be very aggressive.

So far, scientists have not been able to target leukemia stem cells directly in the bone marrow, says Frisch, who studies the bone marrow environment for clues as to why blood cancers flourish there. His role is to take Fasan's new drug, which will be loaded into Benoit's nano-delivery system, and conduct experiments in cell cultures and mice to find out if the system is effective at binding to cancer cells.

"The idea is to have a perfect bullet," Fasan says. "A very nice feature of this collaboration is that we can take advantage of complementary expertise and run with it."

"By using the proper materials to enhance drug delivery," Benoit adds, "it could potentially revolutionize cancer treatment."

The team won a 2016-17 University Research Award. Funded annually by UR President Joel Seligman, the money goes to scientists with projects that have a high probability of receiving additional external funding. They received $75,000 to generate data to compete for larger grants from the National Cancer Institute, the Leukemia and Lymphoma Society, and the Leukemia Research Foundation.

Matt Wittmeyer

Melvin King, left, a research assistant, looks on as Brad Smith, Ph.D., and Josh Munger, Ph.D., collaborate to study how cancer cells reproduce.

Hot Topic: Manipulating Cell Metabolism to Attack Cancer

Many of us associate the word "metabolism" with the ability to burn calories as our cells convert what we eat to energy.

Cancer cells have their own shrewd metabolism, allowing them to reproduce very quickly – a hot area of research enabling scientists to search for ways to manipulate cancer-cell metabolism to stop or slow the disease.

"Every tissue or cell type in the body has different metabolic needs but as cells become cancerous their metabolism shifts in ways that are very different from normal cells," says Josh Munger, Ph.D., associate professor of Biochemistry and Biophysics at Wilmot. "Being able to identify those differences is critical for developing treatment targets."

He and Hucky Land, Ph.D., the Robert and Dorothy Markin Professor and director of research at the Wilmot Cancer Institute, recently pinpointed a key source of the problem with cancer-cell metabolism. Their work was published by the journal *Cell Reports.*

In a close collaboration between their labs, they showed for the first time that cancer-causing mutations control and alter the way cancer cells biosynthesize and replicate.

It's been known for decades that cancer cells siphon glucose from the bloodstream at alarming rates. But cancer's sugar addiction is only one part of the story, Land explains.

Sugar is metabolized differently by cancer cells. They switch from burning to fermenting sugar, a process that's fueled by cancer-causing mutations, the Land and Munger labs discovered. Wilmot researchers also found that in cancer cells, sugar fermentation facilitates the consumption of glutamine, another nutrient source. Glutamine is abundantly available in the bloodstream, and cancer cells devour it to support cell division.

"Our paper demonstrates that cancer cells, but not normal cells, depend on this link between sugar fermentation and glutamine consumption," Land says. "This suggests a novel way that we might be able to intervene with treatment."

Bradley Smith, Ph.D., a scientific staff member in the Land lab, led the laboratory experiments conducted with colon cancer cells. Early data show that by blocking enzymes that are specific to colon cancer cell metabolism, tumor growth can be slowed or stopped. Elsewhere, scientists are studying the metabolism of pancreatic cancer cells and other cancers.

Next, Land says, researchers want to learn whether the metabolism of cancer cells changes and adapts as the disease spreads, and if different cancers have different metabolic actions.

"How can we break disease recurrences by manipulating metabolism?" Land raises the question, noting that the answer may not be far off. When Wilmot published its important discovery in October, three other worldwide science labs weren't far behind with their own intriguing new data on cancer cell metabolism.

"There's a huge interest in this topic," he says. "We're at a crucial point in truly understanding cancer-cell metabolism and how we can exploit it for treatment." WCI

Matt Wittmeyer

Beverly Canin, left, a patient advocate, talks with Supriya Mohile, M.D., at the Wilmot Cancer Center. Mohile is part of Wilmot's Cancer Control and Survivorship Program and a national leader in geriatric oncology and research into aging and cancer.

With Fresh Perspectives, Research Team Studies Needs of Older Patients

Wilmot Cancer Institute's "cancer and aging" scientific team could be a model for marrying distinctly different perspectives into one big project.

The team's secret weapon isn't even a scientist; she's Beverly Canin, a sharp, energetic 82-year-old breast cancer survivor from the Hudson Valley region of New York. Canin became a patient advocate after dealing with her own diagnosis, aiding women who needed help navigating the health care system or talking candidly with their doctors. She is as comfortable asking questions as she is listening and learning, qualities that eventually earned her an invitation to become a reviewer for cancer research grants at the U.S. Department of Defense.

As her interest in research expanded, Canin started regularly attending the biggest gathering in the world for oncologists, the American Society of Clinical Oncology (ASCO) annual meeting.

In her initial visits to ASCO, Canin says she noticed something odd: Few people, if anyone, seemed to be studying aging as it relates to cancer, a topic of personal interest as she grew older.

Canin found an exception, though, when she met Supriya Mohile, M.D., a geriatric oncologist at Wilmot who, during her early years of medical training, was struck by the same blaring gap in research. Their mutual interest sparked a long relationship that continues to flourish.

"I walked up to Supriya and others at ASCO and said, 'If you ever think there's a way I can be helpful, I'd love to talk,'" recalls Canin. Subsequently, Canin was invited to join a national coalition of pioneering geriatric oncology researchers.

"It's been a big learning curve for all of us," Canin says. "But for researchers to accept an advocate like myself as a peer is hugely rewarding."

Mohile was similarly inclusive when she began assembling a new research team at Wilmot to expand the mission of improving disease outcomes for older adults. The voices of patients and advocates like Canin were loud and clear – the field is still in need of a lot of information, and fast. The Wilmot team is working toward that goal with diverse perspectives from molecular biologists, geriatricians, oncologists, and behavioral scientists. They're taking on a wide variety of investigations all under the umbrella of "cancer and aging," including studies of biomarkers for aging, the way aging cells respond to the stressful assault of cancer treatment, and how to use decision-making tools to help older patients prioritize their concerns and make trade-offs when it comes to treatment.

