CELEBRATING TEN YEARS OF breakthroughs

YALE CANCER CENTER
SMILOW CANCER HOSPITAL

SMILOW CANCER HOSPITAL

AND YALE CANCER CENTER

DELIVER TRANSFORMATIVE

SCIENTIFIC BREAKTHROUGHS

AND PATIENT CARE

INNOVATIONS TO BRING US

CLOSER TO A WORLD

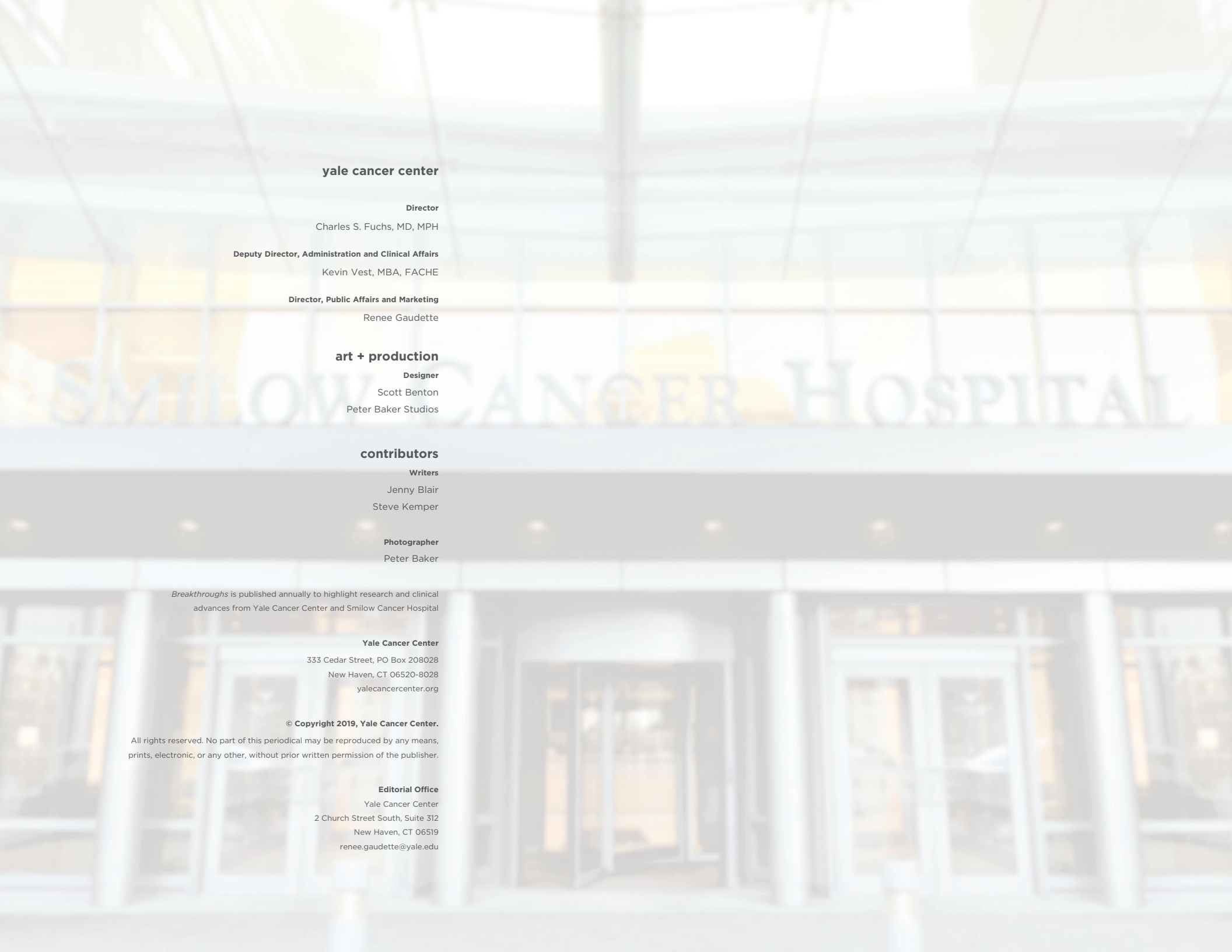
FREE OF CANCER –

ONE PATIENT AT A TIME.


CELEBRATING TEN YEARS OF

BREAKTHROUGHS AT SMILOW


SMILOW
CANCER
HOSPITAL
CELEBRATING TEN
YEARS
OF PATIENT CARE
10



yale cancer center

Director

Charles S. Fuchs, MD, MPH

Deputy Director, Administration and Clinical Affairs

Kevin Vest, MBA, FACHE

Director, Public Affairs and Marketing

Renee Gaudette

art + production

Designer

Scott Benton

Peter Baker Studios

contributors

Writers

Jenny Blair

Steve Kemper

Photographer

Peter Baker

Breakthroughs is published annually to highlight research and clinical advances from Yale Cancer Center and Smilow Cancer Hospital

Yale Cancer Center

333 Cedar Street, PO Box 208028

New Haven, CT 06520-8028

yalecancercenter.org

Editorial Office

Yale Cancer Center

2 Church Street South, Suite 312

New Haven, CT 06519

renee.gaudette@yale.edu

features

research programs

leadership, membership, and data

As Smilow Cancer Hospital celebrates 10 years of exceptional patient care and groundbreaking research and discovery, I pause to recognize the countless patients and families who have put their faith in our outstanding faculty and staff in New Haven and across our 15 Smilow Cancer Hospital Care Centers. I am equally appreciative of our physicians, scientists, caregivers, and staff who continue to strive to advance cancer care each and every day. I am confident that the incredible breakthroughs reported from our laboratories and clinics are impacting cancer treatment and care globally, and we are collectively proud to share those advances directly with our patients throughout the Smilow Cancer Hospital Network.

The impact of immunotherapy over the last decade has been transformational, and Yale Cancer Center and Smilow Cancer Hospital are leaders in the cancer immunotherapy revolution, beginning with Dr. Lieping Chen's early discovery of PD-1 and PD-L1. In the subsequent years, clinical trials using immunotherapy blossomed at Smilow Cancer Hospital with patients Maureen O'Grady and Bob Amendola paving the way in 2010. While immunotherapies have changed the outcome for many patients, there is still considerably more progress to be made. We are confident in the promise of the exciting new discoveries at our Center that will launch the next generation of breakthroughs in cancer immunotherapy.

Members of our seven research programs led 935 scientific publications last year, generating new data, new discussions, and new outcomes to meaningfully improve the course of cancer care. Our total direct research funding hit an all-time high at $99 million and continues to grow with new grants submitted each month. The collaborations between our research programs and clinical programs, through our Disease Aligned Research Teams, are effectively advancing innovations from our laboratories to benefit patients in our clinics while, at the same time, bringing data back from our clinics to inform future laboratory discoveries.

While this 10th anniversary is a historic milestone, we know our work continues and look forward to the next decade of innovation and breakthroughs at Smilow Cancer Hospital and our Smilow Cancer Hospital Network. Our leadership team is relentlessly committed to the clinical, research, educational, and outreach missions of Yale Cancer Center and Smilow Cancer Hospital, as we lead new discoveries in cancer prevention, early detection, and treatment for patients across the globe.

While this 10th anniversary is a historic milestone, we know our work continues and look forward to the next decade of innovation and breakthroughs at Smilow Cancer Hospital and our Smilow Cancer Hospital Network.

Sincerely,

Charles S. Fuchs, MD, MPH
Director, Yale Cancer Center
Physician-in-Chief, Smilow Cancer Hospital

SMILOW

Celebrating a Decade of Cancer Care

In October of 2009, the first patients walked into the new Smilow Cancer Hospital at Yale New Haven. Cancer care has not been the same since. "Our 10th anniversary is so exciting because Smilow catalyzed one of the most impressive trajectories of clinical care, cancer research, and education and training that has ever been witnessed in an NCI-designated cancer center," said Charles Fuchs, MD, MPH, Physician-in-Chief of Smilow and Director of Yale Cancer Center. "The opening of Smilow was transformative. It has had an extraordinary impact in terms of discovery and clinical care, not only regionally, but nationally and internationally as well."

The hospital is named for the generous philanthropist who made it happen, Joel Smilow. "The dream of the hospital leadership," said Roy S. Herbst, MD, PhD, Ensign Professor of Medicine, Chief of Medical Oncology at Yale Cancer Center and Smilow Cancer Hospital, and Associate Cancer Center Director for Translational Research, "was to have a cancer hospital with everything

there—one-stop shopping. You could get your biopsy, your blood work, your echocardiogram. You could see your oncologist, your surgeon, your radiation oncologist, all together. Their vision, transformed the care of our patients."

Dr. Herbst remembers walking around the Smilow construction site in a hard hat when he was being recruited from MD Anderson Cancer Center in Houston and getting excited by the ambitious plans for the hospital. Needless to say, he signed up.

"Having the beds and state-of-the-art operating rooms and clinical spaces helped us recruit top doctors and nurses," he said. "We populated the space with the best people, the best technology, the best innovative medicine, and the best clinical trials. We had a vision to build personalized care in terms of the patient's feelings and experiences. I have to give big credit for all this to Tom Lynch, Abe Lopman and Cathy Lyons."

Dr. Herbst is referring to the trio who steered Smilow into existence and then into national prominence, and who set the hospital's guiding principles: Thomas J. Lynch, Jr., MD, Smilow's founding Physician-in-Chief; Abe Lopman, the hospital's founding Executive Director; and Catherine A. Lyons, RN, MS, the inaugural Chief Nursing Officer. While they have moved on, their legacy continues.

Smilow's trajectory over the last 10 years shows vectors of rapid expansion in every area. A few statistics tell part of the story. The staff at Smilow has grown by 55 percent, to nearly 2,000 people. The number of patient visits has risen steeply, from 179,000 in 2014 to 236,000 in 2019, a figure that Dr. Fuchs says rivals any of the major cancer centers in the United States. In Connecticut, about 48 percent of all patients newly diagnosed with cancer are cared for by a Smilow physician. "That's an incredibly impressive statistic, considering that Smilow opened only 10 years ago," said Dr. Fuchs.

The hospital has also expanded geographically. Fifteen Smilow Cancer Hospital Care Centers are scattered across Connecticut and, with the recent addition of a Center in Westerly, Rhode Island, Smilow has started to bring its services to the broader region. Another new Center will open this year [2020] in Springfield, Massachusetts and planning has started for one in Westchester, New York. About a quarter of all Smilow patients are enrolled in clinical trials at the Care Centers, rare among major cancer center networks.

"We are dedicated to addressing the clinical care needs of the wider community," said Dr. Fuchs. "Our commitment is that patients should not have to travel more than 30 minutes to get destination cancer care, which allows us to provide care across the state and beyond. We want to make clinical research and clinical trials available to patients throughout the region." He points out that 85 percent of the cancer patients in the United States don't receive their care from academic research cancer centers such as Smilow because such centers are few and far between. The NCI has designated only 51 institutions as

"The commitment to our mission by our faculty and staff and everyone involved is inspiring. It's a privilege to work here every day." - DR. CHARLES FUCHS

comprehensive cancer centers; Smilow/Yale Cancer Center is the only one in Connecticut.

Clinical trials are another area that has boomed at Smilow over the last 10 years. When the hospital opened, about 250 patients were enrolled in trials. That number is now close to 900 per year.

But numbers alone don't tell the story. In the last decade, discoveries from clinical trials at Smilow have altered the treatment of cancer patients worldwide. Breakthroughs in immunotherapy pioneered by Lieping Chen, MD, PhD, United Technologies Corporation Professor in Cancer Research and Professor of Immunobiology, of Dermatology, and of Medical Oncology, and tested in trials at Smilow by Yale clinicians, have led to six FDA-approved checkpoint inhibitors that have revolutionized the standard of care in more than a dozen types of cancer. Dr. Chen's newest checkpoint inhibitor, targeting Siglec-15, is now in early trials and may usher in a new generation of important immunotherapies. Smilow is also in the forefront for other advances. Early last year [2019] Smilow launched a program that delivers CAR T-Cell therapy to appropriate patients, an exciting new immunotherapy that collects and alters a patient's own T cells, then injects them back into the patient to fight cancer. Smilow scientists are also developing and testing therapies based on protein degradation, DNA repair, and other biological opportunities.

