



The Growth of the Cancer Biology Institute

# breakthroughs

YALE CANCER CENTER | SMILOW CANCER HOSPITAL | THE YEAR IN REVIEW



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*“We are fortunate to have enormously bright, talented, dedicated, and collegial faculty and staff. These individuals are making contributions to cancer care, research, and education daily. The prospects for even greater success are humbling and inspiring.”*

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**As I begin my tenure as Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital,** I am struck by the incredible opportunities before us. We are fortunate to have enormously bright, talented, dedicated, and collegial faculty and staff. These individuals are making contributions to cancer care, research, and education daily. The prospects for even greater success are humbling and inspiring.

The Yale Cancer Biology Institute is an outstanding example of a substantial investment in science that is paying incredible dividends. Under the leadership of Mark Lemmon, PhD, FRS, and Joseph Schlessinger, PhD, the Institute has flourished in just a few short years. Drs. Lemmon and Schlessinger have recruited a group of scientists with diverse expertise in cancer biology to expand the breadth and depth of Yale Cancer Center’s research programs. The Institute’s faculty have added critical knowledge in signaling,

transcription, proteomics, and mouse modeling. Planning continues to add expertise in metabolism, immunology, epigenetics, and chemical biology.

The COVID-19 pandemic pushed Smilow Cancer Hospital and the entire Yale New Haven Health System to develop more creative and nimble approaches to clinical care and clinical research. Patient care was quickly transformed, and new models emerged. In some cases, the COVID-related innovations will lead to sustained improvements. One such success at Smilow was the development of our oncology hospitalist program. The approach is already making a significant difference by reducing the length of inpatient hospital stays. Both patients and clinicians have shared their appreciation for our new group of oncology hospitalists.

I am grateful for the opportunity to lead Yale Cancer Center and Smilow Cancer Hospital. I know that there will be great successes to share with you in future publications.

I look forward to sending updates of clinical and research advances, which are closely linked, in the months ahead.

Sincerely,



*Eric P. Winer, MD*

*Director, Yale Cancer Center*

*Physician-in-Chief, Smilow Cancer Hospital*

*Alfred Gilman Professor of Medicine and Pharmacology*

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SPITAL





Claudio Alarcón, PhD

# THE GROWTH OF THE CANCER BIOLO

**One eminent Yale scientist envisioned the** Yale Cancer Biology Institute. Another brought it to life and has overseen its growth. The visionary was Joseph “Yossi” Schlessinger, PhD, William H. Prusoff Professor of Pharmacology, Chair of Pharmacology, and founding director of the Yale Cancer Biology Institute (YCBI). The engine of growth has been Mark Lemmon, PhD, FRS, David A. Sackler Professor of Pharmacology, Deputy Director of Yale Cancer Center, and Co-director of the YCBI.

When Dr. Lemmon came to Yale from UPenn in 2015 to start the YCBI, the Institute consisted of a single two-person lab—his. Six years later, the YCBI has seven dynamic

laboratories filled with 60 scientists—including a diverse and talented group of 14 graduate students and 20 postdocs. In addition, the population swells each summer with great cohorts of undergraduates getting their first taste of cancer research. Dr. Lemmon intends to add several more labs soon.

He and Dr. Schlessinger began with a blueprint for the institute they hoped to assemble. The plan covered everything from recruitment strategy to the number of labs and the scientific focus of each. The plan also called for the labs to be intensely collaborative, not only with each other but with the other research institutes on Yale West

Campus and Yale Cancer Center. Dr. Lemmon wanted the YCBI’s scientists to understand the core biology underlying all cancers, to complement the excellent work being done in Yale Cancer Center labs on all cancers. The goal was for YCBI to use discoveries in basic science to shine new light on every facet of cancer biology and then to translate those discoveries into new drugs and treatments across cancer types.

An ambitious blueprint. Six years later, much of it has been realized—but there is still a lot to do. The rapid success is noteworthy, but especially so considering how Dr. Lemmon achieved it. The typical model for starting



# GY INSTITUTE

a large Institute from scratch is to hire renowned senior scientists to provide instant credibility. Dr. Lemmon discarded that model for something riskier. He recruited up-and-comers with unlimited scientific potential and offered them their first labs. “We want to hire people as an investment in the future of cancer research at Yale,” he said at the time.

He has invested well, building the institute around young scientists he calls “superstars.” He describes the first recruit, Kathryn Ferguson, PhD, Associate Professor of Pharmacology, as “a little bit of a cheat, since she happens to be my wife.” Dr. Ferguson, who often collaborates with

Dr. Lemmon, studies the detailed molecular mechanisms that regulate signaling, and is particularly well known for her work on how antibody therapeutics like cetuximab act. Dr. Lemmon’s next recruit was a physician-scientist straight from a postdoc at Harvard Medical School, Daryl Klein, MD, PhD, Assistant Professor of Pharmacology.

“The four of us—Yossi, myself, Kathryn, and Daryl—are all focused on signaling,” said Dr. Lemmon, “which means understanding how a particular subset of proteins on the cell’s surface direct cell growth or restrain cell growth. I would say that the four of us make up one of the leading groups in the world in this area.”

Dr. Lemmon divided cancer biology into key processes and recruited scientists to start labs in each of those areas. All were young postdocs accepting their first faculty positions. For chromosomes, that was Lilian Kabeche, PhD, Assistant Professor of Molecular Biophysics and Biochemistry and the newest addition to the Institute. “Dr. Kabeche is working to understand how cells respond to errors in their DNA and how the pathways to correct these errors differ in cancer—which can lead to defects in DNA and the genome,” said Dr. Lemmon. “She started her lab only six months before the pandemic and is already writing up her lab’s first papers.”

Mark Lemmon, PhD, FRS



DNA gets transcribed into RNA, Dr. Lemmon continued, to give the transcriptome, which is the collection of all the RNAs in a cell. “The transcriptome is incredibly complex, and defects in keeping it under control cause cancer—so that’s the next aspect to study after the chromosome,” said Dr. Lemmon. To explore RNAs and the transcriptome, he recruited Claudio Alarcón, PhD, Assistant Professor of Pharmacology.

The level beyond RNAs involves proteins and the proteome, the complete set of proteins expressed by a cell.

In cancer, proteins and the proteome have often gone haywire. “We recruited a world leader in understanding how the whole proteome gets remodeled,” said Dr. Lemmon. That scientist is Yansheng Liu, PhD, Assistant Professor of Pharmacology. “He can actually look at every protein in the cell with mass spectrometry techniques, and see how genetic changes have altered the cell’s biochemistry.”

This brought Dr. Lemmon to what he called “the organism, the animal. There we recruited another superstar, Mandar Muzumdar [MD, Assistant Professor of Genetics,

Scientific Director of the Center for Gastrointestinal Cancers at Smilow Cancer Hospital and Yale Cancer Center, and Co-Director of the Pancreas Program].” Dr. Muzumdar creates innovative mouse models to study the development of cancer caused by defects in genetics, signaling, DNA repair, the proteome, and metabolism.

Dr. Lemmon expects to add four or five more labs by 2025 in the areas of metabolism, immunology, chemical biology, epigenetics, and understanding the complex networks mathematically. Each search draws more than 200 applications. “The trick is not just to identify the best people, but to identify terrific scientists who also will mesh well with the Cancer Center’s scientific needs,” said Dr. Lemmon. “If a sector within the clinical aspects of the Cancer Center gets excited about the candidate’s basic research, it’s a good fit. Recruitment is a team effort, with input from the director and associate directors of the Cancer Center.”

All the basic scientists at the institute work with the clinic in mind. They also collaborate heavily with each other and with other institutes and centers at Yale. “We all know what’s going on in everybody’s lab at an early stage,” said Dr. Lemmon, “and any question you ask will be answered on multiple levels. It works well.”

He mentions a few statistics as evidence. In 2021, the Institute’s grant money from the National Institutes of Health alone came to \$5 million. “That’s quite phenomenal,” he said. Since the YCBI’s inception, members have published about 100 papers, including at least one per year in the prestigious journals *Nature*, *Science*, and *Cell*. “Given the size



## “The trick is not just to identify the best people, but to identify terrific scientists who also will mesh well with the Cancer Center’s scientific needs.” – MARK LEMMON, PHD, FRS

of the Institute,” said Dr. Lemmon, “that’s pretty impressive, because these things don’t come along for anyone very often.”

Dr. Klein’s recent *Nature* paper described his team’s findings about the oncogenic molecule ALK (anaplastic lymphoma kinase), known to drive pediatric neuroblastomas and other tumors of the brain and central nervous system. No one knew what the switchable part of the molecule looked like, or how it worked, so ALK couldn’t be targeted. “Trying to solve this part of ALK’s structure seemed futile,” explained Dr. Klein. “Everyone stayed away from it, because it is mostly glycine.”