The team's objective is to win a Program Project Grant from the National Institutes of Health, a prized award given to groups of collaborating scientists intent on solving well-defined problems. As a start, the Wilmot team recently received a pilot grant for $100,000 from Wilmot donor funds to seed the gathering of preliminary data needed to apply for the program award, with Mohile as the principal investigator.

"We've made a lot of progress in this field in 10 years and in the next 10 years we'll have many more answers," says Mohile. "But structure is still lacking and there is still not enough evidence to influence clinical care. We need ways to accurately predict what will happen to older patients when we give them cancer treatments."

Jeff Witherow

Biological Age vs. Chronological Age

Older adults traditionally have been excluded from clinical trials, usually due to co-existing medical conditions that make them ineligible. The result is a lack of national consensus to provide evidenced-based treatments for this fast-growing population. Most community oncologists are poorly prepared to cope with the complex care needs of older cancer patients, Mohile wrote in a recent review article published by the journal *Cancer.*

The facts underline the need for more research. By 2020, two-thirds of all cancer survivors are expected to be at least 65 years old. By 2030, 70 percent of all cancer patients are expected to be older than 65. Living longer has created new categories of old: "older old" (70-80 years), and "oldest old" (80+ years).

"The problem with cancer and aging is that normal issues associated with aging are layered on top of cancer," says Dirk Bohmann, Ph.D., Senior Associate Dean for Research at the University of Rochester Medical Center and a molecular biologist who is collaborating on the project. "You really have to consider the specific circumstances of each individual patient."

The true health status and age of older cancer patients is not always clear, he says, even when taking into account birth dates and routine measures such as blood pressure, gait, and cognitive function.

"Sometimes you see an 80-year-old rowing on the Erie Canal, looking as healthy as a much younger person, while another 80-year-old might be near death," adds Bohmann, the Donald M. Foster M.D. Professor of Biomedical Genetics. "It's tricky to get a good assessment of a patient's biological age without the appropriate data."

To do this, three different investigations will look at aging cells in new ways.

Michelle Janelsins, Ph.D., an assistant professor in the Cancer Control and Survivorship Program at Wilmot, is leading the collaborative efforts between basic and translational scientists on the team.

Her own investigation will focus on telomere length and epigenetic changes in older breast cancer patients receiving chemotherapy, to see if these DNA markers are a viable, objective predictor of frailty as opposed to chronological age, the number of years a patient has lived.

Telomeres are DNA sequences at the end of chromosomes; they have been compared to the small plastic or metal coverings at the end of shoelaces to keep them from fraying. Telomere length is a known biomarker for aging, with shorter telomeres often associated with early death, according to several prior studies.

Epigenetic changes also occur to DNA to alter gene expression related to aging. Scientists generally believe that cancer patients age at an accelerated rate, but no scientific studies have correlated telomere length and epigenetic aging to frailty or age in cancer patients. Janelsins has been collaborating with epigenetics researchers at the Roswell Park Cancer Institute in Buffalo, and their preliminary work suggests that epigenetic age is more highly correlated to actual age than telomere length – meaning that it might be a better indicator of a person's biological age and therefore could be used as a biomarker in cancer outcomes such as frailty.

For his part, Bohmann is investigating what happens when aging cells must cope with chemotherapy and other treatments. Under the best of circumstances (say, in a healthy 20-year-old), cells rapidly activate antioxidants to combat a stressful assault, whether it's from chemo, an infection, or disease. But the genes that regulate antioxidants become "rusty" with age, Bohmann says.

Such disruptions can leave older adults with fewer natural defense mechanisms and make them more vulnerable to the side effects of chemotherapy. Conversely, a patient who is chronologically old but has maintained younger, fitter genes can usually tolerate chemotherapy better.

Bohmann is developing a reliable blood test to measure "biological age" based on the genetic stress response observed in blood cells. In the laboratory, researchers expose cells collected from old and young breast cancer patients to chemotherapy and then measure how well the cells rally antioxidants. Researchers are also correlating the cellular stress response with other classic elements of frailty – such as dementia or a number of falls – which can be assessed independently. If a simple blood test proves to be accurate, doctors might be able to predict how well an older adult will tolerate treatment before it's prescribed and tailor the treatment individually.

Another collaborator and

Matt Wittmeyer

Marsha Wittink, M.D., studies how to empower older patients.

biologist, Vera Gorbunova, Ph.D., the Doris Johns Cherry Professor of Biology and professor of Oncology at Wilmot, studies aging, DNA repair, and cancer. She and Bohmann direct the Rochester Aging Research Center on campus. For the Wilmot project, Gorbunova is focusing on a set of genes known to fuel chemotherapy complications in older patients. Called "genomic parasites," L1 transcripts are particularly active in aging mice but can be repressed by antiretroviral medications commonly used to treat HIV patients, the Gorbunova lab recently discovered.

She's testing whether the level of L1 transcription in a cancer patient's blood can predict the ability to tolerate chemotherapy, and furthermore, whether elevated L1 might contribute to side effects such as "chemo-brain," the mental fogginess that burdens many cancer patients. A short course of an antiretroviral drug might reduce chemotherapy side effects, she hypothesizes.

"It would help oncologists and patients enormously if we had objective biomarkers for aging," Mohile says. "Biomarkers will let us know: If we give treatments to patients in the real world, what happens? What does the evidence say?"

The Human Side

In the "real world," older cancer patients also struggle with issues that have little to do with molecular aging. Like their younger counterparts, they may experience intense fear or misunderstandings with their doctors. But older patients also have some distinct needs, such as being able to express what they really want without feeling like they're a burden.

Marsha Wittink, M.D., MBE, a primary care physician and researcher at the University of Rochester whose work focuses

Michelle Janelsins, Ph.D., studies biomarkers for aging.

on improving health communication, recalls an episode of the *Seinfeld* sitcom in which Elaine asks her doctor a lot of questions and then frets about being labeled "difficult."