Dr. Fuchs points out that just in the past 18 months, more than half a dozen studies and trials by Smilow scientists have significantly changed medicine's understanding of lung, gastric, bladder, head and neck, colon, endometrial, and urothelial cancers. "Each of these is practice-changing," said Dr. Fuchs, "leading to new FDA approvals. Most cancer centers, if they get just one of these in five years, that's a sign of success."

As Smilow's reputation has grown, so has its research funding—from $58 million in 2012 to $99 million. The institution's most recent CCSG (Cancer Center Support Grant) from the NCI increased in funding by 73 percent. "A pretty unprecedented increase," said Dr. Fuchs. The next highest increase for a cancer center was 38 percent.

Success creates its own challenges. The hospital's 15 floors are always full. "Smilow is bursting at the seams," explained Dr. Fuchs. "We have to think innovatively about how we use the space and create new space. And as we grow the clinical operation, we have to make sure we do not lose the important intimacy between the patient, their family, and the clinicians. That's paramount. We also have to make sure our caregivers—and by that I mean everybody in the hospital, not just doctors and nurses but the people who clean rooms, who provide meals, who enroll people in clinical trials—that we make sure we create an environment that recognizes their contribution. Because we not only want to be the best place to receive care, but the best place to work in healthcare."

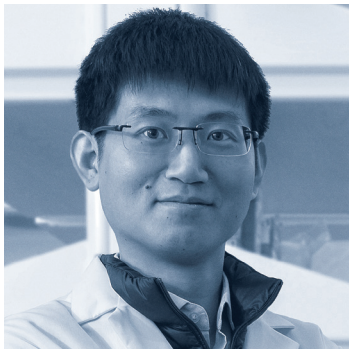
The leadership are working together on many plans to make Smilow's second decade as impressive as its first. All are aimed at maximizing the hospital's impact on patient care, cancer science, and the community. The community has responded. Everyone at Smilow has stories. Dr. Herbst remembers going to a restaurant one evening with his daughter, who was wearing a Smilow jacket. The couple at the table next to them noticed and said they were visiting their child in Smilow, where everyone had been wonderful to them.

Dr. Fuchs started hearing such stories from patients and their families as soon as he arrived from Harvard three years ago. "It's an amazing hospital," he said. "It has been far beyond my expectations. The talent here, the commitment of the university and the system to invest in Smilow and the Cancer Center, the commitment to our mission by our faculty and staff and everyone involved is inspiring. It's a privilege to work here every day."

OUR CARE CENTERS GIVE US THE OPPORTUNITY TO OFFER OUR PATIENTS ACCESS TO SMILOW RESOURCES AND CLINICAL TRIALS IN OUR COMMUNITY WHERE PATIENTS ARE COMFORTABLE RECEIVING THEIR TREATMENT.

$99M
IN DIRECT CANCER RESEARCH FUNDING

236,202
OFFICE VISITS IN 2019



300+
CLINICAL TRIALS ADVANCING CARE

30
MINUTE DRIVE TO SMILOW CANCER CARE

WE NOT ONLY ASK A PIVOTAL QUESTION IN OUR LABS, WE ASK IF THAT SCIENCE WILL MEAN IMPROVED OUTCOMES FOR OUR PATIENTS IN OUR CLINICS.

85,408
INFUSIONS

CARING FOR
48%
OF NEWLY DIAGNOSED PATIENTS IN CONNECTICUT


TEN YEARS OF LEADERSH
2010
2011
2012
2013
2014

In 2009, Mario Sznol, MD, Professor of Medicine (Medical Oncology) and Co-Leader of the Cancer Immunology Research Program, walked across the hall to the office of Scott Gettinger, MD, Professor of Medicine (Medical Oncology), and made a suggestion. Dr. Gettinger listened and thought, 'He's lost his marbles.' Dr. Sznol wanted Dr. Gettinger to put a few of his lung cancer patients onto a new clinical trial testing another attempt at immunotherapy.

Then, as now, lung cancer killed more people in the United States than any other type of cancer, and it killed them fast. Dr. Gettinger had devoted himself to lung cancer patients and was always looking for better ways to treat them. Nothing really worked, including previous forms of immunotherapy, so he was deeply skeptical of Dr. Sznol's suggestion. On the other hand, when your patients are likely to die within six months without some kind of miracle, why not take a shot at a miracle? Dr. Gettinger agreed to put a few patients on the trial.

Dr. Sznol, on the other hand, had believed in the potential of immunotherapy for more than two decades, ever since his fellowship at Mount Sinai in New York, where he saw some of the first patients successfully treated for melanoma and kidney cancer with a new immunotherapy called interleukin-2 (IL-2). From Mount Sinai he went to the NCI, where he studied new immunotherapy agents.

"The studies done early on at the NCI provided proof of concept for immunotherapy," he said, "even though IL-2 only worked with melanoma and kidney cancer. But there was the promise that if we could figure out why, we could translate that into other diseases."

Dr. Sznol had been following the work of an immunobiologist at the Mayo Clinic named Lieping Chen, MD, PhD, now the United Technologies Corporation Professor in Cancer Research and Professor of Immunobiology, of Dermatology, and of Medical Oncology at Yale. Dr. Chen had shown that several types of cancers expressed molecules, later named PD-1 and

IP IN IMMUNOTHERAPY

2015 → 2016 → 2017 → 2018 → 2019

Bob's Story

In 2006, life was good for Bob Amendola, his wife, and their two young children. "We had a normal life, career was going well, everything going as planned," he said. "Then I felt a lump in my collarbone." His diagnosis: Stage IV metastatic lung cancer. It had spread to his lymph nodes, esophagus, and brain. His oncologist gave him a prognosis of six months to maybe a year and recommended palliative care.

Mr. Amendola had other ideas as he looked into the eyes of his oncologist and said, "I'm not going anywhere, you and I are going to grow old together." Six years later, after enduring wave after wave of various chemotherapies, radiation to the chest and head, which left him exhausted and nauseated, he was still alive, but eventually the treatments were no longer effective. Mr. Amendola wasn't willing to give up, however, and his oncologist sent him to Dr. Scott Gettinger at Yale.

In early 2012, Mr. Amendola joined Dr. Gettinger's trial of a new immunotherapy drug called atezolizumab. Mr. Amendola also said to Dr. Gettinger, "We're going to grow old together, doc." At that time, there was a tumor pushing about two inches through his rib cage. Soon after he started the trial, he noticed the lump in his chest seemed to be getting smaller. Three months after his first series of treatments, on a Friday afternoon, he had a follow-up CT scan and was anxiously waiting for the results, which were scheduled for the following week.

That Saturday his phone rang, "I'll never forget seeing Dr. Gettinger's name come up on the caller ID, my knees were weak, and my heart was POUNDING," he remembered. Dr. Gettinger asked, 'Are you sitting down? I cannot believe this, but your mass has shrunk about 50 percent.' As you can imagine, Mr. Amendola and his family were jumping for joy.

After twelve months of atezolizumab, Mr. Amendola's scans showed no signs of cancer. "Because of immunotherapy," he said, "I am cancer free and I get to do the things I love to do and live a normal life." Eight years later, his semi-annual scans remain clean.

"I owe a lot to Dr. Gettinger and his team," he said. "He's one of the nicest guys you'll ever meet and he has a great team of nurses and doctors around him. The whole facility is top-notch with friendly and accommodating staff who will do whatever you need," he added. "They could rest on their laurels, but they are learning from my data so they can help others achieve the same success."

"It's an exciting time at Yale, with a contagious enthusiasm among basic scientists and clinical investigators to collaborate on efforts to understand sensitivity and resistance to current immunotherapies, and develop the next generation of immunotherapies."

– Dr. Scott Gettinger

PD-L1, that destroyed T cells and thus boosted tumor growth. Dr. Sznol's excitement grew in 2002 after Dr. Chen published data showing that when PD-1 and PD-L1 were blocked, the immune system bounced back and attacked cancers. In 2009, now at Yale, Dr. Sznol noticed that the first small trial of Dr. Chen's new anti-PD-1 compound, called nivolumab, had shown encouraging results in several cancers, including melanoma. He immediately began planning a trial at Yale for patients with melanoma. A lung cancer patient also had responded well, and so Dr. Sznol tapped Dr. Gettinger's interest.

The following years would be packed with revolutionary developments in immunotherapy, the decade's biggest story in cancer treatment. Yale scientists have played leading roles in that story. In December 2009, Dr. Sznol's clinical trial treated the first patient in the world to receive a combination of nivolumab and ipilimumab, a CTLA-4 antibody. The results were amazing. About 70 percent of the patients benefitted. In more than half of them, the tumors shrunk by at least 80 percent.

Meanwhile, Dr. Gettinger had put a few patients into a small trial using nivolumab against non-small cell lung cancer. He was pessimistic. Everybody in the trial had already failed on multiple therapies and had a prognosis of three to six months.

The first thing he noticed was that patients tolerated the drug well, mostly without side effects. That encouraged him to enroll more patients in 2010. He could barely believe what he was seeing. Not all patients responded, but some responded dramatically. Tumors shrank and in a few cases, disappeared. [See sidebars.] In metastatic lung cancer, such responses were unprecedented.

When Dr. Gettinger and others reported these results, lung cancer doctors around the world were dumbfounded. A friend of Dr. Sznol's at the NCI refused to believe the results until he sent him scans.

As time passed, the data continued to surprise. Previously, the five-year survival rate for patients with metastatic lung cancer had been close to zero. Among the 129 patients around the country who participated in that early trial, the rate was 16 percent. "That was just unheard of," said Dr. Gettinger. "Since those early trials, the way we treat lung cancer has changed dramatically. Immunotherapy has become the standard for patients with advanced lung cancer, with most patients receiving this as their first-line therapy. No one could have predicted that 10 years ago."

For Dr. Sznol's melanoma patients who took nivolumab with ipilimumab, the five-year survival rate was even more remarkable, jumping from between five and 10 percent to nearly 50 percent. For patients with advanced melanoma, this combination is now standard treatment.

In fact, immunotherapies have become standard for more than a dozen cancers, either in combination with other therapies or as first-line treatment. The field is dominated by six FDA-approved drugs based on Dr. Chen's original discovery about the PD-1/PD-L1 pathway.

Thanks to Drs. Chen, Sznol, Gettinger, and many other Yale scientists, Smilow has consistently been among the first to offer clinical trials in these breakthrough drugs.