“When structural biologists see a region of glycines in a protein,” said Dr. Klein, “we generally think that it’s just floppy and disordered—there’s no real structure there, so the regions would never form ordered crystals.” He asked an undergrad to try anyway, expecting it to be an instructive exercise in failure.

The undergrad found crystals. After picking up his jaw, Dr. Klein handed the project to a postdoc in his lab, Tongqing Li, who spent five years optimizing the crystals, diffracting X-rays with them using the Institute’s X-ray facility, and using math to solve the structure. “All these glycines that we predicted to be disordered are in fact highly ordered,” said Dr. Klein. “Very highly ordered. That was the big structural surprise, completely unexpected—and the part that everyone had ignored turned out to contain ALK’s ‘switch.’”

With the structure now visible, the scientists could see how ALK works. “We have the structure and the blueprint, and we know how ALK is activated,” explained Dr. Klein, “so

we want to make designer antibodies and have them inhibit ALK exactly the way we want to. We already have some potential candidates.” Eventually he expects this approach to be used against pediatric neuroblastoma.

A recent *Nature* paper from the labs of Drs. Lemmon and Ferguson answers a question that has long puzzled researchers: why is it that many lung cancer patients with epidermal growth factor receptor (EGFR) mutations respond well to EGFR inhibitors, yet these drugs don’t work at all on glioblastomas with mutations in the same molecule?

Their teams found that the EGFR mutations seen in glioblastomas change the way EGFR signals, rather than simply activating the receptor. EGFR can normally respond differently to its seven distinct ligands. “Remarkably, with the mutations seen in glioblastoma, EGFR can no longer tell which ligand it has been activated by,” said Dr. Lemmon. “So, we don’t think these mutations drive the cancer per se, but increase the likelihood of it forming by changing the distribution of cell types. That may be why EGF receptor inhibitors don’t help—EGFR’s role in cancer development may be long past by the time the tumor is seen.” Someday, he added, it might be possible to correct these early signaling defects with an antibody-type drug and head off the formation of glioblastoma or other cancers where similar mutations are seen.


Dr. Liu does breakthrough research in mass spectrometry and proteomics. Using proteomics and an Orbitrap Fusion Lumos, the fastest mass spectrometer available, he can define the protein components of the cell, how they

change with time, and how they are chemically modified—all with remarkable precision. This gives unprecedented detail on the cell’s biochemistry, which is vital for cancer research and future therapeutic design.

One clear indication of his essential expertise is that he is the only member of the YCBI in collaborative projects with everyone in the institute. He is working with Drs. Lemmon and Ferguson to understand signal-related phosphorylation in EGFR. He is working with Dr. Kabeche to identify important phosphorylation sites related to the cell cycle, and with Dr. Alarcón to identify protein phosphorylation events important in controlling RNA modification. He and Dr. Muzumdar are looking at changes in the proteome caused by *KRAS* mutations in a pancreatic cell line. He is also working with Dr. Klein to better understand protein structures.

“I have a strong independent research program, and exciting questions in proteomics that my lab is answering,” said Dr. Liu. “But I’m also so happy to embrace the collaborative effort and to do science together with other PIs [principal investigators] because of our mutual scientific interests.”

“We’re a group of basic scientists and physician-scientists,” said Dr. Lemmon, “who are studying the fundamentals of biology with more than half an eye on the clinical applications—so we can understand how to fix it when it has gone wrong in cancer. That sums up the vision and the core mission of the Institute.”



Kerin Adelson, MD

Jensa Morris, MD

# Smilow's New Hospitalist Program Benefitting Patients, Physicians

A new program designed to further enhance patient care at Smilow Cancer Hospital is already reaping benefits and leaving indelible impressions on the young physicians at its core.

Smilow Cancer Hospital launched its first Hospitalist Program in July 2021 with five physicians—Erin Gombos, MD, Mathew Kottarathara, MD, Jensa Morris, MD, Nathaniel Parker, DO, Urs Weber, MD—and will expand to 10 later this year, including board-certified hematologists.

As the name implies, hospitalists are doctors dedicated to treating hospitalized patients. They are on staff around the clock to coordinate medical care among a team of physicians and specialists, analyze lab results, admit and discharge patients, and communicate with patients and family. “They really are experts at acute medicine and inpatient care,” said Kerin Adelson, MD, Chief Quality Officer and Deputy Chief Medical Officer at Smilow. “And our patients, so far, love it.”

“The oncologists provide the oncologic expertise of the disease process, cancer

therapies, side effects, and complications of therapy,” Dr. Morris said. “And the hospitalists bring the management of general medical diseases and all the complications thereof.”

Dr. Parker said he likes that his new position allows him to focus on patients. “I have the opportunity to be a vital stakeholder in the overall continuum of patient care,” he said. “This is important to me because I feel patient care can be fragmented between the inpatient and ambulatory settings. I enjoy being a stakeholder who works towards eliminating that fragmentation.”

The hospitalist’s work, while rewarding, is not easy. They typically log 12-hour shifts, seven days a week, followed by seven days off. One works a 13-hour overnight shift. It can be a demanding position, but some, including Dr. Parker, don’t mind it. “I like the hustle and bustle. I enjoy the inpatient setting, the pace, and the breadth of content,” he said. “Also, I like the patient interactions and seeing results in real-time.”

Dr. Gombos said she’s already been inspired by her new position. “My patients are the best part of the job,” she said. “Everyone admitted to Smilow is on an incredible journey. By having the privilege to care for them, I have witnessed pure individuality, bravery, love, and loss. I believe everyone who works at Smilow appreciates this.”

The Smilow Hospitalist Program is already making a significant difference in reducing patient hospital stays. “The business plan was built on reducing patient stay by one-quarter of a day,” Dr. Adelson said. “We actually reduced patient stay by 1.1 days, which is a huge number. That’s four times what was expected.”

That opens beds for other patients who need them. The

key is a hospitalist’s ability to manage general medical diseases as well as navigate the hospital system and be available around the clock to admit and discharge patients.

“A hospital is probably the most complex system you could work in, in terms of figuring out where to get the resources and determining how to get things done,” Dr. Morris said. “Hospitalists manage the day-to-day care with prompt and complete attention to all patient needs, from the mundane to the complicated.”

Dr. Morris was one of the first hospitalists when Yale New Haven Hospital began its program 20 years ago and remains clinically active as a Smilow hospitalist. There are now more than 200 hospitalists in the Yale New Haven Health System, including those at Smilow.

“I think the Smilow Hospitalist Program is going to become so vital that we couldn’t do without it,” Dr. Adelson said. “The patients love having a doctor who spends time with them and is always accessible.”

With much of the hospitalists daily focus on collaborating and coordinating with all physicians, care team members, and patients and families, effective communication is essential to the position. “The staff hospitalist must possess excellent communication skills and exhibit these through communication with primary oncologists, hematologists, in-house consulting physicians, and colleagues,” Dr. Morris said.

Dr. Parker agrees good communications skills are important. “From in-person patient encounters to multidisciplinary rounds to phone calls/texts/emails between other specialists or attending physicians and


beyond, it’s simply such an important part of being a hospitalist,” he said. “It’s truly a skill and something I’m always trying to improve.”

Dr. Gombos explained how effective communication is imperative when the care team often includes nurses, nurse practitioners, residents, interns, medical students, pharmacists, the consulting oncologist or hematologist, and the hospitalist.

“It can be confusing for patients when four or five providers walk into their room. Communicating upfront everyone’s name and role and providing a united plan for the day is extremely important,” she explained. “I often tell my patients that my role as a hospitalist is to coordinate their inpatient stay, while ensuring their outpatient providers are kept up to date so that there is a seamless transition when it is time for discharge.”

Dr. Adelson, a medical oncologist who specializes in breast cancer, said she’s constantly working to improve her communication skills, because the field of oncology—and the sensitive nature of some conversations she has—requires it. “The one thing that I’m still getting better at is communications, especially around end-of-life,” Dr. Adelson said. “It is really the hardest thing and the highest art of medicine that we still do. And it’s so important in terms of aligning care with patient values and making sure that there’s an environment where they can express their wishes.”

“These hospitalists are going to become experts at that form of communication because they’re doing it all day long every day, and they’re also seeing the impact. They really are experts in medicine and inpatient care.”