Cancer patients may avoid asking certain questions because they fear it will change the way their oncologist views them, Wittink says. They worry that their lives teeter on the actions of their doctors, and they want to leave a good impression. The role of anxiety and all of its manifestations – from treatment anxiety to fear of death – can be paralyzing for many patients, adds Paul Duberstein, Ph.D., a UR psychologist and professor of Psychiatry, Medicine, and Family Medicine.

When older adults are not fully informed and their perspective is not understood, it can lead to unnecessary and toxic treatments that are unlikely to prolong life and could possibly reduce the quality of the time they have left with family, he says.

"The big unknown, what we haven't asked older patients is: What is it that you really want?" Wittink says. Too often, health care providers make assumptions without empowering patients to ask the difficult questions. "Unpacking this information is so important. And the issues are more pressing for older people, who may have other health problems and varying degrees of family support."

Wittink developed a decision tool for primary care doctors that she's adapting exclusively for cancer patients. It consists of a short survey taken on an iPad, with questions designed to focus on health goals, and risks and benefits of treatment options. Older patients may want more information on how treatment will impact their brain function, mood, and independence. The software being used for this research project is similar to that which is used in consumer market research – allowing the respondent to make trade-offs in line with their personal preferences and values. For example: Are you willing to live with daily nausea if the treatment could significantly extend your life? Or would you rather live mostly symptom-free for the rest of your days?

Wittink plans to recruit patients from Mohile's specialized geriatric oncology clinic, based at UR Medicine's Highland Hospital, to test the decision tool in a randomized clinical study. "We believe the questions will help people feel a little bit more comfortable opening up," she says.

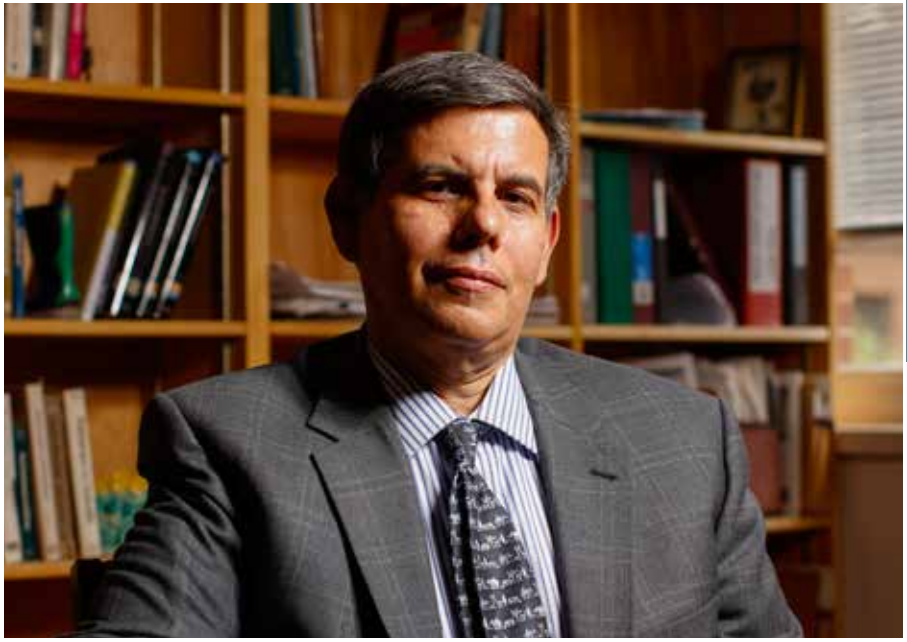
Duberstein is planning a separate research project to assess the role of anxiety among older patients and physicians in terms of treatment decisions, disease outcomes, and quality of life.

Including physicians in the study is unique, Duberstein says. His concern is that sometimes their anxiety influences doctors to offer more treatment, even when it's not warranted, because they don't want to feel as if they're "abandoning" their patients.

Other research has shown that a doctor's personality influences patient care – for example, more risk-averse physicians tend to order more tests – but no one has studied this in the high-stakes cancer setting.

"Our goal is to help cancer patients obtain the best quality of life they can," Duberstein says. "Not only do patients need tools to deal with anxiety, but doctors need the skills to handle very delicate situations. They should

Vera Gorbunova, Ph.D., studies genes that lead to chemotherapy complications.



Paul Duberstein, Ph.D., studies the role of anxiety in cancer care.

be able to say 'no' while being incredibly careful that they don't unwittingly send a message that we're 'giving up' once we run out of treatment options."

Until scientists come up with a cure for cancer, he adds, the doctor-patient relationship is perhaps the most powerful part of a patient's cancer journey.

Canin, the patient advocate, couldn't agree more. In fact, in 2015 she delivered a talk at the ASCO annual meeting giving the patient perspective on what "value in patient care" means to patients. Citing results from two surveys of people with advanced breast cancer, her message was: For cancer patients, "value" isn't primarily based on money or cost of care – but rather the relationship between patient and doctor. Canin received a standing ovation from the doctors in the audience, Mohile says.

"There's no way we could do this type of research without having people with different perspectives guiding us and taking part," Mohile says. "Beverly, among others, has really opened my eyes: What should I look at first? What's the most important area to focus on from all of my data? She's made me realize that it's not all about the researchers."

"Having said that," Mohile adds, "it's also very important to have a diverse and talented research team to explore the many aspects of this growing field." WCI

Researchers Matt Asare, left, and Charlie Kamen, look at a map with a group of refugees at Mary's Place Outreach Center in Rochester. The pair is investigating the best ways to deliver clinical trial information to underserved and minority communities.

Building Bridges: Researchers Link to Community

On a blustery afternoon in October, Charles Kamen, Ph.D., and Matt Asare, Ph.D., could be found at Mary's Place Refugee Outreach Center, helping a group of women from Bhutan, Nepal, and Somalia read a map of the city of Rochester. The women take part in classes, receive donations of food and clothing, and learn how to get on the path to citizenship with help from Mary's Place.