Maureen's Story

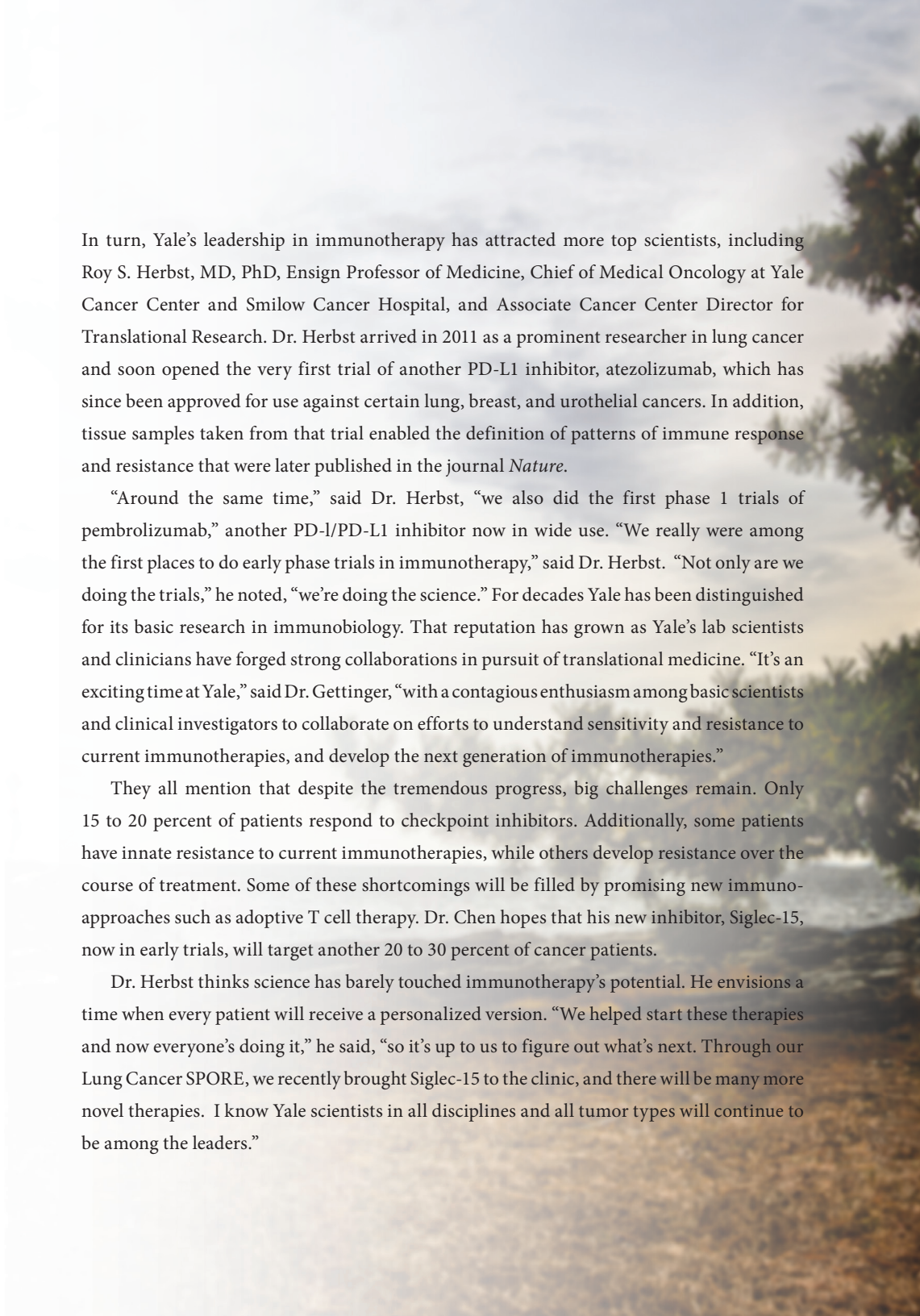
In January 2009, at 55, Maureen O'Grady received devastating news. Though a smoker for 16 years, she had given up cigarettes 25 years earlier. But now, an oncologist was telling Maureen that she had metastatic lung cancer with a prognosis of 12 to 18 months to live. He offered no hope. Ms. O'Grady asked a friend whose sister worked at Yale to get the name of the best lung cancer doctor at Smilow. The name that came back was Dr. Scott Gettinger.

Ms. O'Grady saw him in February. "He was invested in me from day one," she said. "That's the kind of people they are there. The diagnosis didn't change, but he gave me a little bit of hope."

Still, her cancer had spread to her liver, adrenal glands, and heart. Three rounds of chemotherapy didn't slow it. In mid-2010, with few options left, she joined Dr. Gettinger's clinical trial for a new immunotherapy drug called nivolumab.

Just eight weeks later, all of her tumors were substantially smaller, and they continued shrinking until they finally disappeared from her scans. The study ended after two years. Ms. O'Grady hasn't taken nivolumab since, nor have the tumors returned in the nearly 10 years since she began her treatment. She has been able to celebrate her wedding anniversaries, the marriages of her two daughters, and the births of four grandchildren.

"I live in Milford, 10 minutes away from Smilow," she said. "I'm so lucky I happened to be in the right place at the right time. When you receive that diagnosis, your whole world turns upside down. Dr. Gettinger and Smilow and Dr. Chen turned my world right side up again. They extended my life."



In turn, Yale's leadership in immunotherapy has attracted more top scientists, including Roy S. Herbst, MD, PhD, Ensign Professor of Medicine, Chief of Medical Oncology at Yale Cancer Center and Smilow Cancer Hospital, and Associate Cancer Center Director for Translational Research. Dr. Herbst arrived in 2011 as a prominent researcher in lung cancer and soon opened the very first trial of another PD-L1 inhibitor, atezolizumab, which has since been approved for use against certain lung, breast, and urothelial cancers. In addition, tissue samples taken from that trial enabled the definition of patterns of immune response and resistance that were later published in the journal *Nature*.

"Around the same time," said Dr. Herbst, "we also did the first phase 1 trials of pembrolizumab," another PD-l/PD-L1 inhibitor now in wide use. "We really were among the first places to do early phase trials in immunotherapy," said Dr. Herbst. "Not only are we doing the trials," he noted, "we're doing the science." For decades Yale has been distinguished for its basic research in immunobiology. That reputation has grown as Yale's lab scientists and clinicians have forged strong collaborations in pursuit of translational medicine. "It's an exciting time at Yale," said Dr. Gettinger, "with a contagious enthusiasm among basic scientists and clinical investigators to collaborate on efforts to understand sensitivity and resistance to current immunotherapies, and develop the next generation of immunotherapies."

They all mention that despite the tremendous progress, big challenges remain. Only 15 to 20 percent of patients respond to checkpoint inhibitors. Additionally, some patients have innate resistance to current immunotherapies, while others develop resistance over the course of treatment. Some of these shortcomings will be filled by promising new immuno-approaches such as adoptive T cell therapy. Dr. Chen hopes that his new inhibitor, Siglec-15, now in early trials, will target another 20 to 30 percent of cancer patients.

Dr. Herbst thinks science has barely touched immunotherapy's potential. He envisions a time when every patient will receive a personalized version. "We helped start these therapies and now everyone's doing it," he said, "so it's up to us to figure out what's next. Through our Lung Cancer SPORE, we recently brought Siglec-15 to the clinic, and there will be many more novel therapies. I know Yale scientists in all disciplines and all tumor types will continue to be among the leaders."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to be in the right place
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When you receive that
diagnosis, your whole
world turns upside down.
Dr. Gettinger and
Smilow and Dr. Chen
turned my world right
side up again.
They extended my life."
– Maureen O'Grady

LEARNING


CONSENT FOR CANCER RESEARCH STUDY
What is research?
What is the purpose of this research?
What will my participation involve?
Do I have to agree to participate?

FROM EACH PATIENT:

Umbrella consent eases translational research

Every cancer patient is distinctive, with their own genetic fingerprint and their own response to treatment. To researchers working to develop better, more tailored cancer treatments, those differences can be crucially relevant.

To help ensure such important data can be included in research studies, Yale Cancer Center and Smilow Cancer Hospital have instituted a new umbrella consent protocol. This will smooth the way for patients at Smilow Cancer Hospital and the Smilow Cancer Hospital Care Centers to make their unique contributions to the research process.

"We're asking patients in advance for permission to use leftover blood samples and specimens to help us further cancer research," explained Maureen Major Campos, RN, MS, Director, Patient Services for Smilow Cancer Hospital's Ambulatory Clinics. "No additional biopsies or labs are required. This will give us great insight into cancer and how we treat it."

Typically, when researchers need to seek patients' consent to use clinical information and tissue samples as part of a research question for their study, they need to approach patients in advance, one at a time. Umbrella consent, on the other hand, gives patients the opportunity to agree to participate in research studies universally, allowing their de-identified, relevant clinical and laboratory information to be included in a variety of studies. The process saves time and energy for both researchers and patients, and it ensures that patients who are eligible for a particular study don't get left out.

Having both patient samples and background medical information in hand "will allow us to ask questions which we never really could ask before," said Edward Kaftan, PhD, Assistant Director for Translational Research Administration. Dr. Kaftan works to help bring basic scientists and clinicians together to translate lab discoveries swiftly into advances in patient care.

"A new therapy—either a new regimen or a new drug itself—could eventually evolve out of information that was gathered through this umbrella consent process," Lajos Pusztai, MD, DPhil, Professor Professor of Medicine (Medical Oncology) and Principal Investigator of the protocol explained. "The possibilities," he added, "are almost endless in terms of the health impact it could have for cancer patients."

In the planning stages since 2015, the full consent process was approved in July 2019 by the Institutional Review Board (IRB) at Yale University, which carefully reviews the ethics of all proposed research protocols. It is expected to roll out to all 15 of the Smilow Cancer Hospital Care Centers by early 2020. Smilow is the only cancer hospital in Connecticut to offer this broad consent option.

It's important to understand that patients agreeing to the umbrella consent are not signing up to participate in a

clinical trial. A trial involves the testing of a specific intervention, such as a new drug. Rather, umbrella consent allows researchers, both within and beyond Yale, to study excess tissue such as blood or biopsy materials from patients who are already having those materials collected as part of their care, as well as de-identified information from their medical records. This information strengthens present-day and future studies that rely on examining multiple patients' cancer data and outcomes, such as comparing how patients with differing genetics respond to the same standard-of-care treatment.

For example, a newly diagnosed cancer patient will undergo blood tests as part of their routine care. Once all those tests are completed, some blood is typically left over. Normally, that blood is safely discarded. But if patients agree to the umbrella consent, researchers may use the blood for future research studies. Similarly, under umbrella consent, researchers may examine surgically excised tumor tissue once pathologists have finished analyzing it for diagnosis.

All data collected are kept strictly anonymous. Any protected health information that could be used to identify a patient—including name, date of birth, Social Security number, and medical record number, is stripped away from tissue samples and information in the medical record—reflecting Yale's commitment to patient privacy in accordance with federal law.

Researchers interested in analyzing patient data covered under the umbrella consent will need to submit a query through the IRB to obtain prior approval for their research protocol. Once approved, data analysts will then send researchers information for those patients that meet the study's inclusion criteria —again, stripped of all patients' personal identifying information.

For example, if a researcher has an IRB approved protocol to study the genetics of multiple myeloma using bone marrow samples from 50 patients with the disease, they would request de-intentified information and leftover tissue samples for patients fitting their criteria.

Alternatively, if the researcher is interested in the blood pressure of multiple myeloma patients, an application can be submitted to access and study de-identified medical records of those who signed the umbrella consent in the past.

Patients have the option to opt out of the umbrella consent after signing, or to speak with their physicians first to learn more about the process. Their decision will not in any way affect the care they receive. Currently, registration staff are reaching out to consent new patients during their first appointment at Smilow. The umbrella consent is first introduced during their initial phone call for appointment scheduling, and is finalized as part of their check-in process. As of late 2019, 624 patients have agreed to participate. Front-desk staff, nurses, and other staff are trained to answer questions patients may have.

"Our goal is to ensure that the support providers in all of our clinics will also be able to talk to our patients about the process, and answer their questions," Ms. Major Campos said. "The implications for this are really huge."

"A new therapy – either a new regimen or a new drug itself – could eventually evolve out of information that was gathered through this umbrella consent process."

–DR. LAJOS PUSZTAI


Cancer Research Study
Please complete the following section
By signing this document, I agree that:
researchers may study tissue samples leftover from procedures I have
undergone or will undergo in the future as a part of my routine care and can
look at my medical records now and in the future to learn about my health.
Patient ID Barcode
or
Print Participant name
Participant date of birth
Participant Medical Record number
Print name of legally authorized Representati
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Nearly 40 percent of Americans over the age of 20 are obese, and another 32 percent are overweight. These alarming figures grow darker when combined with statistics showing that obesity is second only to smoking as a cause of preventable cancer deaths. Obesity has been linked to more than a dozen types of cancer.

Scientists know that some tumors are fiends for blood sugar—glucose, the fuel that drives their growth. Obesity, with its accompanying overabundance of glucose, makes a natural partner for these cancers. But the biological mechanisms that link the two are still under investigation. A team of scientists at Yale has identified an important key.

"We develop and apply new tools to understand the mechanistic link between obesity and cancer," said Rachel Perry, PhD, Assistant Professor in Medicine (Endocrinology) and Cellular & Molecular Physiology.

That link spotlights the hormone insulin. When we eat, food is converted into blood sugar. The rising level of glucose in the bloodstream signals the pancreas to release insulin. Eventually, insulin resistance can develop and result in a build up of glucose in the body, which leads to fat cells and an accumulation of extra pounds.

Previous studies have associated insulin with several cancers, but Dr. Perry and her colleagues mechanistically demonstrated the link. "Our study is among the first to show directly that the high insulin levels in obesity cause changes in tumor glucose metabolism and then in tumorigenesis," she said.