Harry Aslanian, MD

Yale Medicine  
DIGESTIVE DISEASES  
Harry Aslanian, MD

# SCOPING OUT THE BENEFITS

Hillary Drumm, APRN

## OF SMILOW'S ADVANCED ENDOSCOPY PROGRAM

**Any adult who has had a routine colonoscopy** is intimately familiar with an endoscope—defined most simply as a slender, flexible, steerable, tube-shaped instrument with a light and a camera for viewing the inside of the body or removing tissue. “All gastroenterologists are trained in standard upper endoscopy and colonoscopy,” explained James Farrell, MD, Professor of Medicine (Digestive Diseases) and Director of the Yale Center for Pancreatic Disease. But during his training, Dr. Farrell became captivated by the potential for endoscopes to do even more, not just with screening, but with early diagnosis,

treatment, and even relieving pain and blockages in patients who are critically ill. “It was clear to me that if I wanted to develop a career that involved the diagnosis and management of gastrointestinal cancers, I would need an additional set of skills, beyond standard endoscopy.”

While standard endoscopy is typically used to detect large polyps and tumors in the colon and issues in the upper digestive tract, at Smilow Cancer Hospital, the advanced endoscopy team primarily focuses on the bile duct and the pancreas—two areas that can be difficult to access with standard endoscopic instruments. Using techniques



IT'S A VERY VISUAL FIELD, VERY HANDS-ON. YOU ARE ABLE TO DO A LOT OF PROBLEM SOLVING BECAUSE YOU GET A VISUAL IMMEDIATELY AND CAN GO RIGHT TO THE THERAPY. THAT'S INCREDIBLY GRATIFYING.” – HARRY ASLANIAN, MD

including endoscopic retrograde cholangiopancreatography (ERCP)—which combines upper-GI endoscopy and X-ray—and endoscopic ultrasound (EUS), a combination of ultrasound and endoscopy, “We can, for instance, detect precancerous and cancerous lesions earlier, which makes a tremendous difference in terms of curative treatments,” said Thiruvengadam Muniraj, MD, FRCP, Assistant Professor of Medicine (Digestive Diseases) and Associate Chief for Endoscopy. “When we use these instruments to do a biopsy and give patients an immediate diagnosis, you feel like you’re touching someone’s life and changing things for them in a big way.”

### A BRIDGE TO NEW TREATMENTS

It can help to think of advanced endoscopy as “a bridge” between endoscopy and open surgery, explains Priya Jamidar, MD, FACG, FASGE, Director of Endoscopy at Smilow Cancer Hospital and Professor of Medicine (Digestive Diseases). “It allows us to do a lot of things in a minimally invasive way that just a few years ago would have required open surgery.” One example: Removing gall stones that are left behind in a patient’s bile duct after a gallbladder attack. “In the past, they would have had to undergo a surgical exploration of the bile duct, which generally means a week in the hospital and six weeks of recovery,” explained Dr. Jamidar. “With advanced

endoscopy, we can put a catheter into the bile duct, remove the stone, and have the patient home in a day or two, and back to work in a week, which is tremendously impactful.”

Advanced endoscopic techniques can also be used to remove larger polyps in the colon that would have also once required a major surgical procedure. “We use a technique known as endoscopic mucosal resection to lift the polyp off the lining of the colon and cut it out,” explained Dr. Jamidar.

### ENDOSCOPY ON STEROIDS

The team thanks souped up technology for these advances, including high-definition imaging, and microscopes with resolution powerful enough to allow surgeons to look at individual cells. “What that means is that we can now see very early-stage cancers in the lining of the stomach, esophagus, and colon, as well as do fine needle biopsies in places we can’t get to with a regular endoscope,” said Dr. Muniraj.

With EUS, for instance, “There’s a probe at the tip of the scope that enables us to see structures outside the intestinal tract, which is important for hard-to-detect pancreatic diseases,” said Harry Aslanian, MD, Professor of Medicine (Digestive Diseases) and Director of Endoscopic Ultrasound.

Some of the technology is worthy of a James Bond movie, and it’s evolving fast. “One of the newest tools is called SpyGlass, a tiny camera used in conjunction with

ERCP to go into the bile duct and create images on a large screen TV,” said Dr. Muniraj.

### HANDS ON TREATMENT—AT EVERY STAGE

As important as technology is to Smilow’s advanced endoscopy team, what comes first is patient-centered care. The team has a commitment to getting patients in quickly for their first appointments and follow up visits, which is especially important for individuals coping with difficult-to-treat diseases like pancreatic, esophageal, and bile duct cancers, where early detection is so crucial. With pancreatic cancer, for instance, “We now have the ability to use endoscopic ultrasound to screen individuals who may be at higher risk for developing the disease, with a view toward diagnosing possible cancer earlier and managing it better,” said Dr. Farrell.

If cancer is discovered, EUS allows the team to look at the cells more closely, to take a biopsy with a small needle, to stage the cancer along with colleagues in Yale Pathology, and to determine if surgery is possible. Another advance: Inserting very small 3mm or 10mm gold metallic markers known as fiducials into the tissue of the cancerous organ—typically around the periphery of a tumor—to define its location. “This helps our radiation oncologists know exactly where to focus, especially for very small tumors that can be tough to see on a CT scan,” explained Dr. Farrell. “The



fiducials provide guidance that makes for a more focused, effective treatment that is safer for the patient.”

That’s precision medicine, and advanced endoscopy facilitates it in a very real way. “In 2022, with the help of this technology, we can get down to a molecular level and work with oncologists and radiologists to suggest treatment options based on any mutations we identify,” said Dr. Farrell. “We’ve gone from the ability to merely diagnose a tumor to specifying the type of treatment best suited for each patient.”

### **EASING PAIN AND OTHER SYMPTOMS**

Advanced endoscopic techniques can also be used in a palliative way, producing results that lengthen and improve quality of life for cancer patients and a measure of relief for their families. “A person with cancer should never suffer from pain,” Dr. Jamidar emphasized. With advanced endoscopic tools, it’s possible to inject anesthetic directly where it’s needed. “We do a procedure known as a celiac

plexus block, injecting an anesthetic into the network of nerves behind the pancreas to alleviate pain caused by tumors.”

“ERCP can also be used to place a stent in the pancreas to bypass an obstruction in a minimally invasive way, to relieve jaundice, or enable a patient with blockages to begin eating again,” added Dr. Farrell.

Another minimally invasive technique, known as radiofrequency ablation (RFA), can shrink tumors by delivering radio waves directly to lesions in the bile duct through a tiny probe. “This can increase longevity for patients with bile duct cancer,” explained Dr. Jamidar.

### **TEAM EFFORT**

While advanced technology is all well and good, Smilow’s advanced endoscopy team values the multidisciplinary teamwork even more—that’s what results in the best possible outcomes for patients. “The Advanced Endoscopy team provides a unique set of services, including

very precise diagnosis and staging for patients with liver, bile duct, or pancreatic cancer and related GI malignancies,” said Kevin Billingsley, MD, MBA, FACS, Professor of Surgery (Oncology) and Chief Medical Officer of Smilow Cancer Hospital, who works closely with the advanced endoscopy team. “The diagnostic and staging information they provide is crucial to helping us make the most accurate multidisciplinary treatment decisions.”

And with technology continually being fine-tuned and upgraded, the treatments and patient experiences will only get better. “The types of things we can do through a scope, more safely and effectively than with standard methods, are continually evolving,” said Dr. Aslanian. “It’s a very visual field, very hands-on. You are able to do a lot of problem solving because you get a visual immediately and can go right to the therapy,” he enthuses. “That’s incredibly gratifying.”

**DOCTORS FROM LEFT TO RIGHT:**  
HARRY ASLANIAN, MD | PRIYA JAMIDAR, MD, FACG, FASGE,  
JAMES FARRELL, MD | THIRUVENGADAM MUNIRAJ, MD, FRCP

**The holy grail of dermatology**, says Michael Girardi, MD, FAAD, Professor of Dermatology, is a simple nonsurgical treatment for skin cancers. Dr. Girardi's quest may soon be over. He and his collaborator, W. Mark Saltzman, PhD, Goizueta Foundation Professor of Biomedical Engineering, and Professor of Cellular and Molecular Physiology and of Chemical Engineering, have the grail within their grasp, thanks to sticky nanoparticles.

"Skin cancer is an enormous burden to our patients and our healthcare system," said Dr. Girardi. "There are more skin cancers in the world than all other cancers combined. The incidence is mindboggling, and it keeps growing." Some of his patients with basal cell carcinomas or squamous cell carcinomas have had five, ten, even twenty surgeries, with scars that run together. "An alternative that's simpler for the patient, for the caregiver, and for healthcare management is a tremendous unmet need," he said.

Enter Dr. Saltzman, an expert in nanobiotechnology who designs biocompatible polymers that deliver

chemotherapy via nanoparticles small enough to penetrate a cell. Researchers in Dr. Saltzman's lab had discovered, to their surprise, that they could make particles stick to tissues. They called them bioadhesive nanoparticles (BNPs) and sensed that they might be valuable, but at first didn't know how.