While Asare's and Kamen's immediate task was to help tutor the refugees in English, their long-term goal was to build a bridge—one that starts at the University of Rochester Medical Center and the Wilmot Cancer Institute and extends into new and unfamiliar communities.

As researchers in Wilmot's Cancer Control and Survivorship Program, Kamen and Asare have been focusing on the best ways to deliver clinical trials to underserved patients and minorities, and to educate cancer patients everywhere about clinical research. Their goal is to design studies that are accessible to people in all types of communities, from center cities to rural outposts.

"What we've found is that we can design studies very well but the community piece is a lot more difficult," Kamen says. "We're trying to figure out how to modify studies to make sure everyone who wants access has access."

Most cancer patients learn about clinical trials through their physicians. But a lot of opportunity for education exists outside of doctors' offices.

As a starting point, Kamen conducted a pilot research project with the objective of pushing Wilmot research coordinators into areas that are often underserved by the health care system. The project is titled the Minority/Underserved Research, Action, and Learning (MURAL) program. Eight research staff members agreed to take part. They reached out to African Americans, Latinos, the LGBTQ community, older adults, and adolescent cancer survivors.

"We wanted the research coordinators, who are on the front lines, to be able to sit down with someone who didn't look like them and might have a different cultural background, but still be able to help them understand a clinical trial," Kamen says.

That's how Sandy Plumb, a research program manager at the UR, met Annette Jimenez, a writer for the local Spanish-language newspaper, *El Mensajero Catolico.* They talked about diversity and health care barriers such as communication and transportation; and then Jimenez wrote a newspaper story about Kamen's and Plumb's goal to educate local Latino groups about clinical studies.

Other research coordinators linked up with the Women of Color group at Gilda's Club and Out and Equal NY Finger Lakes, an organization associated with the Gay Alliance that supports safe and inclusive workplace environments.

"If you really look into the community, you can find events, organizations, and plenty of places to showcase what Wilmot is doing," Kamen says. "People have been really appreciative that we're bringing information to them."

Anne Tischer, coordinator for a Gay Alliance-associated program called SAGE (Services and Advocacy for GLBT Elders), couldn't agree more. Kamen presented information directly to 35 SAGE members at a luncheon, and they ended up having a "very lively and smart discussion" about clinical trials, cancer, and Wilmot, she says.

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"Ours is a community that responds to direct, face-to-face outreach," Tischer says, noting that because the LGBT community has for years been labeled "at risk," its members tend to avoid doctors and therefore have significant levels of chronic disease. Sometimes they also lack traditional family and faith community support, which creates the need for new safety networks.

"Everybody knows somebody that has cancer," Tischer says, "and knowing about options is important."

Word-of-mouth about the outreach efforts is starting to pay off. Kamen received a call from an out-of-town cancer patient, for example, who heard about his diversity initiative in Rochester.

"You can't just dip your toe in and then jump out," he says. "This must be a sustained effort and it will take some time."

New Directions

Another bridge is being built, too, but this one is within the URMC: It links Wilmot more closely to the Center for Community Health. Led by Nancy Bennett, M.D., M.S., the Center for years has been connecting with community partners to address health concerns, improve access to care, and encourage healthy lifestyles to prevent disease. Going forward, Bennett says, the Center will become the cancer prevention arm of Wilmot.

For example, Bennett and Candice Lucas, director of the Cancer Services Program of Monroe County at the Center for Community Health, plan to bring healthy lifestyle programs and services to promote education about cancer prevention and risk reduction into rural communities in the Finger Lakes region where Wilmot has satellite treatment centers.

They're already spreading the cancer-prevention message through collaborations with the Livingston County Health Department and at Dansville, N.Y.-based Noyes Health, an affiliate of UR Medicine. Encouraging more exercise and reading food labels are two examples of what they preach. The Center's research shows that the best approach is to focus on permanent lifestyle changes that improve health.

New research directions, Bennett says, include finding out how to implement the Center's successful diabetes prevention program – which is essentially a cancer-prevention program because it emphasizes physical activity, no smoking, and proper nutrition – into the general population.

"Primary cancer prevention is still a challenge," Bennett says. "Although we have solid evidence that many cancers are preventable by not smoking and maintaining a healthy weight, science is just not where it needs to be. Our health care system was predominantly built on providing treatment and very little has been spent on disease prevention or prevention research. So there's a lot of room for change."

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Candice Lucas, in orange jacket, of the UR Center for Community Health, presents information on breast cancer disparities research to the African American Health Coalition at the Finger Lakes Health Systems Agency. A key mission for the Center is finding the best ways to engage underserved populations.

As Wilmot Cancer Institute has expanded its clinical operations, it has also brought opportunities for regional patients to participate in clinical trials and for local agencies to partner on research projects to improve prevention and care in their communities.

Connection

Laura Calvi, M.D., left, and Jacky Williams, Ph.D., are studying the tumor microenvironment using a recently purchased, high-technology device. The instrument will allow them to look more deeply into connections between cancer cells and surrounding tissues.

Cellular Environment Surrounding Cancer Cells: Friend or Foe?

The cells and tissues located adjacent to and within a tumor make up a unique microenvironment, which may play either a positive or negative role in cancer. Either way, scientists believe that the surrounding neighborhood has a powerful influence on how a tumor behaves – or whether cancer even develops in the first place.

Studying the microenvironment is a research pillar at the Wilmot Cancer Institute, and scientists are looking at it from every angle.

David Linehan, M.D., clinical director at Wilmot and a pancreatic cancer specialist, for example, is studying the role of the tumor microenvironment and the immune response to pancreas cancer. Linehan investigates a type of non-cancer cell known as tumor-associated macrophages (TAMs), which reside in the dense tissues surrounding pancreas tumors. He discovered that patients with high levels of TAMs are more likely to have a recurrence after surgery, and is investigating treatments that may block the mobilization of TAMs. In addition to recent funding from the national Pancreatic Cancer Action Network (PANCAN), Linehan also was recently awarded a SPORE project through Washington University in St. Louis to continue his study of pancreatic cancer.