Her lab followed several paths to this discovery. They took three tumor cell lines associated with obesity—colon, breast, and prostate cancer—and three cell lines not associated with obesity—melanoma, B-cell lymphoma, and small cell lung cancer—and doused them with insulin. Giving extra insulin to the obesity-associated cancers was like throwing gas on a fire. The tumors not associated with obesity showed no change. They concluded that excessive circulating insulin, a condition called hyperinsulinemia, allows tumor cells to bloat themselves with glucose and burn it to fuel fast growth.

Dr. Perry and her colleagues wondered whether lowering insulin might put a kink in this link. "What's particularly exciting are the therapeutic implications," said Dr. Perry, "because there are already many drugs that reduce insulin." She theorized that putting an obese patient with cancer on an insulin-lowering drug might stall the tumor's growth.

She knew that metformin, the most commonly prescribed drug for lowering blood sugar in diabetics, had been tested against cancer in several trials, with mixed results. She decided to test two drugs that reduce blood insulin through different mechanisms. The first was dapagliflozin, an SGLT2 inhibitor, which means that it prevents the kidneys from raising blood sugar by reabsorbing glucose. Instead, the glucose is eliminated through urination. Dr. Perry found that the SGLT2 inhibitor reversed hyperinsulinemia and hence slowed the growth of obesity-associated cancer in mice. However, replacing insulin in mice treated with the SGLT2 inhibitor prevented the beneficial effects of the drug.

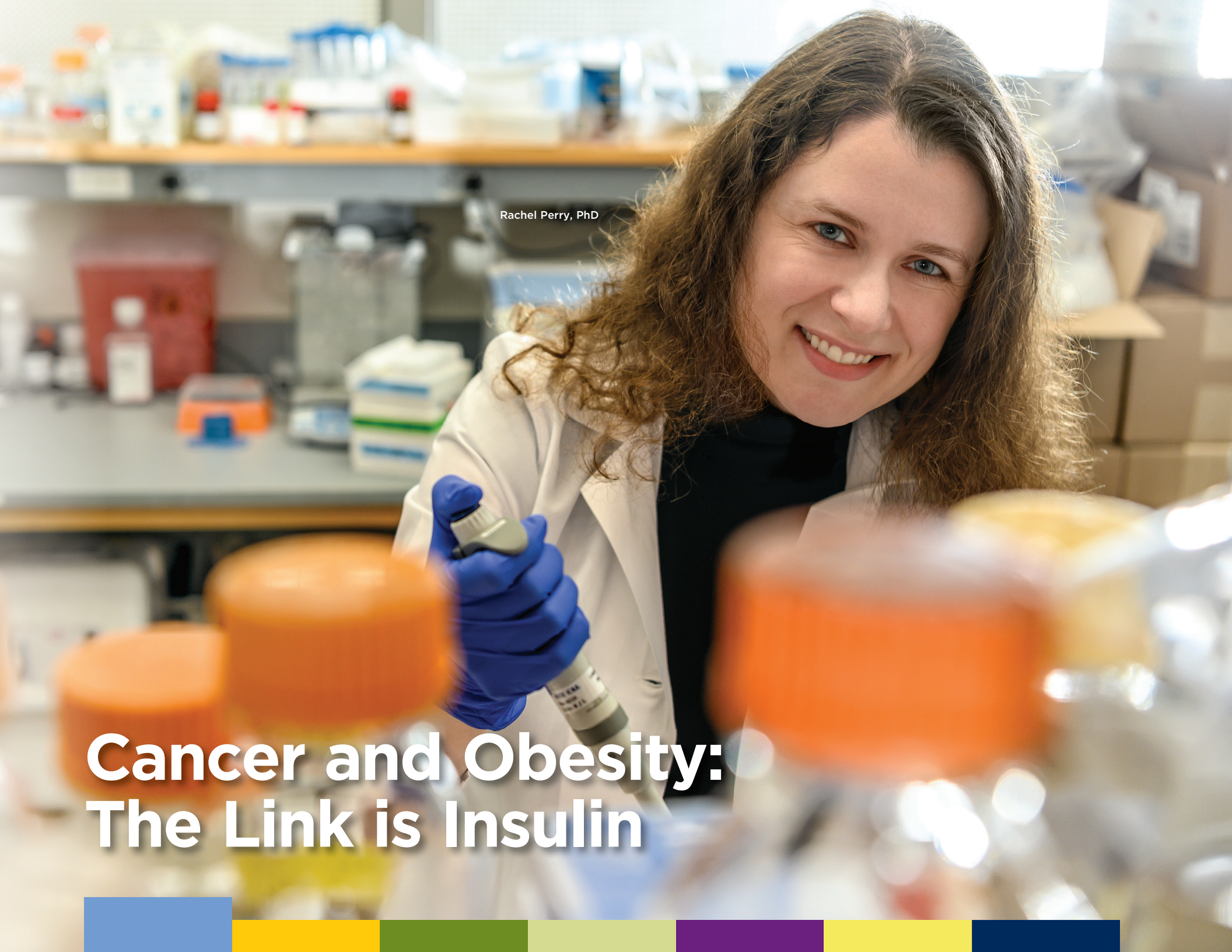
The second drug was a controlled-release mitochondrial protonophore (CRMP) designed by Dr. Perry and her post-doctorate mentor, Gerald Shulman, MD, PhD, the George R. Cowgill Professor of Medicine (Endocrinology) and Cellular & Molecular Physiology. CRMP is an insulin sensitizer, meaning that it lowers blood sugar by reversing insulin resistance. Specifically, it promotes the burning of fat in the liver. Dr. Perry found that CRMP also reverses hyperinsulinemia and slows the growth of tumors associated with obesity.

These findings further confirmed the link between insulin and obesity-related cancers. Significantly, both drugs lowered insulin concentrations whether the mice were fasting or had just eaten a high-glucose meal.

"Conventional wisdom has said that tumors take up a lot of glucose, but it's not hormonally regulated," said Dr. Perry, "so there would likely be no differences in tumor glucose uptake over the course of a day. But we're saying no, it is likely hormonally regulated, a dynamic regulation of insulin signaling and tumor glucose uptake. That suggests that an intervention that lowered both fasting and postprandial glucose and insulin levels would be therapeutically beneficial."

Dr. Perry is working with other scientists at Yale Cancer Center to explore the possibility of clinical trials with a SGLT2 inhibitor as an adjuvant to standard care for colon and breast cancers. She is also running experiments to see whether insulin-sensitizing drugs can enhance the effects of chemotherapy and of immunotherapy.

"My hope," she said, "is that we can apply insulin-lowering therapies to alter tumor glucose metabolism and slow the obesity-associated increase in tumor cell division, and thereby buy more time for curative therapies to work."



Rachel Perry, PhD

Cancer and Obesity: The Link is Insulin

The Race to the Next Target

To Parker Sulkowski, the next step was obvious, but he also knew that others would be racing to get there first. A PhD student in the lab of Peter Glazer, MD, PhD, Robert E. Hunter Professor of Therapeutic Radiology and Professor of Genetics, and Chair of the Department of Therapeutic Radiology, Dr. Sulkowski was about to take what he learned from their groundbreaking study of glioma and look for other targets.

In 2016, he joined a Yale project that originated in the lab of Ranjit Bindra, MD, PhD, Associate Professor of Therapeutic Radiology and Pathology. Working collaboratively, the Glazer and Bindra labs discovered a new, counterintuitive tactic for fighting cancer. Instead of trying to stop certain mutations, said the scientists, let's exploit them.

They reached this conclusion by studying the biology of gliomas. Research had shown that many gliomas are driven by mutations of the gene IDH and its mutant metabolite 2HG. Yet a new drug designed to block these mutations was proving curiously ineffective on glioma patients who were also receiving chemoradiotherapy.

Dr. Bindra wondered if IDH mutations somehow made patients more sensitive to chemoradiotherapy. He took this hunch to Dr. Glazer, which is how Dr. Sulkowski entered the picture. Using basic biology, the team learned that IDH mutations drive glioma partly by hindering the tumor's ability to repair damaged DNA, thereby causing more mutations. But the damaged DNA also leaves the cancer cells vulnerable to attack, like a fortress with an unlocked back door.

The Yale researchers knew that if a cell's broken DNA isn't fixed or removed, it eventually will die. They also knew that repair of damaged DNA in many cases fell largely to a group of proteins called PARP—poly (ADP-ribose) polymerase. And they knew that drugs called PARP inhibitors have successfully targeted BRCA1 and BRCA2, proteins involved with DNA repair that, when mutated, can cause breast, ovarian, prostate, and pancreatic cancers. The scientists discovered that IDH mutations (via excess 2HG metabolite levels) suppress the same DNA repair pathway as is impacted by BRCA mutations, and so they reasoned that a PARP inhibitor might make IDH-mutant cancer destroy itself. They tested an inhibitor called olaparib on brain cancer cells. It worked spectacularly.

IDH mutations are found in many other cancers, including acute myeloid leukemia, gastric cancer, colorectal cancer, melanoma, and cholangiocarcinoma. Based on the Yale team's work, seven clinical trials have started or are about to launch, at Yale and across the United States.

The team's discovery had never been described before, so Dr. Sulkowski knew it would start a scramble to find similar mechanisms and related cancers. "The second I knew our IDH/2HG finding was real," he said, "the race was on."

Dr. Sulkowski had a head start and knew just where to look first. Like other scientists in cancer metabolism, he was familiar with two rare inherited cancer syndromes, Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) and Succinate Dehydrogenase-related Hereditary Paraganglioma-Pheochromocytoma (SDH PGL/PCC). He also knew that they overproduce metabolites, succinate and fumarate, whose molecular structures and functions are very similar to that of 2HG.

"Even for someone in this field," said Dr. Sulkowski, "it's almost impossible to tell the difference between 2HG, succinate, and fumarate. So we hypothesized that there would be converging DNA repair defects there, and I immediately tested them."

The time from his hypothesis to his lab work to a major paper in *Nature Genetics* took only a year, and in late 2019 a clinical trial opened at Yale and at UCLA to test PARP inhibitors against these two rare cancer syndromes. "That's a lot faster than most projects tend to go," said Dr. Sulkowski.

It's easier to win the second leg of a race when you're far ahead after the first leg. But another reason Yale won the race, said Dr. Sulkowski, is that it cultivates amazing science. He pointed to the great relationship and collaboration between the Bindra and Glazer labs, and to the fruitful relationship of both labs with Brian Shuch, MD, a renal cell surgeon and genetics expert who was formerly at Yale and continues to collaborate while at UCLA.

"I don't think we could have done this anywhere else," said Dr. Sulkowski. Obviously it's not luck, it's that Yale puts the top scientists and clinicians all under one roof."

Dr. Sulkowski graduated in early 2020. He says he's most proud of two things from his work at Yale: "Number one is understanding the molecular mechanisms that drive these cancers, and number two is exploiting those mechanisms for therapeutic gain. When you hear gratitude from people with IDH mutations who had been failing other trials and succeeded on ours, that's pretty incredible. It's a reminder of the tremendous responsibility we have as scientists to do high quality work, because it can have really amazing effects."

Andrew Goodman, PhD, C. N. H. Long Professor of Microbial Pathogenesis and Director of the Microbial Sciences Institute at Yale West Campus, studies the abundant flora in the gut, but he initially trained in ecology and sees many parallels. "I think of the microbiome as an ecosystem," he said, "and the members of the ecosystem are bacteria."

Lately he has been looking into the connections between that ecosystem and cancer patients' responses to therapeutics. Patients often react differently to the same therapy, showing different side effects or outcomes. These differences are usually ascribed to variants in people's genomes, but Dr. Goodman doubted that was the whole story.

"People have enormous differences in their gut microbes," he said, "far greater than the differences within their genomes. We wondered whether differences in drug responses could be affected not only by activities of the liver—the primary organ for drug metabolism—but also by differences in people's microbiomes."