"In fact," said Dr. Saltzman, "we had spent 10 years trying to make particles nonadhesive. One of the paradigms in the field of cancer nano-medicine is that you want particles that you can inject intravenously and that will circulate for a long time."

Someone in Dr. Saltzman's lab suggested that since the new particles would stick to tissues, which included skin, maybe there were dermatological applications. Dr. Saltzman took the idea to Dr. Girardi. The two researchers had been in vague contact before, but this time they met and took a half-hour walk. "That first meeting was a big spark," remembered Dr. Girardi, "this incredibly powerful brainstorming where we could understand each other's worlds and then start to build a whole series of possibilities."

Both had a family connection to skin cancer. Dr. Saltzman grew up in Iowa, where his grandparents were all farmers. "There's lots of skin cancer in my family," he said, "so this is personally important to me." When Dr. Girardi was young, his uncle died from melanoma, leaving his three cousins fatherless. "That has always stayed with me in my research," he said.

Dr. Girardi had long been concerned about sunscreens containing possibly toxic ingredients that penetrate the skin and circulate in the body. So, he and Dr. Saltzman first focused on developing a sunscreen made of sticky nanoparticles that wouldn't wash off, wouldn't breach the skin's surface, and would better prevent the DNA damage that can lead to skin cancer. "It worked fabulously," said Dr. Girardi. They published the results in 2015 in *Nature Materials*. The new sunscreen is under development by Stradefy Biosciences, a company started by both doctors.

Next, they turned their attention to skin cancer itself. Could sticky particles be used to treat basal cell and squamous cell carcinomas that penetrate the skin? Dr. Saltzman knew from research in his lab that nonadhesive


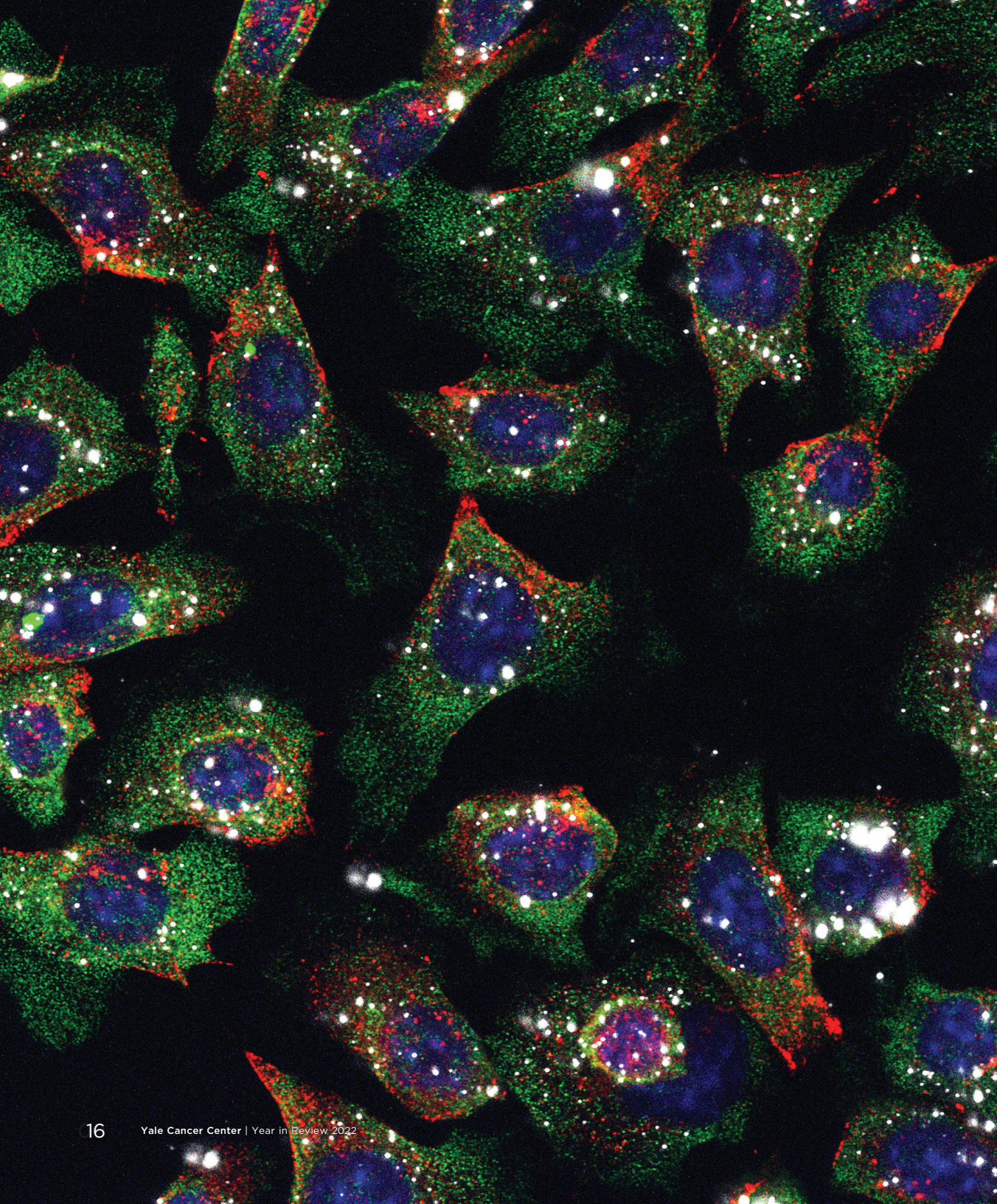
# *sticky nanoparticles*



W. Mark Saltzman, PhD

Michael Girardi, MD, FAAD

*fight skin cancer*



I call it kill and thrill. You have a very efficient way of killing a bunch of tumor cells locally, and then the thrill of stimulating the immune system to get an even better response. And treating something locally in this way has the huge advantage of preventing systemic toxicity.”

—Michael Girardi, MD, FAAD

particles injected into cancer cells simply diffused away. But when he tested the adhesive particles, they stuck to the cancer cells and slowly released their drug into the tumor. The most efficient way to deliver the BNPs turned out to be simplest—through a needle.

“The cancer cells took up the particles in a way we hadn’t fully predicted,” said Dr. Girardi. “We saw that we could deliver them right where we wanted them, into and around the tumor. In some iterations, a single injection basically cured our preclinical model of squamous cell carcinoma. To see that is incredibly exciting.”

He and Dr. Saltzman credit key colleagues for advancing the research on BNPs and skin cancer: Hee-Won Suh, PhD, an associate research scientist in Dr. Saltzman’s lab, and Julia Lewis, PhD, a research associate in Dr. Girardi’s lab.

In their initial tests, the scientists loaded nanoparticles with a potent chemotherapy agent called camptothecin (CPT). CPT is highly potent but imperfect, with many side effects and flaws related to its unstable structure. Drs. Girardi and Saltzman found that encapsulating it in nanoparticles made it more effective and less problematic.

“The nanoparticles do two things to CPT,” explained Dr. Saltzman. “They stabilize it and slowly release it, so that’s one advance. But also, since the nanoparticles deliver the chemotherapy locally, the CPT isn’t going into bone marrow or gut or tissue where it could have a side effect. The particles sit there delivering the drug right around the nucleus of the cancer cell. That overcomes many of the resistance pathways that cancer cells develop to survive chemotherapy.”

Next the two scientists loaded another weapon with the sticky particles—an agent called CpG, which stimulates the immune system. The one-two punch of chemotherapy plus immunotherapy devastated tumors in preclinical models. The scientists believe this combination could eradicate a tumor and prevent it from recurring. These results were published in 2021 in *Proceedings of the National Academy of Sciences*.

“I call it kill and thrill,” said Dr. Girardi. “You have a very efficient way of killing a bunch of tumor cells locally, and then the thrill of stimulating the immune system to get an even better response. And treating something locally in this way has the huge advantage of preventing systemic toxicity.”

For example, he continued, clinicians have learned that some drugs work powerfully in combination but administering them together and systemically at high doses is too toxic for most patients. BNPs make it possible to deliver one of those doses locally, thus preserving the synergy of the combination without causing toxicity.

To emphasize what these new possibilities means for skin cancer patients, Dr. Girardi contrasts two scenarios, present and future. In the first, the doctor numbs the patient with lidocaine, makes an incision, removes a piece of cancerous skin, then stitches up the patient, who returns a week later to have the stitches removed.

“Now imagine a parallel patient,” said Dr. Girardi. “In the same time it took to numb up the first patient, this other patient has already been treated and is gone, because instead of injecting lidocaine you’ve injected the

nanoparticles. So, it takes less time for the caregiver and the patient, it’s more efficient, and there are fewer demands on the healthcare system, so the costs go down. And that’s just on the skin cancer side.”