Another Wilmot researcher, Jacky Williams, Ph.D., a professor in Environmental Medicine and Radiation Oncology, studies how radiation treatment disrupts the microenvironment. Even when radiotherapy is aimed precisely at cancer cells, she explains, the environment of the surrounding normal cells can become chronically imbalanced. This might lead to serious treatment effects, such as fibrosis experienced by some patients following radiation therapy for lung cancer. It also might offer an explanation for second tumors that arise years after treatment ends.

"In the past, much of the focus of preventative measures for radiation has been on inflammation as the cause for the changes after therapy," Williams says. "But we believe that when the normal microenvironment near cancer cells is disrupted, it might undergo a chronic remodeling that can cause treatment side effects and also create a comfortable place for a new cancer to develop."

Williams recently received a large instrument grant from the National Institutes of Health, supporting a new, high-technology device enabling scientists to study models of lung, kidney, bone, prostate, and brain tumors, to learn exactly what happens in the microenvironment as cancer develops, during treatment, and when the tumor disappears or re-appears.

Wilmot is investing further in the new equipment, which is a type of tomotherapy (a delivery system for radiation), to study cancer's interaction with the microenvironment more deeply. Because the microenvironment is so complex, it's difficult to untangle the positive and negative impact on cancer, says Laura Calvi, M.D., Dean's Professor of Medicine, Wilmot investigator, and an endocrinologist. Her interest is to focus on ways that the cells and tissues surrounding a tumor can be rallied to eliminate the cancer. For several years she has been studying the microenvironment in the context of blood cancers, which arise in the stem cells of the bone marrow. Her approach has been unique among blood cancer researchers, as she is looking for ways to target the bone marrow microenvironment to spur production of healthy blood cells.

"If we can activate those components that are normal and healthy to combat cancer," she says, "we'll have an additional tool."

Williams and Calvi received a pilot grant from Wilmot, leveraging the new equipment, allowing them to gather preliminary data and apply for a larger award from the National Cancer Institute.

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"We're part of the movement to change the future of gynecologic oncology," says Sajeena Thomas, M.D., of a growing portfolio of clinical trials for women with gynecologic cancers at Wilmot Cancer Institute.

New Clinical Trials Advance Treatment, Diagnosis of Gynecologic Cancers

For nearly five months, Christine Snyder traveled from her home south of Syracuse to Wilmot Cancer Institute to participate in a clinical trial. She came every three weeks for treatment as part of a study evaluating whether chemotherapy alone would be as effective as chemo and surgery for recurrent ovarian cancer.

The trial is one of about a dozen that have opened this year at Wilmot through the National Cancer Institute and NRG Oncology, a nonprofit cooperative group that leads clinical research with institutions nationwide. These trials address persistent questions about treatment for a variety of gynecologic cancers, including cervical, endometrial and ovarian, and Wilmot offers the most extensive portfolio of these trials in the region.

In addition to large national treatment trials, Wilmot also offers trials that are available only in Rochester, including one that is evaluating potential molecular biomarkers to predict the risk of a pelvic mass becoming cancerous.

"We're part of the movement to change the future of gynecologic oncology," says Sajeena Thomas, M.D., one of Wilmot's gynecologic oncologists. "It's phenomenal to offer patients trials that will have a role in shaping what will become the standard of care."

For many gynecologic cancers, progress in improving survival has been slow, and there have been few advances over the last decade. Researchers are now looking at treatment options beyond chemotherapy, and many of the trials at Wilmot focus on targeted therapies. Unlike chemotherapy – which is relatively indiscriminate in its impact on cells – targeted therapies act on specific genes or other molecules involved in the growth, progression and spread of cancer.

"We're learning more about how cancers develop, what their weaknesses are and how to exploit them," says Richard Moore, M.D., chief of Gynecologic Oncology at Wilmot Cancer Institute. "Every day, new targets are identified, as are new drugs that can take advantage of that target."

Among those is a new class of drugs called PARP inhibitors, which block an enzyme in cancer cells that helps repair damaged DNA. These drugs, which are in trials at Wilmot, have shown promise in delaying the recurrence of ovarian cancers among women who have mutations of the BRCA genes and for those with different genetic profiles.

"Especially at a center like this, it's important to offer our community cutting-edge care and to allow access to drugs that aren't widely available," Moore says.

Although targeted therapies and precision medicine are promising, their very nature means they do not work on every cancer, and scientists at Wilmot are looking for more possibilities.

Moore leads a team in Wilmot's Targeted Therapeutics Laboratory for Gynecologic Cancers who are developing new molecules that could one day become therapies that leverage different features of tumors. For example, they are focusing on molecules that would counteract a protein called HE4, which is a marker for ovarian cancer.

In addition, this team is part of a clinical trial studying tumor cells circulating in the blood of women who have a pelvic mass. The aim of the study is to identify biomarkers and develop a test that uses them to estimate the risk of the mass being malignant. Wilmot is the only site in the U.S. to participate in this study, which is also being conducted in Europe.

Patients like Snyder, whose cancer returned in the spring, are coming from hours away to participate in these studies.

"Being involved in a clinical trial has been no inconvenience for me by any stretch," Snyder says. "I firmly believe in the research that goes on and anything we can do to evade cancer."

Although she had never before considered taking part in a trial, Snyder agreed after Thomas presented the option to her. A tax accountant, Snyder has never been one to sit idle.

"You can lay around and bemoan the fact that you're sick," she says with a shrug. "Do what you can."

Matt Wittmeyer

Pathologist Jennifer Findeis-Hosey, M.D., is working with colleagues at Wilmot Cancer Institute to find ways to identify families affected by Lynch syndrome as early as possible.