To test their hypothesis, Dr. Goodman and his lab settled on the interaction between a widely used chemotherapy drug named 5-fluorouracil (5-FU) and an antiviral drug often given with it named brivudine. In some patients this combination had proven to be extremely toxic, even lethal. Researchers determined that brivudine can interfere with the metabolic processing of 5-FU, itself a toxin. It turned out that 80 percent of 5-FU gets cleared from the body through a specific chemical pathway, but if that pathway is blocked and 5-FU isn't expelled, patients can overdose on it. Further research revealed the cause: In some patients, brivudine produces a toxic metabolite that blocks the pathway.

"This was a case where not understanding the microbiome and the microbial contribution was a huge problem," explained Dr. Goodman.

The problem wasn't brivudine itself, but its metabolite, which interfered with chemotherapy. Dr. Goodman knew that gut bacteria can make this toxic molecule, but not how. He also knew that the liver was capable of making the same toxic molecule. Since both the microbiome and the liver can make the molecule, which one was the main actor when combining brivudine and 5-FU to cause a toxic reaction?

First, the scientists determined the bacterial chemistry that transformed the drug into a toxic molecule. Next, they altered the microbiomes in mice to include or exclude the responsible bacterial enzyme. That allowed the team to study how much of the toxic molecule came from the liver and how much from the microbes.

"We learned that even though the liver is capable of doing this," said Dr. Goodman, "about 70 percent of this toxic metabolite that interferes with chemotherapy is coming from what the microbes are doing."

Equally significant, the toxicity sometimes showed up in the liver, where 5-FU accumulated if it wasn't eliminated. "We could see that changing just one microbial enzyme in the gut can impact how toxic the drug is in the liver. So, what the microbes are doing in the gut can reach far beyond the gut itself."

He sees implications for the management of chemotherapy's side effects, which can limit a patient's dosage and affect outcomes. "What's new is that we found there is another player to the story. It's not only what drugs you are taking, but it can be what microbes you have, because some of them can interfere with chemotherapy." These findings were published in 2019 in the journal *Science*.

In another major paper published in *Nature*, they tested about 75 bacterial species typically found in the gut against hundreds of drugs currently in use, some for cancer and some not. The surprising result: two-thirds of the drugs were altered by at least one of the gut bacteria.

"So we think the example of bacteria that can change a drug like brivudine into something that interferes with chemotherapy or causes some other harm isn't an exception. It's much more common than we had previously appreciated."

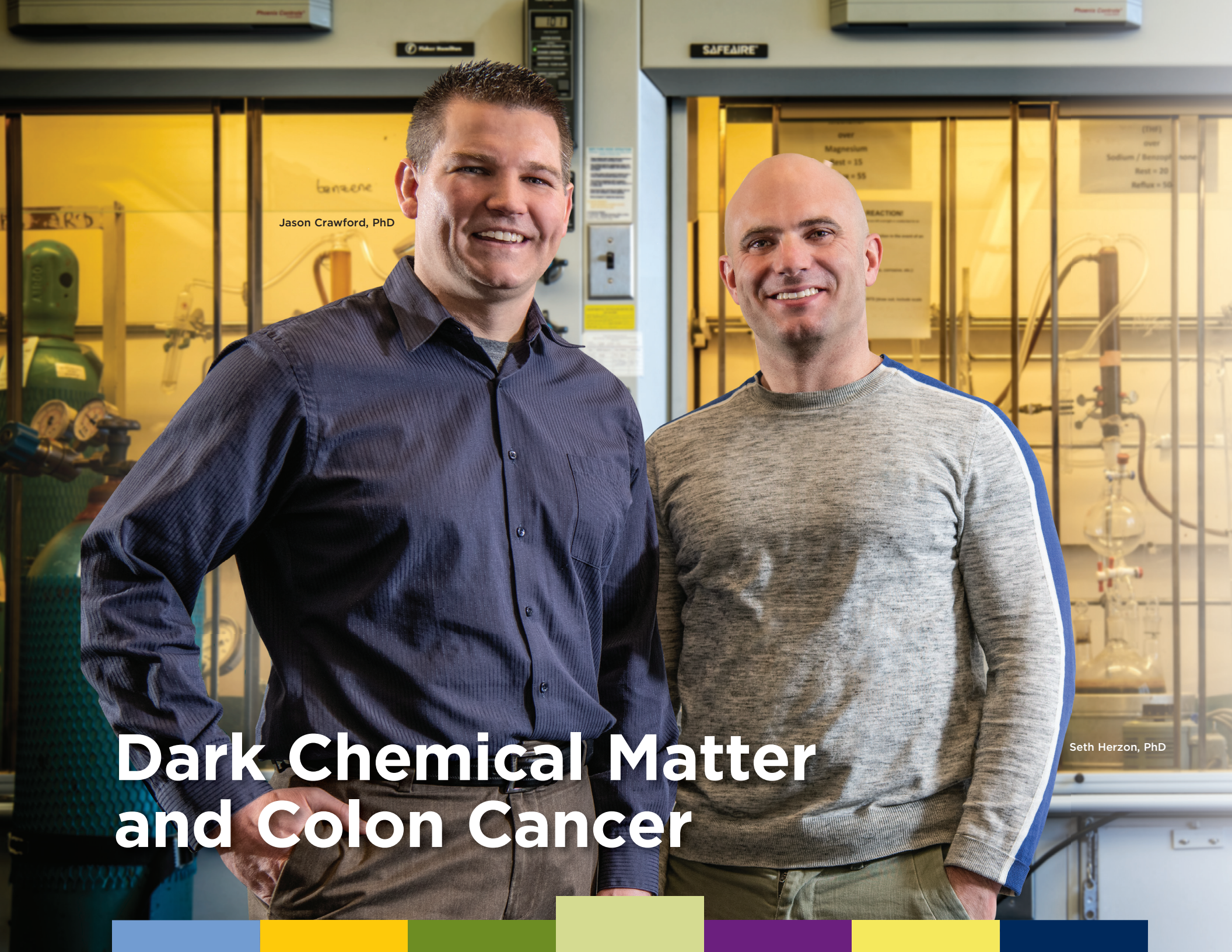
He notes that this isn't necessarily bad news. Bacterial activity can enhance the efficacy of a drug, not just corrupt or negate it. The point is that microbes are dynamic agents that should be considered in medical care. "We're just starting to understand this," said Dr. Goodman, "and the work we're doing is very basic research, but we think there will be translational implications."

In the future, he envisions being able to predict how patients might respond to a particular drug based on their microbiome. He can imagine changing people's microbes to avoid a dangerous drug reaction, or replacing certain microbes with others that would diminish poor side effects.

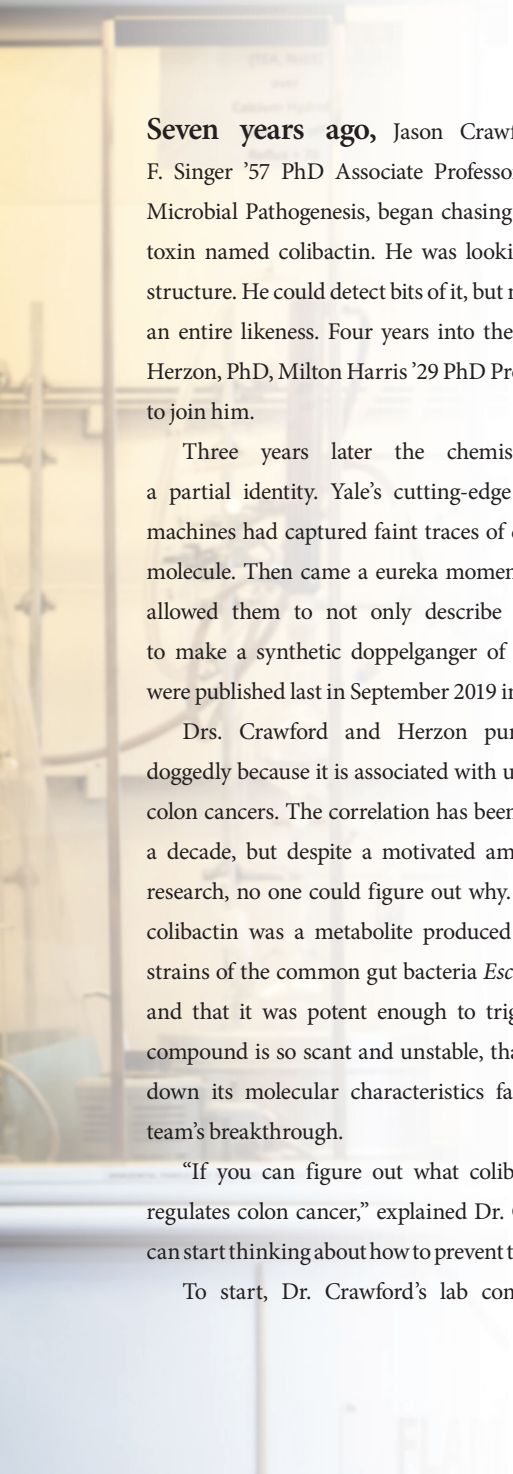
"That's very different from the way we think about personalized medicine today, which holds that if we understand a person's genome, we can choose which drugs to give them," he said. "We don't think about changing people's genomes in order for them to respond to a drug, but it's not crazy to think we could change people's microbes to do that, to maximize the chances for the best response."

Andrew Goodman, PhD

The Microbiome and Cancer Treatment



Dark Chemical Matter and Colon Cancer



Seven years ago, Jason Crawford, PhD, Maxine F. Singer '57 PhD Associate Professor of Chemistry and Microbial Pathogenesis, began chasing a ghost—a bacterial toxin named colibactin. He was looking for its molecular structure. He could detect bits of it, but never enough to form an entire likeness. Four years into the hunt he asked Seth Herzon, PhD, Milton Harris '29 PhD Professor of Chemistry, to join him.

Three years later the chemists still had only a partial identity. Yale's cutting-edge mass spectrometry machines had captured faint traces of colibactin's phantom molecule. Then came a eureka moment: the final clue that allowed them to not only describe colibactin, but also to make a synthetic doppelganger of it. Their discoveries were published last in September 2019 in the journal *Science.*

Drs. Crawford and Herzon pursued colibactin so doggedly because it is associated with up to 67 percent of all colon cancers. The correlation has been clear for more than a decade, but despite a motivated amount of competitive research, no one could figure out why. Scientists knew that colibactin was a metabolite produced by a few genotoxic strains of the common gut bacteria *Escherichia coli (E. coli),* and that it was potent enough to trigger cancer. But the compound is so scant and unstable, that all attempts to pin down its molecular characteristics failed—until the Yale team's breakthrough.

"If you can figure out what colibactin is and how it regulates colon cancer," explained Dr. Crawford, "then you can start thinking about how to prevent this from happening."

To start, Dr. Crawford's lab completed a metabolic analysis of ~40,000 molecules associated with the colibactin producer, eventually isolating and mapping more than 100 associated with the colibactin pathway. Then they stalled.

In 2015, Dr. Crawford mentioned to Dr. Herzon that he was working on a molecule that he couldn't isolate. Dr. Herzon, a synthetic chemist, said his lab probably could make a synthetic version in a couple of months. They began, as usual, with biomimetics, mimicking how nature might assemble the molecule. That process took them through "biosynthetic intermediaries" that revealed the chemical reactions that occur before colibactin becomes colibactin.

"We made the biosynthetic precursor, precolibactin, that some people had been studying and showed that that precursor transforms into a bunch of things that had been overlooked in the literature," said Dr. Herzon. "Building on the parts of colibactin that were well established, we began to make more complex fragments that we hypothesized might be generated. Those structures turned out to be extraordinarily potent genotoxins."

That excited the chemists, momentarily. Then they reached an impasse. They couldn't isolate the complete genotoxins from the bacteria. "By 2018," said Dr. Herzon, "I was thinking about making a graceful exit."

Then, in early 2018 another group of researchers cultured the bacteria that make colibactin, added DNA, and re-isolated the DNA. They found that the DNA now had an interstrand crosslink. This news reanimated the chemists. This synthetic compound, which Drs. Crawford and Herzon describe as containing two "warheads," was not colibactin itself, but behaved like the natural molecule. They hypothesized that colibactin itself was stuck in the crosslink.

"We decided to use the DNA as a hook to fish out colibactin," explained Dr. Crawford.