He and Dr. Saltzman are now looking into wider applications of what they’ve learned, in conjunction with Stradefy. In preliminary tests, BNPs seem to work across different tumor types. The sticky particles bind firmly to the tumor matrix and slowly release their load into the tumor cells. Drs. Girardi and Saltzman have been meeting with surgical oncologists at Yale to develop a way to use BNPs to treat metastatic melanoma. Dr. Saltzman is exploring BNPs against ovarian cancer cells, pancreatic cancer cells, and glioblastomas. He has been using nanoparticles on glioblastomas for a long time, he noted, “but we’ve discovered that these sticky particles work a lot better. There are probably many other solid tumors where this would work brilliantly, like in the prostate, if you could get the tumor at the stage where it’s accessible by needle.”

He and Dr. Girardi have started talking about how to conduct clinical trials for BNPs in skin cancer, which they hope to begin late in 2022 with a clinical treatment available in three to five years. The holy grail is within reach.

### Cancer research is awash with databases

that capture widely different aspects of the disease, from tumor samples and genomic sequencing to clinical study results, sociodemographics, and billing. This information typically gets warehoused in unconnected data sets, investigated by different types of researchers, and published in journals specific to their focus of research. Michaela Dinan, PhD, Associate Professor of Epidemiology (Chronic Diseases) and Co-Leader of the Cancer Prevention and Control Research Program at Yale Cancer Center, sees that as a lost opportunity. Her research demonstrates that when disparate data sets are pushed into conversation with each other, they can disclose new insights about cancer, cancer care, and the healthcare system.

“If you can think of novel ways to use data that have been around a long time,” said Dr. Dinan, “you can make real contributions to the field.”

Her most recent contribution was published in *JAMA Network Open* in October 2021. The paper describes a pilot study that investigated how breast cancer screening impacts clinical, genomic, and sociodemographic factors associated with newly diagnosed breast cancer. Dr. Dinan and colleagues did this by combining and cross-analyzing information from separate databases to create a first-in-kind linkage of genomic data with real-world, population-level diagnoses of breast cancer.

The National Cancer Institute (NCI) hosts the Surveillance, Epidemiology, and End Results (SEER)-Medicare Program and collects the information through the linkage of two distinct data sets. The SEER dataset

provides cancer incidence and survival, including detailed information such as each tumor’s stage of diagnosis and histology. The database also includes general socioeconomic information such as income and education levels based on zip codes. The NCI then links data from Medicare claims, which include the medical care that an individual has had over time, such as cancer tests and treatments. All patients have their identity protected by extensive checks and balances to ensure that no individual patient can ever be identified from the research. The novelty of the project is that Dr. Dinan and her colleagues combined this SEER-Medicare data with physical tumor specimens from the SEER-Residual Tissue Repositories (RTRs) and then conducted gene expression analysis.

“This was the first study to link physical tumor samples for these patients in this SEER database to Medicare claims data, and to create one novel data set,” said Dr. Dinan. “If you only look at one data set, you’re not getting the whole picture.”

The combined data revealed that socioeconomic status and access to screening remained associated with mortality among patients with breast cancer. “That’s probably our number one finding,” said Dr. Dinan. “Our research suggests that living in resource-poor neighborhoods with less access to care may be important as well.”

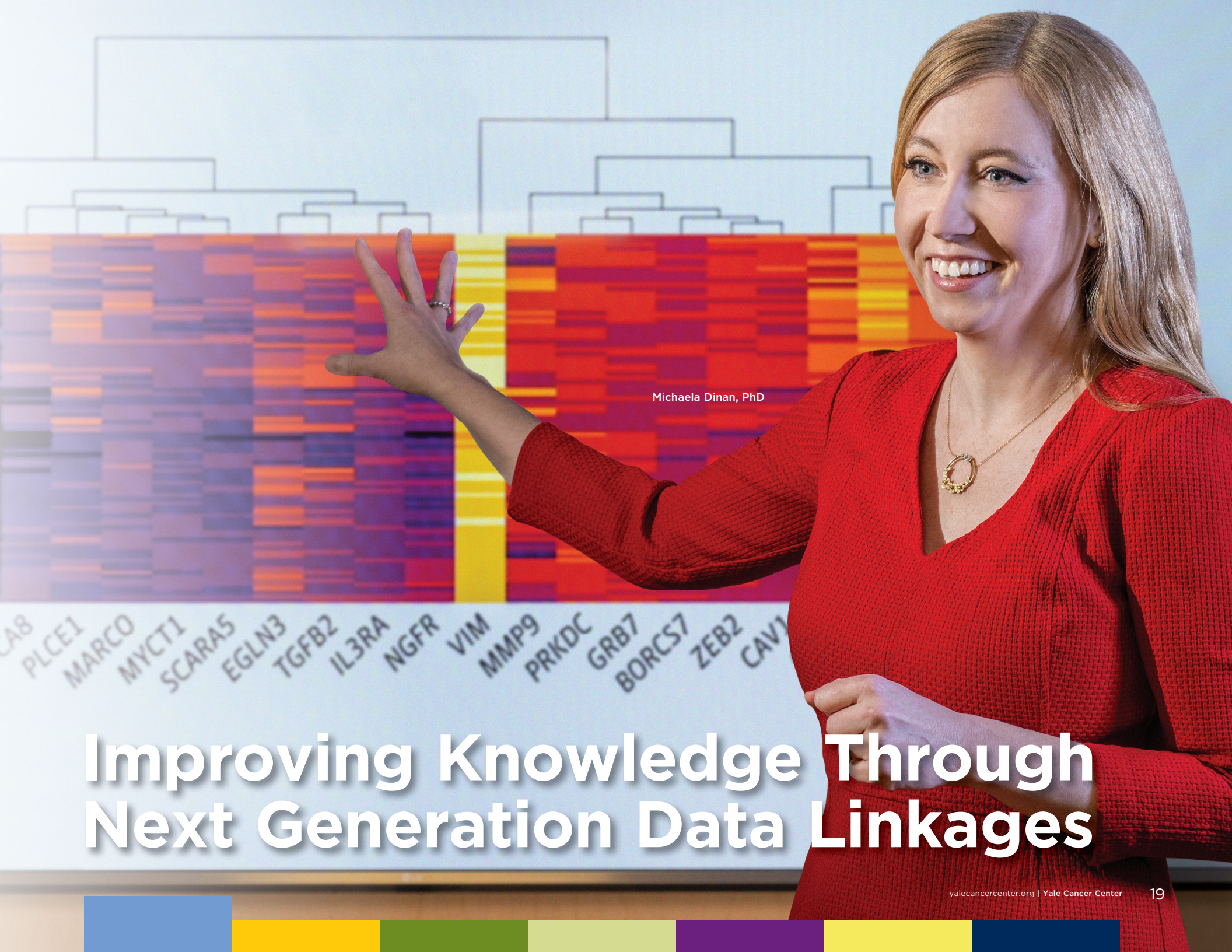
To link and cross-analyze databases might seem obvious in retrospect, but Dr. Dinan understands part of the reason it had not been done before. To collect and interpret the merged data took almost a decade. “There were lots of roadblocks,” she said. “One of the main challenges in obtaining funding was the concern that ‘It isn’t feasible.’ But now we can say it’s

possible because we’ve done it.”

Dr. Dinan is now proposing the first-ever linkage between the SEER-Medicare databases and the SEER-Virtual Tissue Repository (VTR), which is a prospective, forward-facing version of the work done with the SEER-RTR. Dr. Dinan wants to mine the databases to answer two questions about the use of immunotherapy to treat renal cell carcinoma (RCC). About 20 percent of RCC patients have a “durable response” to these therapies, meaning a potential cure, but no one can predict who those patients will be. Second, between one to three percent of RCC patients have severe toxic reactions to immunotherapies. Again, no one knows beforehand who those patients will be.

This is where Dr. Dinan’s methodology shows its value. Dr. Dinan will use the SEER-Medicare data to identify everybody who received immunotherapy for RCC and identify two cohorts of patients, one that shows evidence of a durable response and another that shows evidence of a severe autoimmune toxicity.


“So, we’ll cherry pick these people,” said Dr. Dinan. “Instead of waiting to see what happens in a clinical trial, we’re going to find the outcome of interest first, and then go back and pull those patients to study what’s different about them. We’ll have their whole clinical profile from the SEER data, their whole treatment profile from Medicare claims, and then we’ll use the SEER-VTR to do genomic sequence analysis on their tumors to see if we can figure out what’s driving these rare events, whether a durable response or a severe reaction. This has huge implications for our ability to study rare events and rare cancers in the future.”