Pathologist Seeks Earlier Answers for Families with Lynch Syndrome

Lynch syndrome is one of the most common inherited conditions that raises a person's risk of colorectal cancer. It can also raise the risk of developing other gastrointestinal and gynecologic cancers, often at younger ages than average.

Until recently, diagnosis of Lynch syndrome has relied on family history – at least three relatives with a Lynch-associated cancer, among other criteria – or on tumor testing, if a physician indicated a patient might be at risk. Without those pieces, individuals are not referred for the genetic testing that would confirm Lynch syndrome.

As families have gotten smaller and knowledge about relatives' health history has become more limited, applying those criteria have been less effective in identifying people at risk for Lynch syndrome.

Pathologist Jennifer Findeis-Hosey, M.D., is trying to improve that process. Her goal is to identify clinical and pathological features of colon polyps that may indicate the condition before an individual at risk has developed cancer. An estimated 3 percent to 5 percent of new colorectal cancers are associated with Lynch syndrome, and the presence of the condition can affect treatment options for those who already have cancer. Many people, however, are diagnosed after they have not only developed cancer but also after they have had surgery.

"This would shift the clock back," says Findeis-Hosey, who specializes in identifying gastrointestinal cancers. "We could identify patients at an earlier age and earlier stage."

Her work aligns with the national public health objective of increasing the proportion of people who receive genetic testing to identify Lynch or other familial colorectal cancer syndromes. She is also collaborating with colleagues across the University of Rochester Medical Center to develop a system that ensures patients with Lynch syndrome and their families get the genetic testing, counseling and follow-up care they need.

Four years ago, Findeis-Hosey began performing immunohistochemistry (IHC) testing on all colorectal cancer resections performed at Strong and Highland hospitals – regardless of whether they had been flagged for possible Lynch syndrome. She used special dyes to stain the tissue and determine whether certain proteins were absent. The absence of those proteins indicates that an individual may have Lynch syndrome, and that person is then referred for genetic testing.

But that was still identifying people after they had already undergone surgery.

"For some patients, if they are identified early, this could alter their disease management and treatment options," says Chin-To Fong, M.D., who leads the Genetics team at URMC and works with Findeis-Hosey. "They may be at higher risk of other cancers and would benefit from other surveillance options."

Their families also need to be screened for Lynch syndrome, and those who are identified could also benefit from more aggressive surveillance.

"For every affected person, there are about five or six at-risk people who are invisible to us without screening," Fong says. First-degree relatives of individuals with Lynch syndrome – parents, siblings and children – have a 50 percent chance of also having the condition.

Findeis-Hosey and her team then began to explore whether using IHC on biopsied tissue would be just as effective. After verifying that this technique produced comparable results, they began routinely staining all colorectal cancer biopsies, allowing patients and their families to be referred for genetic testing and counseling before surgery.

Findeis-Hosey is now conducting a study that uses the same technique on large, advanced polyps that are removed during a colonscopy – before cancer has developed.

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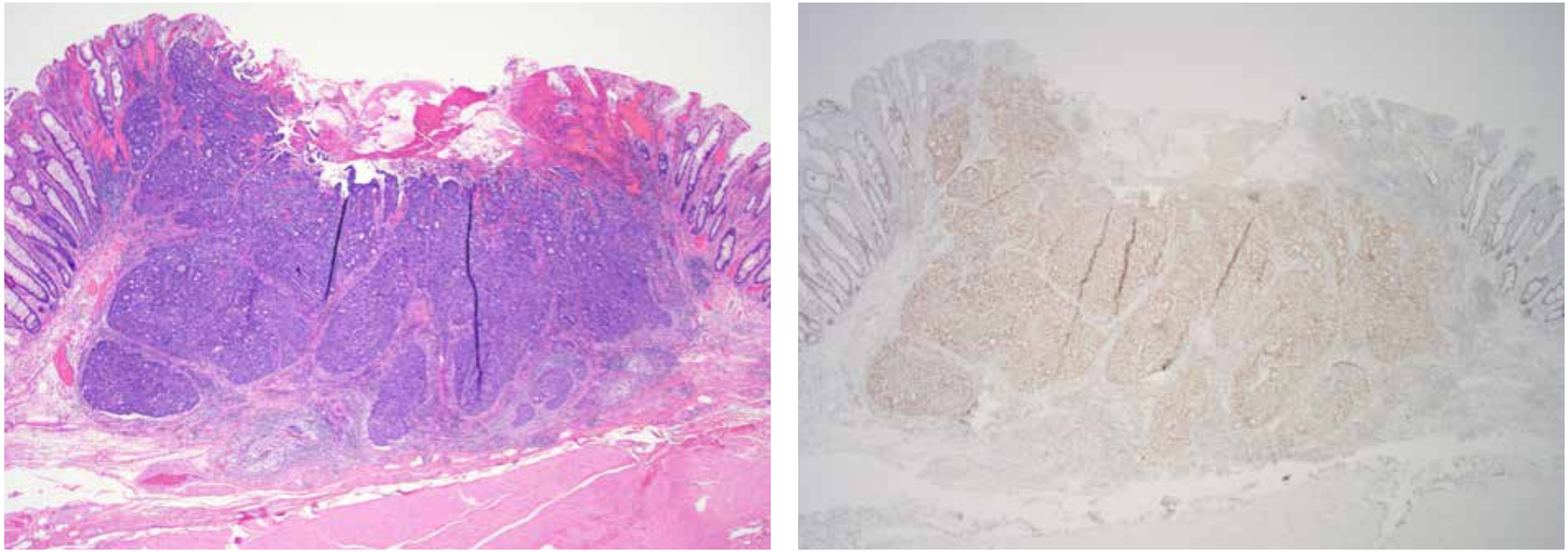

When pathologists examine tissue samples under a microscope, they stain the specimen to highlight different types or parts of cells. In the colon tissue specimen on the left, the presence of cancer – adenocarcinoma – is indicated by the closely packed bright purple cells. The specimen on the right, obtained from the same tissue sample, was stained with a different set of dyes to detect mismatch repair proteins associated with Lynch syndrome. In this specimen, the brown staining highlights the normal expression of one of those proteins, indicating that Lynch syndrome is less likely.