Dr. Herzon asked one of his graduate students, Mengzhao (Lucy) Xue, to see if she could dig the molecule out of the crosslink and isolate it. Xue crosslinked DNA with the bacteria, then used enzymes to gnaw down the DNA until all that remained were the two DNA bases and the molecule that had reacted with them. Using extremely powerful mass spectrometry and isotope labeling, Xue eventually found the molecule's mass.

"That was the bit of data we needed," said Dr. Herzon. "It was the most exciting scientific moment of my career." This data allowed them to predict a structure for colibactin, and then chemically synthesize it.

"That was a magic moment," agreed Dr. Crawford. "It took seven years to get there. We quickly went from not having a clue to knowing almost everything about the entire mechanism, because we could mine seven years of data."

Dr. Crawford is developing an antibiotic that selectively removes colibactin-producing bacteria from the intestinal tract, with the goal of preventing colon cancer. Dr. Herzon hopes to repurpose colibactin as targeted chemotherapy.

"There is probably a world of metabolites out there that are biologically significant and relevant to human health but that pass completely undetected by existing methods. We refer to it as, 'Dark Chemical Matter.' You can't detect it, but it's there and it probably matters a lot." Looking forward, the researchers are trying to develop approaches to reveal the structures and function of this dark chemical matter.

In December 2018, the U.S. Attorney General announced, "I am officially declaring e-cigarette use among youth an epidemic in the United States." He noted that the number of 12th graders who had used e-cigarettes had doubled in just one year. "Now is the time to take action."

In 2019 the statistics grew more alarming. The Centers for Disease Control and Prevention (CDC) reported that more than five million middle and high schoolers had vaped within the past 30 days—27.5 percent of all high school students and 10.5 percent of all middle schoolers.

These figures represent a startling reversal. By 2010, thanks to stringent regulations and effective anti-smoking campaigns, the percentage of teenagers using tobacco products had plummeted. Health officials hoped this trend would eventually lower the incidence of the many diseases caused by tobacco, including cancer.

Then came e-cigarettes. They deliver their nicotine load into the lungs and include appealing flavors, and the cool high-tech devices that produce an odorless sweet-tasting aerosol were easily hidden. Recent studies suggest that teenagers who would not otherwise have started smoking have been enticed back to tobacco products by e-cigarettes.

"What I'm most worried about," said Suchitra Krishnan-Sarin, PhD, Professor of Psychiatry and Co-Leader of the Yale Tobacco Center for Regulatory Science (TCORS), "is that we have all these kids now using nicotine, sometimes at very high levels, and there is evidence that some of them are moving on to cigarettes. Then there's the toxicity of the nicotine itself. It changes the functioning of almost every organ, and the teen brain is particularly sensitive to its effects."

"It takes years to see the consequences of any epidemic," said Stephanie O'Malley, PhD, Elizabeth Mears and House Jameson Professor of Psychiatry, who co-leads TCORS. "There's a huge uncontrolled experiment going on."

"Some flavors, like menthol, are soothing and may make it easier to vape higher concentrations of nicotine," added Dr. Krishnan-Sarin, "and therefore may make it easier to get addicted."

She points out that no studies have yet linked vaping to cancer, most likely because e-cigarettes are young and cancer trends need time to emerge. But she adds that "vaping liquids" contain solvents such as glycerin and propylene glycol, as well as flavor chemicals called aldehydes—all known inflammatory agents. "Repeated inflammation and repeated injury," she explained, "can potentially lead to cancer."

A study in 2019 by Yale TCORS found that when flavor additives are combined with solvents and then heated, the process generates a chemical reaction that creates previously undetected byproducts called acetals. The effects of inhaling acetals are unknown.

To date, the makers of e-cigarettes have not been required to list the ingredients in their products or to prove their safety. That is supposed to change by May 2020, the FDA's long-delayed deadline for requiring manufacturers to submit scientific evidence about the contents and health effects of their products. But the vaping industry—a $7 billion business in the United States—has vigorously resisted deadlines and transparency. The public has also been alarmed by reports that vaping has caused respiratory illnesses that killed more than 40 people and sickened 2,000.

"The kind of science being generated by tobacco centers such as ours," said Dr. Krishnan-Sarin, "is intended to support decisions that the FDA will continue to make around how these products will be regulated."

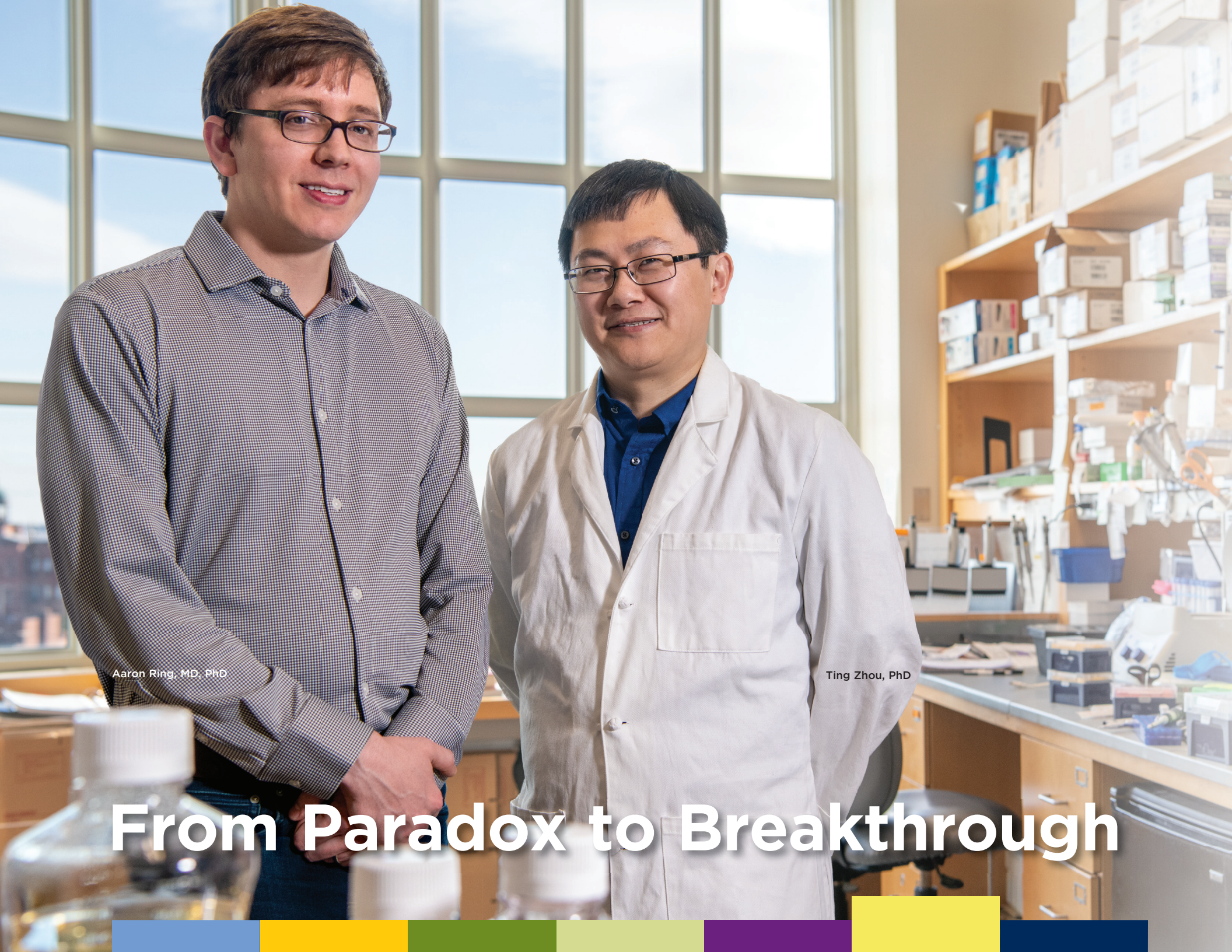
A good start might be to treat e-cigarettes like other tobacco products. It seems sensible to require additives to be identified and tested for their effects on health. Tobacco companies are not allowed to market their products toward youth, but youth is the focus of the packaging and marketing used by many e-cigarette companies. Special taxes on cigarettes have raised their price so high that many young people never buy a pack, but e-cigarettes and liquids have been exempted and are affordable by teens.

"If you look historically," said Dr. O'Malley, "flavors were banned from cigarettes because kids were using them. I think there may be some good rationale for taking some of these flavors off the market because of who they appeal to. We also might want to limit the concentration of nicotine the way they do in Europe."

Neither Dr. Krishnan-Sarin nor Dr. O'Malley advocates banning e-cigarettes, because the devices might still deliver on their original purpose—to help wean smokers off of cigarettes by giving them an alternative source of nicotine, minus the carcinogenic particulates of tobacco smoke.

"I hope we can regulate these products in such a way that they continue to be helpful to people who want to use them to quit smoking," said Dr. Krishnan-Sarin, "but without having the appeal to youth."

Vaping: A Huge Uncontrolled Experiment



From Paradox to Breakthrough

Aaron Ring, MD, PhD, Assistant Professor of Immunobiology, was hooked by a paradox. He had been studying cytokines, hormone-like proteins that control immune responses, to understand their potential to stimulate anti-tumor immunity. Though cytokines such as interleukin-2 (IL-2) have been in clinical use for decades, they have historically shown only limited effectiveness.

To look for potential new cytokine therapies, Dr. Ring took a bird's-eye view to see if any cytokine pathways had been overlooked. He had been intrigued by a study that used cutting-edge "single-cell" profiling to identify the genes most closely associated with tumor-infiltrating lymphocytes (TILs). His lab used the study's findings to analyze every cytokine pathway that could be detected in the data. Dr. Ring was hunting for interleukins that could deliver a potent, but specific signal to activate TILs.

"Looking at it from the standpoint of someone trying to hack into the immune system and turn on a response," he said, "we found that the IL-18 pathway had the desirable features. It appeared to be an 'open port' on these elite anti-tumor T cells."

Since IL-18 seemed so promising, Dr. Ring and Ting Zhou, PhD, a postdoctoral associate in Dr. Ring's lab, dove into the clinical data surrounding it. They found a set of clinical trials in which cancer patients had received high doses of the cytokine. "It shocked us to find that IL-18 failed— there were no responses in several dozen patients tested," said Dr. Ring, "It was an incredible paradox. How could this powerful cytokine pathway be so ineffective?"

They learned that IL-18 had a 'decoy receptor,' IL-18BP, which was produced at very high levels in tumors. Dr. Ring and Dr. Zhou hypothesized that IL-18BP counteracted IL-18 and curtailed its power to elicit immune responses—sensible in healthy people but self-defeating for fighting cancer. They thus set out to build a molecule that could evade IL-18BP and thereby unleash full IL-18 activity in the tumor microenvironment.

To approach this difficult problem, they used a method called 'directed evolution.' "Sometimes we can't settle for nature's solution," explained Dr. Ring. "We have to create our own. The odds were stacked against us. IL-18 has evolved to be tightly regulated by its binding protein and IL-18BP plays an important role to protect us from runaway IL-18 activity and autoimmune disease."

They created a large collection of genetically-modified yeast in which each yeast cell presented one unique variant of IL-18 on its surface. Using magnetic and fluorescent cell sorting, they screened about 250 million variants, looking for those that retained the binding for IL-18's receptor but didn't bind to the decoy, IL-18BP. They repeated the process for several weeks until they pinpointed the best candidate. This became their synthetic 'decoy resistant' molecule, DR-18.

They then tested DR-18 in mouse models, including melanoma tumors in collaboration with the laboratory of Marcus Bosenberg, MD, PhD, Professor of Dermatology, Pathology, and Immunobiology. What came next, said Dr. Ring, "was a eureka moment. The activity of DR-18 in these tumor models in mice was much stronger than anything I'd ever seen. It was like flipping a switch." By contrast, the tumorous mice that received normal, or 'wild-type' IL-18 showed no response, just like patients in IL-18 clinical trials.

"IL-18BP sends a jamming signal that prevents the activation of lymphocytes in the tumor," he said. "With DR-18 we made a version of IL-18 that can't be jammed."

In many mice, the tumors entirely disappeared. But Dr. Ring was even more excited by the underlying immunological effects. As expected, T cells jumped into action, but the innate immune cells also showed major changes, including activation of natural killer (NK) cells.