Michaela Dinan, PhD

# Improving Knowledge Through Next Generation Data Linkages

LA8  
PLCE1  
MARCO  
MYCT1  
SCARA5  
EGLN3  
TGFB2  
IL3RA  
NGFR  
VIM  
MMP9  
PRKDC  
GRB7  
BORCS7  
ZEB2  
CAV1



Yajaira Suarez, PhD

# Attacking Cancer Cells from the Outside



## Most cancer treatments are a direct assault

on cancer cells through radiation, chemotherapy, or targeted therapy. Yet, new alternative approaches are also showing tremendous promise. “Targeting cancer cells is important,” said Yajaira Suarez, PhD, Deputy Chair and Anthony N. Brady Associate Professor of Comparative Medicine, “but we are interested in the other side.”

Dr. Suarez is referring to the ecosystem surrounding the cancer cells, the ‘tumor microenvironment.’ She studies how that environment influences the tumor growth. More specifically she is interested in two types of cells within the tumor microenvironment: endothelial cells, which create blood vessels, and macrophages, white blood cells integral to the immune system. Her research focuses on the novel mechanisms that regulate the functions of these two cell types.

When normal cells become cancerous and start to proliferate, she explains, they secrete factors whose signals cause two responses. One signal stimulates endothelial cells to produce blood vessels to feed and oxygenate the tumor. Another signal tells the immune system to send white blood cells to fight the mutating cancer cells. “But because these macrophages are in the microenvironment, with factors secreted by the tumor,” explained Dr. Suarez, “they become addicted, let us say, and transform from their normal function. Instead, they start helping the tumor to grow.”

To understand the mechanisms behind these two actions, Dr. Suarez and her colleagues turned their attention to microRNAs within the tumor microenvironment. MicroRNAs are small noncoding fragments of RNA that don’t produce protein. That makes them sound like molecular

nonentities, but the reality is far different.

“They interact with RNAs that produce proteins,” said Dr. Suarez, “and they regulate gene expression. That leads to controlling the level of these proteins and therefore controlling cell function. And these microRNAs can control not just one RNA molecule, but different RNA molecules, so they control different proteins.”

More importantly, she adds, the RNAs targeted by microRNAs are not random, but are selected to command signaling pathways and metabolic pathways. “This is the beauty of microRNAs,” she said. “Because they control different pathways and different proteins, they give you this ability to target more than one protein in antitumor treatments, so you can get an overall effect that is more pronounced.”

Dr. Suarez and her colleagues knew that the most upregulated microRNA in solid tumors is microRNA-21 (miR-21). It is also overexpressed in cells from the tumor microenvironment. Dr. Suarez’s team used animal models to analyze the links between miR-21, the tumor microenvironment, and growth. They found that miR-21 sends signals from the tumor microenvironment that regulate cells associated with tumorigenesis, including endothelial cells and tumor-associated macrophages (TAMs).

Next, using a mouse model, they removed miR-21 from the macrophages to see what would happen. “Everything changed,” said Dr. Suarez. In the paper reporting their results, published in the *Journal of Clinical Investigation*, the scientists wrote that the absence of miR-21 in the macrophages “caused a global rewiring of their transcriptional regulatory network.” The macrophages shook off their addiction and started instructing

T cells to kill cancer cells, shrinking the tumor. To a similar effect, the endothelial cells stopped forming blood vessels that fed the tumor.

“By targeting miR-21 in the macrophages, we were able to reduce tumor growth through two different mechanisms,” explained Dr. Suarez. These findings suggest clear benefits of targeting not only the cancer cells but its surrounding microenvironment. When signals from the microenvironment don’t reach the tumor, the power of the cancer treatment gets amplified because the T cells strengthen as the tumor’s vasculature withers.

Dr. Suarez calls the paper a proof-of-concept that points the way to other possible uses of this strategy. For instance, tumors often develop resistance to immunotherapies. Combining such therapies with a drug that targets microRNAs in the tumor microenvironment could unleash fresh hordes of T cells that boost the immune effect. A common side effect of radiation therapy, continues Dr. Suarez, is masses of macrophages, which can overwhelm the radiotherapy. That might be reversed by targeting miR-21 in the macrophages.

Dr. Suarez and her colleagues are now testing all these possibilities. She believes that other microRNAs could be targetable as well, not only in macrophages and endothelial cells, but in other cells within the tumor microenvironment.

She emphasizes that her research emerges from her collaborations at Yale. “The Yale environment is fantastic,” said Dr. Suarez. “The investigators, the teams, the meetings with people in the Cancer Center about signaling—everything is set up to produce more insight and better ideas to do better research.”

**Faye Rogers, PhD, was puzzled, a fruitful** state for a scientist. The Associate Professor of Therapeutic Radiology knew that cells respond to DNA damage by alerting a network of pathways to manage it and thus preserve genomic integrity. “One of the foundational questions of my lab,” said Dr. Rogers, “is how do these pathways talk to each other? And, if too much damage occurs, and the DNA can’t be repaired efficiently, how do cells determine to activate apoptosis [cell death] to preserve genomic integrity?”

The answers she found to those questions point to new possibilities for cancer treatment. Dr. Rogers and her team have discovered a way to turn on the apoptotic pathway in cancer cells, tricking them into killing themselves while leaving normal cells unscathed. Their research was published in October 2021 in *Nature Biotechnology*.

Working with a model of HER2-positive breast cancer, the scientists had been studying nucleotide excision repair (NER). NER is one of the main pathways for removing damaged strands of DNA and replacing them with healthy strands that restore the normal structure, a double helix. At a specific sequence on the DNA, Dr. Rogers and her team inserted a three-stranded structure using a triplex-forming oligonucleotide (TFO) that binds to the site. Then they watched how the NER pathway responded. Instead of removing and mending the damaged DNA, the pathway signaled for cell death within the tumor.

“We realized that if we created multiple triplex structures, we could induce apoptosis,” explained Dr. Rogers. “That gave us a really unique opportunity in cancers that have gene amplification.”

Here’s why: gene amplification is an abnormality in which multiple copies of a gene appear on a segment of DNA, a disorder that occurs frequently in cancer cells. HER2-positive breast cancers, for instance, are marked by gene amplification. Dr. Rogers realized that those duplicate genes could become targets.

“In HER2 amplified genes, there are multiple TFO binding sites because there are so many copies,” she said. “We knew that if we could create enough of these triplex structures at those specific sequences within the cancer, the cell would decide, ‘There’s too much damage, we can’t fix it, so we should just activate apoptosis.’ You basically hijack the cell’s own mechanisms to make it do what you want it to do.”

This ingenious method of attack also spares healthy cells, which carry only two copies of a gene, so NER easily mends damage from the two binding events caused by the TFO.

In animal models of HER2-positive breast cancer, TFOs caused tumors to shrink by about half. That’s comparable to the drug trastuzumab (Herceptin), the primary targeted therapy for HER2-positive breast cancer. Trastuzumab inhibits the overexpressed HER2 receptor protein that helps cancer grow.

But TFOs offer a major advantage over drugs that work by inhibiting the overexpressed protein driving the cancer. Gene amplification often allows cancer cells to figure out ways to sidestep the inhibitor and resume growth. This drug resistance has proven to be the Achilles heel of many therapies, including trastuzumab.

“But the gene amplification in the cell remains the same,” said Dr. Rogers, “so we can use our strategy to overcome drug

resistance in these cancers. We don’t need an overexpressed protein to target. In fact, we don’t even need the amplified gene to be the driver for our strategy to work against the cancer, because it’s not a factor of protein or cellular function, it’s a factor of DNA damage response that activates either repair or apoptosis.”

The TFO strategy offers another major advantage. Dr. Rogers and her team have designed TFOs that can target and bind to many different sites in the genome. She expects to be able to target genes anywhere within the genome.

That leads to what may be the most exciting vista opened by Dr. Rogers’s research. HER2 is just the beginning. More than 460 amplified genes have been implicated in 14 cancer subtypes. All these genes are potentially vulnerable to specific TFOs. Currently, Dr. Rogers and her team are focusing on cancers that lack targeted therapies, such as ovarian cancer. At the top of Dr. Rogers’s most-wanted list is *c-Myc*, an oncogene amplified in up to 70 percent of human cancers, including ovarian.

“Right now, we’re designing new TFOs and getting ready to test them to see if we see the same kind of bioactivity we saw when we targeted HER2,” said Dr. Rogers. Her lab is also exploring different ways to deliver the TFOs, from nanoparticles to antibodies.

“We’re really excited about this work,” she added. “I think it has the potential to serve as the foundation for a platform that can be beneficial for the next generation of precision medicine for a wide range of patients who suffer from many different cancers.”