She is collaborating with UR Medicine gastroenterologists Danielle Marino, M.D., and Arthur DeCross, M.D., who work closely with a community group called Strollin' for the Colon, which was started by a family with Lynch syndrome and which is funding some of Findeis-Hosey's research.

"This is the type of research that will have an impact on national guidelines," DeCross says. "The old clinical guidelines of identifying Lynch families are hard to apply today where nuclear families are smaller."

Earlier identification means that individuals with Lynch syndrome may begin cancer screenings at younger ages and more frequently than the national recommendations. That means that their cancers may be caught earlier, giving them more treatment options.

"Early detection is so important," says Tina Cottone, who started Strollin' for the Colon. "It saves lives."

It also requires a system that ensures these individuals have genetic testing in a timely manner and that meets their ongoing needs, a feat proving more complicated than the science.

"The science is straightforward," Findeis-Hosey says. "But you need a multimodal process to make sure people get the genetic testing."

Once a person is identified as a candidate for testing, they have to be referred to Genetics by their primary care provider,

Chin-to Fong, M.D.

Arthur DeCross, M.D.

Danielle Marino, M.D.

surgeon or other physician. Because the pathologists can't make that connection directly, Findeis-Hosey is working with DeCross and Marino, involving their colleagues from Gastroenterology, Gynecologic Oncology and Hematology/ Oncology to close that gap. They are also collaborating to create a multidisciplinary clinic for individuals at high risk for certain cancers because of genetic predisposition.

"We are pulling in other disease areas because Lynch syndrome isn't just colorectal cancers," Findeis-Hosey says. It can also lead to endometrial, ovarian, urinary tract, stomach and liver/ bile duct cancers, among others.

They are also working to educate community physicians – including primary care physicians and gastroenterologists – about Lynch syndrome and the importance of testing patients who are at risk.

"Community education is key," Marino says. "Hopefully we can identify families earlier and ultimately prevent some cancers." WCI

Bruce Zicari, center, and his brother John tour the laboratory of Wilmot scientist Michelle Janelsins, Ph.D. Through their nonprofit Nancy and Friends, the Zicaris funded a seed grant that was awarded to Janelsins to study chemo-brain.

Return on Investment: Wilmot's Seed Grants Program Supports Promising Research Projects

When his sister Nancy was diagnosed a second time with breast cancer in 1999, Bruce Zicari and his family established a nonprofit organization devoted to supporting cancer research. The group, called Nancy and Friends Fighting Cancer Inc., began raising money and looking for the best ways to use those funds.

"We felt we had so much more we could do to come up with better treatment options," says Zicari, whose sister died in 2002. "We wanted to make a difference so others wouldn't have to go through the same thing down the line."

They decided to use their funds – over $400,000 raised to date – to support seed grants for researchers at Wilmot Cancer Institute. Seed grants, also known as pilot grants, are akin to start-up funding in the business world. These grants are competitive, and applications are carefully reviewed by a select committee of Wilmot faculty. They are funded by local donors who, like angel investors, support the initial stages of a project.

Seed grants allow researchers to build a case for further investment in their work by such major funders as the National Cancer Institute and National Institutes of Health. They are a critical resource for researchers seeking to submit competitive grant proposals at a time when less than 20 percent of applications to the NIH are likely to be funded.

Over six years, Wilmot's seed grants program has awarded nearly $2 million to researchers at the University of Rochester. It has enabled them to begin exploring new questions about the biology of cancer, novel therapeutic approaches and ways to mitigate side effects of treatment. With one-time seed grants of $25,000 to $50,000, these researchers have been able to demonstrate the promise of their work and secure $12.3 million in NCI, NIH and other major funding – a 523 percent return on investment – to continue it.

Scientist Michelle Janelsins, Ph.D., MPH, received a $25,000 seed grant funded by Nancy and Friends in 2011. The grant allowed her to open a pilot study examining the role of exercise in alleviating treatment-related cognitive problems commonly called chemobrain. The findings from that study provided the basis for her to launch the largest study to date investigating the impact of cancer treatment on cognitive function.

"The seed grant was really key because it allowed me to gather important initial feasibility data and helped establish me as a scientist with early publications," says Janelsins, a member of Wilmot's Cancer Control and Survivorship research team. "Knowing that the money for the seed grant came from people who had in some way been impacted by cancer really touched me. I am able to use that money to make a difference."

As a result of her seed grant, Janelsins has been able to secure an NCI career development award, an NIH Director's New Innovator Award and other funding totaling more than $5 million to continue her research.

Her main hypothesis is that inflammation may fuel cognitive impairment in cancer patients, and she is bringing a new approach to cancer-control research by starting with bench science, rather than the more typical route of focusing on clinical studies with patient volunteers. She is developing a clinically relevant mouse model to study key mechanisms for chemobrain and then test potential treatments including exercise, fish oil, and over-the-counter anti-inflammatories.

"We're thrilled that Michelle has been able to turn a small donation into something larger, that she parlayed it into millions of dollars and useful research to make people's lives better," Zicari says. "It means a lot to my entire family. It keeps the spirit of my sister alive."

While the primary goals of

Matt Wittmeyer

Andrei Seluanov, Ph.D.

the seed grant program are advancing science and cancer care, the program also serves as an economic amplifier.

"Seed grant funding has a strong impact on our ability to employ individuals, and it strengthens the economic health of our community," says Hucky Land, Ph.D., Wilmot's co-director and director of research.

The funds can help cover the salaries of lab staff, and when researchers are able to secure federal funding as a result of their work with seed funds, they can also create jobs.

Janelsins, for example, has been able to add three full-time staff to her lab, as well as offer paid positions to undergraduate and graduate students seeking research experience. She also has the opportunity to mentor junior faculty.