Dr. Ring notes that anti-PD-1 immunotherapies succeed partly by activating these stem cell-like T cells, though without increasing their number. By contrast, DR-18 boosted the number of these cells more than fivefold. When Dr. Ring reintroduced tumor cells into mice whose cancer had disappeared, tumors didn't return. The mice evidently were protected by their augmented memory cells.

It's often said that anti-PD-1 immunotherapies take the "brakes" off of the immune system. "DR-18," said Dr. Ring, "steps on the gas. It doesn't remove a negative signal, it provides an activating signal."

Equally exciting, Dr. Ring found that DR-18 worked against a subset of tumors that have become resistant to anti-PD-1 therapies. DR-18's mechanism seems to stimulate the immune system in ways that other therapies don't. He has started a company called Simcha Therapeutics to attract investment that is needed to advance the new molecule into human trials in early 2021.

"Moving beyond discovery is the biggest challenge but also the most rewarding aspect of our work," he said. "And Yale is an awesome place to do this kind of translational research."

Humanized mice created at Yale, are opening new avenues of research into cancers caused by disorders in the production of blood, such as acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS). Until recently, such research was hindered because human blood stem cells are difficult to grow in cell cultures or to engraft in mice.

Richard Flavell, PhD, FRS, Sterling Professor of Immunobiology, solved that by designing a new mouse. He genetically modified the murine immune system to make it more human-like. The mice even express human cytokines, growth factors secreted by the liver and other cells in the body that are important regulators of stem cell proliferation and maturation. These humanized "MISTRG" mice accept and nourish human cells, especially bone marrow stem cells, without destroying them and allow them to make mature blood cells.

MISTRG mice have transformed the research of Stephanie Halene, MD, PhD, Associate Professor and Interim Chief of Hematology, who studies AML and MDS. "Now we can model the disease and maintain it in mice for many months," she said, "which allows us to replicate the complexity and changes that can occur in patients over time."

Using MISTRG mice, researchers can track the initiation and progress of these blood cancers—how and when mutations occur, how they alter the production of blood, and how they cause AML and MDS. In 2019, Dr. Halene and her colleagues published a paper in *Nature Communications* describing this process in MISTRG mice. The paper excited MDS researchers all over the world and has led to many collaborations, with scientists traveling to Yale to test new ideas in the mice.

Dr. Halene's work also prompted a translational spinoff closer to home, a collaboration with Ranjit Bindra, MD, PhD, Associate Professor of Therapeutic Radiology. They used MISTRG mice to test PARP inhibitors in combination with other drugs against abnormal isocitrate dehydrogenase (IDH).

Their project is a good example of how breakthroughs are distributed at Yale and applied to different cancers. Since IDH is also a driver of MDS, Dr. Halene noticed Dr. Bindra's research and their collaboration was born.

"These IDH mutations very commonly co-recur in MDS and AML with splicing factor mutations, one of the primary subjects in my lab," said Dr. Halene. "So now we can put Ranjit's expertise in DNA damage repair and mine in RNA biology together and ask, 'how do these two different mutations collaborate to form MDS?'"

When they tested the PARP inhibitor olaparib against IDH-mutant cells in MISTRG mice engrafted with MDS and AML, olaparib showed the same deadly effects as it had in prior research in IDH-mutant gliomas. "We can see exactly the same mechanism," said Dr. Halene, "but we're even more interested in how we can exploit it for new options for MDS and AML patients."

Next, they plan to look at the synergy of PARP inhibitors with other drugs and pathways. "The nice thing," said Dr. Halene, "is that we can figure out optimal combinations in our mouse models and then translate that into a clinical trial." A trial is already planned to launch this year in collaboration with clinician Thomas Prebet, MD, PhD, Associate Professor and Medical Director for Hematology and Cell Therapy.

Dr. Halene is now working with the next generation of MISTRG mice, in which Dr. Flavell solved another research dilemma. MISTRG mice have a humanized immune system, but their red blood cells are murine. When researchers attempt to introduce human red blood cells or platelets, they quickly disappear, eliminated by the mouse's innate immune system.

Dr. Flavell's lab used fluorescence to track introduced human blood cells and found that most of them ended up in the mouse's liver, where they were destroyed. The Flavell lab knocked out a gene, fumarylacetoacetate hydrolase (FAH), in the MISTRG mice, an absence that leads to a buildup of toxic metabolites and eventual liver failure. Next, after the scientists damaged the mice's liver cells, they used injected human liver cells to regenerate the mice livers.

"In the end," said Dr. Halene, "we got a mouse that has human cytokines and 80 to 90 percent human liver cells. Now we can put in human bone marrow stem cells that make human immune cells and red blood and other mature cells, and we can see human red blood cells circulating. That's very attractive, because we can study anemia, MDS, and other diseases of the red blood cell and test new therapies.

She hopes that these scientific breakthroughs will become new therapies that target MDS and AML, slowing progression or inducing remission. Someday it might even be possible to detect these cancers early enough to prevent them. "It's a longshot," she said, "but that's where all fantastic science aims."

Stephanie Halene, MD, PhD

Humanized Mice Lead to Breakthroughs in Blood Cancers

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David F. Stern, PhD

Developmental Therapeutics
Karen S. Anderson, PhD
Barbara A. Burtness, MD

Genomics, Genetics, and Epigenetics
Marcus W. Bosenberg, MD, PhD
Lajos Pusztai, MD, DPhil

Radiobiology and Radiotherapy
Joseph N. Contessa, MD, PhD
Megan C. King, PhD

Yale Cancer Center Shared Resources

Biostatistics and Bioinformatics
Shuangge Steven Ma, PhD

Cesium Irradiator
Ravinder Nath, PhD

Clinical Research Services
Joyce N. Tull, RN, CCRP, MSN
Assistant Director, Administration
Neal Fischbach, MD
Assistant Director, Care Centers
Scott Gettinger, MD
Assistant Director, Medical Oncology Trials
Stephanie Halene, MD, PhD, *Assistant Director, Clinical Research Support Laboratory*
Thomas Prebet, MD, PhD
Assistant Director, Hematology Trials

Flow Cytometry
Ann Haberman, PhD

Functional Genomics
David Calderwood, PhD
Benjamin Turk, PhD

Mass Spectroscopy Metabolic Flux Resource
Richard Kibbey, MD, PhD

Pathology Tissue Services
David Rimm, MD, PhD

Rapid Case Ascertainment
Rajni Mehta, MPH

Yale Center for Genome Analysis
Shrikant Mane, PhD

Yale Center for Molecular Discovery
Craig Crews, PhD

Yale Center for Precision Cancer Modeling
Marcus Bosenberg, MD, PhD

Smilow Cancer Hospital

Charles S. Fuchs, MD, MPH
Physician-in-Chief

Lori Pickens, MHA
Senior Vice President and Executive Director

Kevin G. Billingsley, MD
Chief Medical Officer

Kim Slusser, MSN, RN, CHPN, NEA-BC
Vice President, Patient Services

Arthur Lemay
Vice President, Network Development

Kerin B. Adelson, MD
Chief Quality Officer
Deputy Chief Medical Officer

Anne Chiang, MD, PhD
Chief Network Officer
Deputy Chief Medical Officer

Benjamin L. Judson, MD
Chief Ambulatory Officer
Deputy Chief Medical Officer

Tara B. Sanft, MD
Chief Patient Experience Officer

Sarah S. Mougalian, MD
Deputy Chief Ambulatory Officer

Sonia Grizzle
Director, Administration

Smilow Cancer Hospital Clinical Programs

Brain Tumor
Clinical Program Leaders:
Antonio Omuro, MD
Jennifer Moliterno, MD
Disease Aligned Research Team Leader:
Antonio Omuro, MD

Breast Cancer
Interim Clinical Program Leader:
Brigid Killelea, MD
Interim Disease Aligned Research Team Leader:
Kerin Adelson, MD

Cellular Therapies
Clinical Program and Disease Aligned Research Team Leaders:
Michael Hurwitz, PhD, MD
Iris Isufi, MD

Gastrointestinal Cancers
Clinical Program and Disease Aligned Research Team Leaders:
Jeremy Kortmansky, MD
Jill Lacy, MD

Gynecologic Oncology
Clinical Program Leader:
Elena Ratner, MD
Disease Aligned Research Team Leader:
Alessandro D. Santin, MD

Head and Neck Cancers
Clinical Program Leader:
Benjamin L. Judson, MD
Disease Aligned Research Team Leader:
Barbara A. Burtness, MD

Hematology
Clinical Program and Disease Aligned Research Team Leader:
Steven Gore, MD

Liver Cancer
Clinical Program and Disease Aligned Research Team Leader:
Mario Strazzabosco, MD, PhD

Melanoma
Clinical Program and Disease Aligned Research Team Leader:
Mario Sznol, MD

Phase I
Clinical Program and Disease Aligned Research Team Leader:
Patricia M. LoRusso, DO

Prostate and Urologic Cancers
Clinical Program Leader:
Peter G. Schulam, MD, PhD
Disease Aligned Research Team Leader:
Daniel P. Petrylak, MD

Sarcoma
Clinical Program and Disease Aligned Research Team Leader:
Dieter M. Lindskog, MD

Therapeutic Radiology
Clinical Program Leader:
Lynn D. Wilson, MD, MPH
Disease Aligned Research Team Leader:
Roy H. Decker, MD, PhD

Thoracic Oncology
Clinical Program Leader:
Daniel J. Boffa, MD
Disease Aligned Research Team Leader:
Scott N. Gettinger, MD

Yale Cancer Center Membership

Cancer Immunology

Stephan Ariyan
Philip Askenase
Jeffrey Bender
Alfred Bothwell
Richard Bucala
Lieping Chen
Grace Chen
Joseph Craft
Peter Cresswell
Richard Edelson
Brinda Emu
Richard Flavell
Francine Foss
Michael Girardi
Earl Glusac
Ann Haberman
David Hafler
Douglas Hanlon
Jeanne Hendrickson
Kevan Herold
John Hwa
Nikhil Joshi
Paula Kavathas
Steven Kleinstein
Smita Krishnaswamy
Jonathan Leventhal
Carrie Lucas
Mark Mamula
Jennifer McNiff
Ruslan Medzhitov
Eric Meffre
Kelly Olino
Zenggang Pan
Tristen Park
Joao Pereira
Jordan Pober
Aaron Ring
Carla Rothlin
Nancy Ruddle
Kurt Schalper
David Schatz
Stuart Seropian
Brian Smith
Edward Snyder
Xiaolei Su
Mario Sznol
Robert Tigelaar
Mary Tomayko
Juan Vasquez
Tianxiang Zhang

Cancer Microbiology

Kathleen Akgun
Daniel DiMaio
Ayman El-Guindy
Ellen Foxman
Jorge Galan
Andrew Goodman
Stavroula Hatzios
Ya-Chi Ho
S. Hudnall
Akiko Iwasaki
Sofia Jakab
Caroline Johnson
Benjamin Judson
Amy Justice
Michael Kozal
Priti Kumar
Brett Lindenbach
Jun Liu
I. George Miller
Kathryn Miller-Jensen
Walther Mothes
Elijah Paintsil
Noah Palm
Anna Marie Pyle
Christian Schlieker
Joan Steitz
Richard Sutton
Tamar Taddei
Peter Tattersall
Anthony Van den Pol
Sten Vermund
Craig Wilen
Yong Xiong

Cancer Prevention and Control

Kerin Adelson
Prasanna Ananth
Harry Aslanian
Brett Bade
Steven Bernstein
Brenda Cartmel
Anees Chagpar
Elizabeth Claus
Amy Davidoff
Nicole Deziel
Leah Ferrucci
Charles Fuchs
Lisa Fucito
Cary Gross
Caitlin Hansen
Theodore Holford
Scott Huntington
Melinda Irwin
Ania Jastreboff
Beth Jones
Manisha Juthani-Mehta
Nina Kadan-Lottick
Jennifer Kapo
Brigid Killelea
Tish Knobf
Grace Kong
Suchitra Krishnan-Sarin
Donald Lannin
Michael Leapman
Haiqun Lin
Lingeng Lu
Shuangge Ma
Xiaomei Ma
Asher Marks
Sherry McKee
Rajni Mehta
Sarah Mougalian
Linda Niccolai
Stephanie O'Malley
Jonathan Puchalski
Elena Ratner
Emily Reisenbichler
Ilana Richman
Harvey Risch
Peter Salovey
Tara Sanft
Dena Schulman-Green
David Sells
Sangini Sheth
Andrea Silber
Marcella Nunez-Smith
Mehmet Sofuoglu
Donna Spiegelman
Sakinah Suttiratana
Alla Vash-Margita
Shi-Yi Wang
Wei Wei
Canhua Xiao
Yawei Zhang
Yong Zhu