Faye Rogers, PhD

# Building the Next Platform for Precision Medicine





Gin Yan, PhD

Marcus Bosenberg, MD, PhD

# An Unexpected Ally Against Cancer: Junk DNA

**“I never expected this kind of robust response,”** said Qin Yan, PhD, Associate Professor of Pathology; Director of the Center for Epigenetics and Biomarkers; Scientific Co-Director of the Center for Breast Cancer; and Co-Leader of the Genomics, Genetics, and Epigenetics Research Program at Yale Cancer Center. He was describing what he saw in a melanoma mouse model. “The whole tumor was completely gone.”

“At that point it was very clear that this would be something of interest to work on,” added Dr. Yan’s collaborator, Marcus Bosenberg, MD, PhD, Professor of Dermatology, Pathology, and Immunobiology; Co-Leader of the Cancer Immunology Research Program; Director of the Yale Center for Immunology; and Co-Director of the Yale SPORE in Skin Cancer.

Their research on two enzymes, KDM5B and SETDB1, has revealed epigenetic keys that could open the door to powerful new treatments for melanoma and other cancers, including cancers resistant to immunotherapies. The results of their research, which was supported by the Yale SPORE in Skin Cancer, were published in October 2021 in the prestigious journal *Nature*.

Drs. Yan and Bosenberg’s moment of surprise sounds sudden but was decades in the making. Dr. Yan began studying the KDM5 family of proteins more than 15 years ago during his postdoctoral training at the Dana-Farber Cancer Institute in the lab of William Kaelin, MD, who recently won the Nobel Prize in medicine. He has continued to research KDM5 in his lab at Yale. Dr. Bosenberg runs one of the nation’s leading labs on melanoma research. He has developed numerous mouse models used by scientists around the world to test melanoma

therapies. The two researchers came together about a decade ago over their mutual interest in epigenetics and began exploring KDM5B’s role in melanoma. The new paper is the culmination of five years of collaborative effort.

The first step was their finding that high KDM5B level is associated with poor response to immunotherapy in human melanoma patients. Consistently, when Drs. Yan and Bosenberg’s group depleted KDM5B in the mouse model, the immune system woke up and activated type-1 interferon, which stimulated an increase in T cells, which began killing tumor cells. Drs. Yan and Bosenberg discovered that depleting SETDB1 has the same effect, awakening the immune system to attack cancer cells.

Getting rid of KDM5B and SETDB1 somehow activates “retroelements”—non-coding parts of the genome that are sometimes called junk DNA. “There are a lot of these things,” said Dr. Bosenberg, “almost like barnacles on a ship, that have evolved over the years, and they are kind of silent. When either KDM5B or SETDB1 is removed, these retroelements can then be expressed or seen, and we’ve shown that that process is very important for this enhanced anticancer immune response that we’re seeing in the tumors.”

In fact, he and Dr. Yan found that KDM5B recruits SETDB1 to silence retroelements and stop them from alerting the immune system. These discoveries excite the researchers because the findings suggest that it might be possible to treat tumors that either don’t respond to immune therapies or that develop resistance to them. Such therapies usually target genes expressing a specific protein or showing lots of mutations, and they have been highly effective in some cancers for some

patients. Yet too often the cancer cells defeat the strategies behind such immunotherapies or eventually find ways to overcome them.

“But with these retroelements,” said Dr. Bosenberg, “the tumors are carrying all the things that the immune system might need to recognize them, and they could be turned on to generate effective responses against hard-to-treat tumors and tumors that don’t have a lot of mutations, like pediatric tumors. It’s not clear that’s going to be the case, but it was true for the tumors in our study.”

There is more promising news in this research. When these retroelements are released to express themselves and trigger the immune system, the effect seems to be long-lasting. “This approach might establish the so-called immune memory response,” explained Dr. Yan. “Patients treated this way are likely to have a defense system to prevent future recurrence of these tumors. We have data to show this in the mouse model.”

Both scientists are now trying to decipher the mechanism or mechanisms behind the responses they have documented. They are also working to develop drugs that deplete or inhibit the enzymes, with Dr. Yan focusing on KDM5B and Dr. Bosenberg on SETDB1. Dr. Yan is working with a new class of drugs called degraders that destroy specific proteins such as KDM5B and remove them from the cell. That would stop KDM5B from recruiting SETDB1 to silence the retroelements. He is confident this can be done. “We have found some compounds that can degrade KDM5B,” he said. Dr. Bosenberg is equally confident about finding inhibitors that are effective on SETDB1. “We have enough to work on for ten years to come,” said Dr. Yan.

### Cancerous tumors are hostile environments

where T cells fight to kill cancer cells, which in turn try to kill or silence the T cells. “That’s where we started,” said Nikhil Joshi, PhD, Assistant Professor of Immunology. “We figured that if T cells inside the tumor constantly get killed or shut off, how are there still enough of them in there to get activated when a patient receives immunotherapy?”

The answer surprised him and Kelli Connolly, PhD, a postdoctoral associate in his lab. Using a mouse model, they found that dead or exhausted T cells in the tumor were constantly replenished by a slow trickle of fresh T cells that infiltrate the tumor from reservoirs in nearby tumor-draining lymph nodes. These T cell reinforcements fight the progression of the disease and likely boost the tumor’s response to immunotherapy. Drs. Joshi and Connolly’s findings were reported in September 2021 in *Science Immunology*.

Researchers previously knew that lymph nodes contain T cells that are activated to invade when tumor cells develop nearby. “What wasn’t understood,” said Dr. Connolly, “is that this migration continues as the tumor progresses, which could be for years.”

“It never made sense to look for T cells in the lymph nodes,” added Dr. Joshi, “because once they were activated, why would they stay in the lymph node and not go to the tumor? It’s clever that the immune system hangs on to these cells offsite and sends them out later.”

In fact, noted Dr. Connolly, clinicians often see these lymph nodes as places where the tumor might spread, so clinicians sometimes remove them, thus eliminating the

reservoir of T cells. Dr. Connolly hopes the new paper shifts that perspective.

The discovery of this unknown migration was a breakthrough, but Drs. Joshi and Connolly are more energized by its implications for cancer treatment. Most tumors—typically about 80 percent—do not respond to immunotherapy. What would happen, wonder Drs. Joshi and Connolly, if that reservoir of T cells in the lymph nodes could be induced to migrate en masse into a tumor? Current immunotherapies do not seem to prompt the T cells to leave the lymph nodes.

“I would say the most exciting part of our findings is that they suggest we can target T cells in the draining lymph nodes to make some immunotherapies more effective,” said Dr. Connolly.

Dr. Joshi agrees. In the future, cancer patients whose tumors don’t contain enough T cells to fight the disease might be able to tap a reservoir close by. Figuring out how to make that happen is the next task for Drs. Joshi and Connolly.

They suspect that the T cells in the lymph nodes get a signal telling them to migrate. If the researchers can detect and mimic that signal, they could induce migration. “We envision finding the mechanism that gets T cells out of the lymph nodes and into the tumor,” said Dr. Connolly. “I think that’s what we see as most promising therapeutically. That could help the large group of patients who don’t respond to immunotherapy.” They envision this prospective immunotherapy augmenting current immunotherapy treatments, possibly along with chemotherapy and radiation.