Biologist Andrei Seluanov, Ph.D., who received a $50,000 Wilmot seed grant in 2014 and later NIH funding, was able to add five post-doctoral researchers and two lab technicians, as well as cover the salary of a research associate whose job would have otherwise been eliminated.

Selanuov's grant was funded by donations given through Wilmot's annual Discovery Ball. He and his team are studying the effect of hyaluronan, a chemical that triggers an anti-cancer response in the naked mole rat. These hairless rodents have never been known to get cancer, despite their 30-year lifespan.

The seed funding allowed Seluanov's team to create mice that carry the gene responsible for hyaluronan production in naked mole rats. Seluanov and his colleagues are now testing these mice to determine whether they will also become resistant to cancer.

"Without the grant, we wouldn't be able to have these mice," he says. That work helped support a program grant application to the NIH to study strategies to delay human aging. Seluanov and his team received a portion of the resulting five-year NIH program grant involving faculty from the University of Rochester, Harvard and Albert Einstein College of Medicine.

Seed grant funding is an important mechanism for growing and maintaining a strong research program, Land says. Direct community support is crucial to ensuring that this program continues.

Funding for the seed grants comes from individuals who donate at events such as the Discovery Ball, Wilmot Cancer Research Day and the Wilmot Warrior Walk. It also comes from gifts to local giving circles, such as the Breast Cancer Research Initiative; organizations like Nancy and Friends and the Edelman-Gardner Research Foundation; and from companies such as Kovalsky Carr Electric Supply Co. and Zeller Corp. Although many of the donations that make up these gifts are less than $500, together they have an impact.

"There are very few multi-million-dollar donors out there, and if we're going to do anything meaningful, we have to have many small donations," Zicari says. "It does make a difference." WCI

BY THE NUMBERS

40:
Number of seed grants given since 2011

$1.975 million:
Value of seed grants distributed since 2011

$12.3 million:
Value of NCI, NIH and other major funding resulting from seed-funded research

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Events like the Wilmot Warrior Walk raise funds to support cancer research in Rochester. Thank you to Christian Flooring, the event's signature sponsor.

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At Wilmot Cancer Institute, science helps the people we treat every day. We investigate the roots of cancer, search for new therapies,and provide precision care based on new discoveries. Our research program is unique in upstate New York, and it is growing as we build more diverse teams and form new partnerships. Thank you for supporting our commitment to cancer research and improving care. To stay up-to-date with our programs and progress, please visit wilmot.urmc.edu and follow us on Facebook and Twitter.

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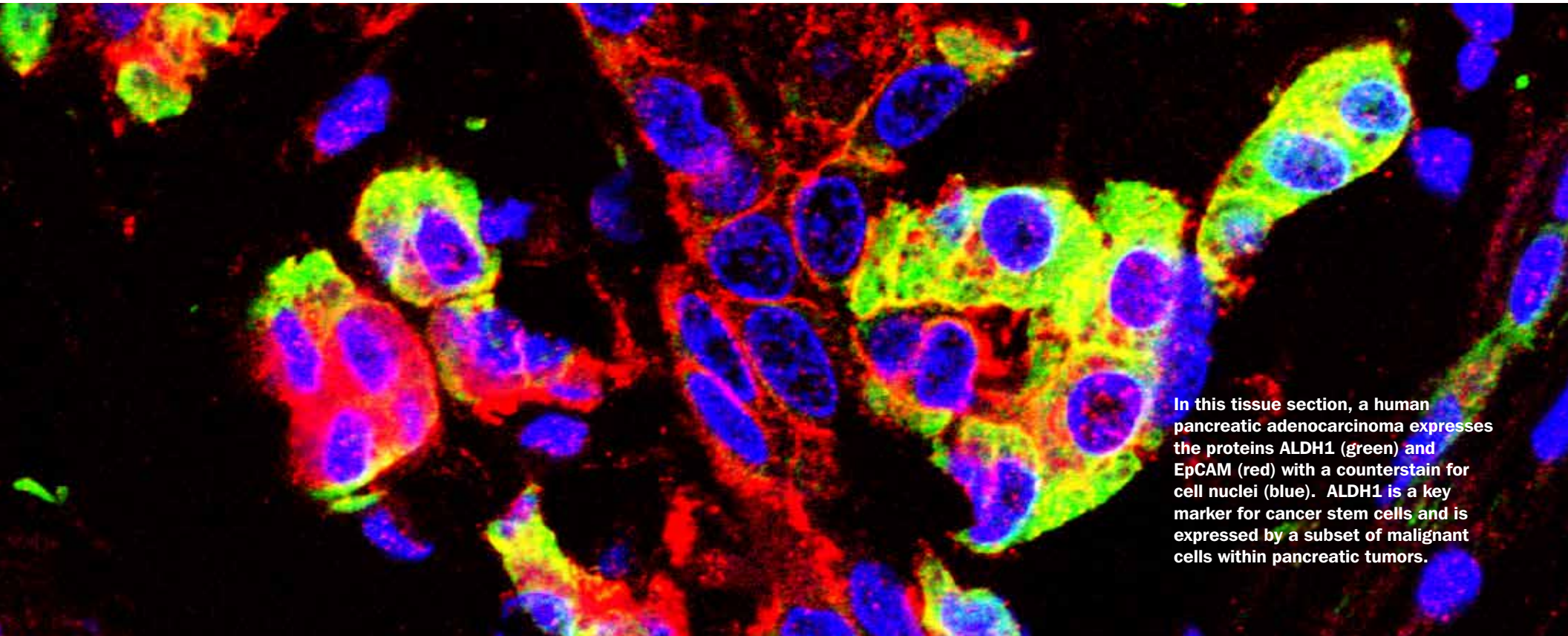

In this tissue section, a human pancreatic adenocarcinoma expresses the proteins ALDH1 (green) and EpCAM (red) with a counterstain for cell nuclei (blue). ALDH1 is a key marker for cancer stem cells and is expressed by a subset of malignant cells within pancreatic tumors.