Cancer Signaling Networks

Anna Arnal Estape
Anton Bennett
Titus Boggon
David Breslow
David Calderwood
Gary Desir
Michael DiGiovanna
Rong Fan
Kathryn Ferguson
Carlos Fernandez-Hernando
Clare Flannery
John Geibel
Sourav Ghosh
Valentina Greco
Julie Hens
Mark Hochstrasser
Valerie Horsley
Michael Hurwitz
Karl Insogna
Richard Kibbey
Joseph Kim
Daryl Klein
Anthony Koleske
Shalin Kothari
TuKiet Lam
Francis Lee
Mark Lemmon
Andre Levchenko
Yansheng Liu
Michael Mak
Darryl Martin
Wang Min
Jon Morrow
Peggy Myung
Michael Nathanson
Don Nguyen
Rachel Perry
Daniel Petrylak
Katerina Politi
David Rimm
Jesse Rinehart
Joseph Schlessinger
Martin Schwartz
Gerald Schulam
David Stern
Yajaira Suarez
Kaelyn Sumigray
Derek Toomre
Benjamin Turk
Evan Vosburgh
Robert Weiss
Kenneth Williams
Dianqing (Dan) Wu
John Wysolmerski
Xiaoyong Yang
Yang Yang-Hartwich

Developmental Therapeutics

Karen Anderson
Masoud Azodi
Joachim Baehring
Aarti Bhatia
Debra Brandt
Ronald Breaker
Barbara Burtness
Michael Cecchini
Charles Cha
Herta Chao
Yung-Chi Cheng
Anne Chiang
Jason Crawford
Craig Crews
Henk De Feyter
Hari Deshpande
Vincent DeVita
Joseph Eder
Barbara Ehrlich
Jonathan Ellman
Donald Engelman
Tarek Fahmy
James Farrell
Scott Gettinger
Sarah Goldberg
Steven Gore
Lohith Gowda
Ya Ha
Navid Hafez
Roy Herbst
Seth Herzon
Nina Horowitz
Iris Isufi
William Jorgensen
Patrick Kenney
Hyun (Kevin) Kim
Harriet Kluger
Jaseok Koo
Jeremy Kortmansky
Jill Lacy
Renelle Lim
Dieter Lindskog
Elias Lolis
Patricia LoRusso
David Madoff
Scott Miller
Jennifer Moliterno Gunel
Bryce Nelson
Natalia Neparidze
Antonio Omuro
Terri Parker
Farzana Pashankar
Pasquale Patrizio
Peter Peduzzi
Joseph Piepmeier
Nikolai Podoltsev
Thomas Prebet
John Roberts
Michal Rose
William Mark Saltzman
Alessandro Santin
Clarence Sasaki
William Sessa
David Spiegel
Preston Sprenkle
Stacey Stein
Mario Strazzabosco
Seyedtaghi Takyar
Vasilis Vasiliou
Sarah Weiss
Amer Zeidan
Daniel Zelterman
Jianbing Zhou

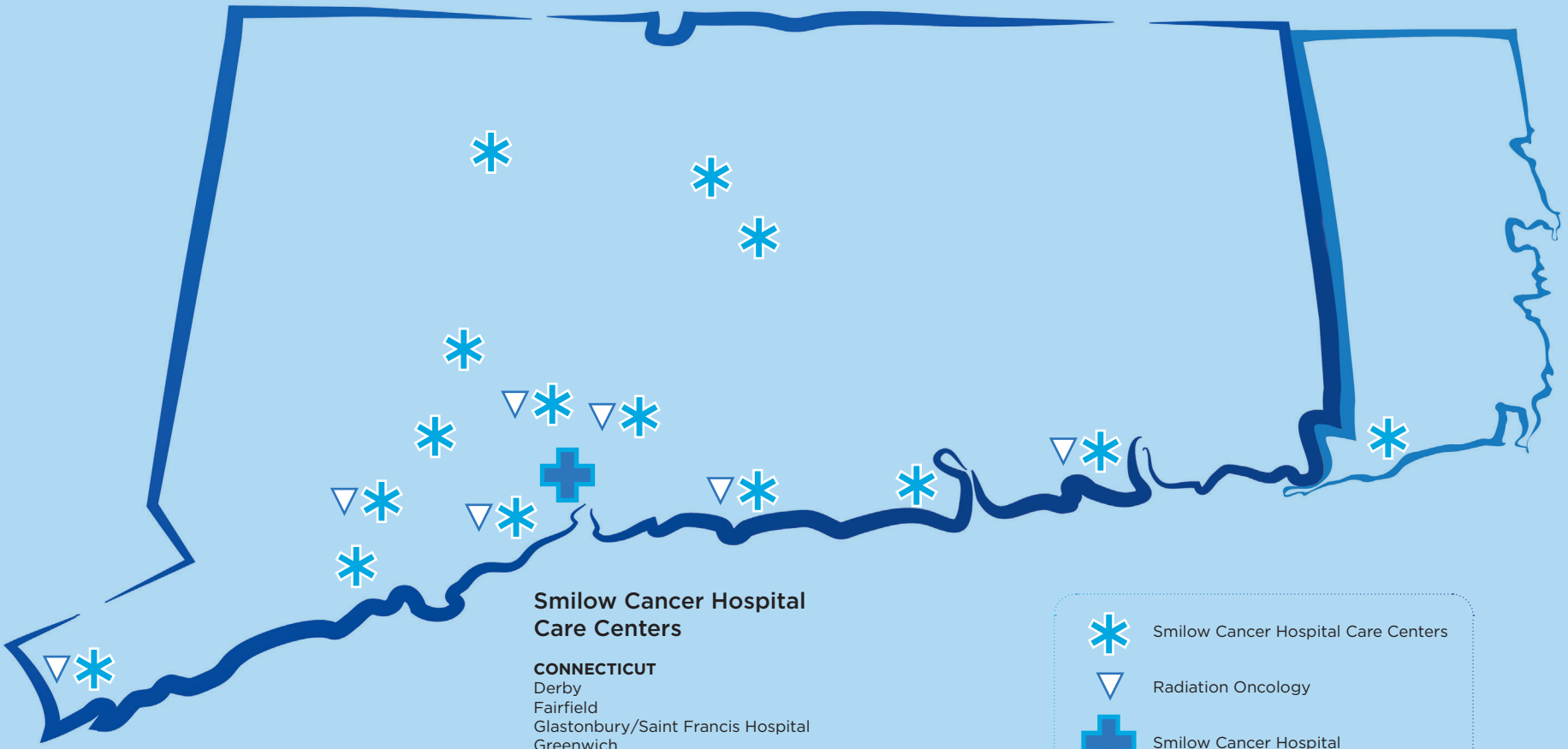
Genomics, Genetics, and Epigenetics

Nita Ahuja
Claudio Alarcon
Allen Bale
Linda Bartoshuk
Susan Baserga
Jean Bolognia
Marcus Bosenberg
Demetrios Braddock
Sidi Chen
Keith Choate
James Clune
Lynn Cooley
Jose Costa
Andrew DeWan
Nadya Dimitrova
Mark Gerstein
Antonio Giraldez
Murat Gunel
Shangqin Guo
Ruth Halaban
Stephanie Halene
Shilpa Hattangadi
Erin Hofstatter
Gloria Huang
Farren Issacs
Dhanpat Jain
Lucia Jilaveanu
Samuel Katz
Sajid Khan
Kenneth Kidd
Yuval Kluger
William Konigsberg
Diane Krause
David Leffell
Peter Lengyel
Bluma Lesch
Morgan Levine
Peining Li
Haifan Lin
Xavier Llor
Jun Lu
Shrikant Mane
James McGrath
Mandar Muzumdar
Karla Neugebauer
James Noonan
Manoj Pillai
Manju Prasad
Lajos Pusztai
Peter Schwartz
Emre Seli
Jeffrey Sklar
Hugh Taylor
Jeffrey Townsend
Sherman Weissman
Frederick Wilson
Andrew Xiao
Mina Xu
Tian Xu
Qin Yan
Hongyu Zhao

Radiobiology and Radiotherapy

Sanjay Aneja
Ranjit Bindra
Justin Blasberg
Daniel Boffa
Douglas Brash
Zhengxin Cai
Richard Carson
Sandy Chang
Zhe Chen
Veronica Chiang
John Colberg
Joseph Contessa
Francesco D'Errico
Shari Damast
Roy Decker
Jun Deng
Frank Detterbeck
James Duncan
Suzanne Evans
Peter Glazer
Fanqing Guo
James Hansen
Susan Higgins
D.S. Fahmeed Hyder
Ryan Jensen
Megan King
Gary Kupfer
Bernadette Marquez-Nostra
Meena Moran
Evan Morris
Rosa Munoz Xicola
Ravinder Nath
Henry Park
Abhijit Patel
Kenneth Roberts
Faye Rogers
Peter Schulam
Christopher Tien
Lynn Wilson
James Yu
Zhong Yun

Yale Cancer Center and Smilow Cancer Hospital Data



Smilow Cancer Hospital Care Centers

CONNECTICUT
Derby
Fairfield
Glastonbury/Saint Francis Hospital
Greenwich
Guilford
Hamden
Hartford/Saint Francis Hospital
North Haven
Old Saybrook
Orange
Torrington
Trumbull
Waterbury
Waterford

RHODE ISLAND
Westerly

Total NCI Funding
(Direct Costs)

Clinical Volume

2018 Top Ten Cancer Sites
at Smilow Cancer Hospital

MALE			FEMALE		
PROSTATE	15.5%	500	1195	32.1%	BREAST
LUNG & BRONCHUS	12.4%	399	402	10.8%	LUNG & BRONCHUS
MELANOMA	8.1%	261	226	6.1%	THYROID
ORAL CAVITY & PHARYNX	6.1%	197	191	5.1%	CORPUS & UTERUS
COLORECTAL	6.0%	192	189	5.1%	BRAIN & CNS
NON HODGKIN'S LYMPHOMA	5.3%	171	182	4.9%	COLORECTAL
URINARY BLADDER	4.9%	159	165	4.4%	NON HODGKIN'S LYMPHOMA
BRAIN & CNS	4.7%	151	160	4.3%	MELANOMA
LEUKEMIA	4.6%	147	110	3.0%	PANCREAS
KIDNEY & RENAL PELVIS	4.0%	128	106	2.9%	LEUKEMIA
OTHER	28.5%	921	793	21.3%	OTHER
TOTAL: 3,226			3,719: TOTAL		

Publications
from Yale Cancer Center Members

June 30, 2018 – July 1, 2019

935 PUBLICATIONS

208 High Impact Publications
IF > 10, including:

- 52 – Nature/Nature Specialty
- 24 – Clinical Cancer Research
- 17 – Journal of Clinical Oncology
- 16 – Cell/Cell Specialty
- 14 – JAMA/JAMA Oncology
- 9 – Journal of the NCI
- 5 – Annals of Oncology
- 4 – New England Journal of Medicine
- 4 – Science/Science Specialty
- 4 – Lancet/Lancet Oncology
- 4 – Cancer Discovery
- 4 – Hepatology
- 4 – Immunity
- 3 – Blood

“I had doctors and nurses who focused on treating my cancer. But at Smilow, they not only treated my cancer, they never forgot that they were also taking care of my family and me.”

YaleNewHaven**Health**

Smilow Cancer Hospital

Yale CANCER CENTER

A Comprehensive Cancer Center Designated by the National Cancer Institute

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SMILOW CANCER HOSPITAL
CELEBRATING TEN
YEARS
OF PATIENT CARE
10