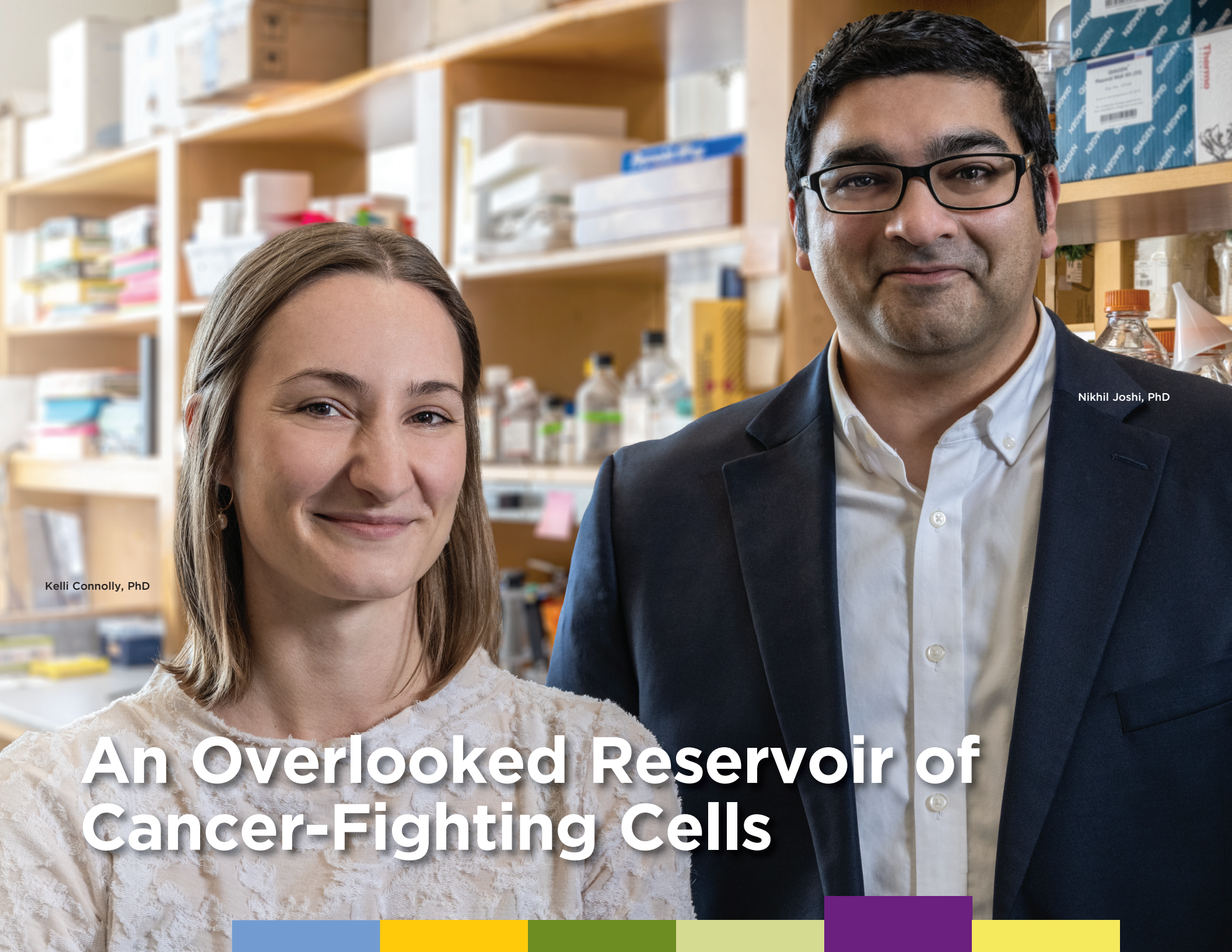
Drs. Joshi and Connolly are already exploring prospects in mouse models, trying various drugs that might stimulate migration of T cells into the tumor. Dr. Connolly mentions another way to translate their research more quickly: CAR T cell therapy, an immunotherapy in which T cells from a patient’s tumor are removed, genetically altered, then grown in high numbers and reinserted into the patient.

“Our research has lots of implications for therapies that currently use T cells from tumors,” she noted, “because our findings show there is this other excellent source of T cells—the tumor draining lymph nodes—where you most likely will get more and better-functioning T cells than you can get from the tumor.”

Drs. Joshi and Connolly have already been approached by clinical researchers at Yale who recognize the promise of this possibility. If the two immunologists can identify the mechanism that releases the T cells from the lymph nodes, there are also clinical collaborators at Yale interested in refining a drug design and running trials.

“Yale is great in that aspect,” said Dr. Joshi, “There are a lot of people here eager to collaborate to solve these problems. So, the chances are high that this discovery gets translated into meaningful gains for patients.”

Their paper also drew attention to Dr. Joshi’s advanced mouse model, which took him eleven years to develop. It was a big reason Dr. Connolly wanted to work in his lab, and now researchers are requesting it from all over, which delights Dr. Joshi. “We’re sending it out,” he said, “and hoping that people will use it to achieve breakthroughs in their own work.”



Kelli Connolly, PhD

Nikhil Joshi, PhD

# An Overlooked Reservoir of Cancer-Fighting Cells



Jong Woo Lee, PhD

Barbara Burtness, MD

# Overcoming Drug Resistance in Lung Cancer



**When asked which aspects of her recent** research on *KRAS* mutations represent breakthroughs, Barbara Burtness, MD, laughed and said, “In its entirety. It’s totally new.” Dr. Burtness is a Professor of Medicine (Medical Oncology); Co-Leader of the Developmental Therapeutics Research Program; Disease Aligned Research Team Leader for the Head and Neck Cancers Program; and Interim Associate Cancer Center Director for Diversity, Equity, and Inclusion. She and her collaborator, Jong Woo Lee, PhD, a research scientist at Yale Cancer Center, recently presented their striking findings.

Non-small cell lung cancer (NSCLC) with *KRAS* mutation accounts for about 30 percent of all lung cancers. “They typically have a poor prognosis,” said Dr. Burtness, “and until recently there had been no great success in targeting mutated *KRAS*.” Recent news has been more encouraging. Two drugs that target *KRAS*-G12C, the most common mutation, have demonstrated response rates of 40 to 50 percent in NSCLCs with the mutation. In May, the FDA approved one of these drugs, sotorasib, for use against these cancers, and in June the agency designated the other drug, adagrasib, as a “breakthrough therapy,” which put it on the fast track toward approval.

But this good news comes with an asterisk. The new *KRAS* inhibitors are not effective for very long. In most patients, the lung tumors eventually sidestep the inhibitor and begin to grow again, typically within five months. “It appears to be extremely common for patients to develop acquired resistance,” said Dr. Burtness. “There’s already a lot of research looking for the mechanisms of resistance.”

Drs. Burtness and Lee have been working on a related target, Aurora Kinase A (AURKA), for many years. Knowing that there is a signaling pathway that connects *KRAS* to AURKA and that overexpression of AURKA seems to drive worse outcomes in lung cancer, they pursued the idea of a combination. “We took a lung cancer cell line with *KRAS* mutations and tested a combination of sotorasib and an AURKA inhibitor called VIC-1911,” said Dr. Lee, “and we found an effect of really profound synergy.” Inhibiting AURKA seems to prevent tumor cells from developing resistance to the *KRAS* inhibitor, and as a result some of the cells begin to die.

Dr. Burtness knew from her work on head and neck cancers, where AURKA is an important target, that the protein kinase WEE1 is also implicated. She and others at Yale had been testing AURKA inhibitors and WEE1 inhibitors alone or in combination on head and neck cancer. The scientists wondered whether inhibiting AURKA and WEE1 simultaneously might replace the need for chemotherapy. Drs. Burtness and Lee began testing that hypothesis five years ago.

“The combination was extremely synergistic, and we have validated it in animal models,” explained Dr. Burtness. “We had also started validating it in lung cancer when the *KRAS* drugs became available, and that’s one reason we moved so swiftly on this.”

When they added the WEE1 inhibitor adavosertib to the AURKA inhibitor VIC-1911 and tested the combination against *KRAS*-mutated lung cancer cells with resistance to sotorasib, the result was what biologists call mitotic

catastrophe—extensive cell death.

Drs. Burtness and Lee are currently testing these combinations in animal models, but the need to find a way to overcome resistance to sotorasib is so urgent that the combination is also quickly moving to patients. Yale will host a clinical trial this year involving sotorasib and VIC-1911. Keeping the trial at Yale is important, said Dr. Burtness. “The goal of the Developmental Therapeutics Program is to do basic and translational science that ends up in clinical trials that benefit our patients.”

The principal investigator of the clinical trial will be Sarah Goldberg, MD, MPH, Associate Professor of Medicine (Medical Oncology) and Research Director of the Center for Thoracic Cancers. Patients with NSCLC who are resistant to the *KRAS* inhibitor will receive either VIC-1911 alone or in combination with sotorasib. Patients who have not been previously treated with the *KRAS* inhibitor will get sotorasib plus VIC-1911.

As the trial proceeds, Drs. Burtness and Lee will test all these drug combinations on cell models, animal models, and tissue samples from the study’s patients. They also think that as more *KRAS* inhibitors come online, the strategy of combining them with inhibitors of AURKA or AURKA plus WEE1 could be effective against other cancers.

“I’m really lucky to work with Dr. Burtness on head and neck cancer and also on lung cancer,” said Dr. Lee. “In my career, working at Yale is the first time I could see some translational perspective. I’m a biologist, always working in the lab, but this is one of my dreams—to come here and to see a clinical trial based on my findings.”

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Xiaomei Ma, PhD

#### Cancer Signaling Networks

Daniel P. Petrylak, MD

Katerina Politi, PhD

David F. Stern, PhD

#### Developmental Therapeutics

Karen S. Anderson, PhD

Barbara A. Burtness, MD

#### Genomics, Genetics, and Epigenetics

Lajos Pusztai, MD, DPhil

Jeffrey Townsend, PhD

Qin Yan, PhD

#### 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

Zhe Jay Chen, PhD

#### Clinical Research Services

Ian E. Krop, MD, PhD

*Chief Clinical Research Officer  
and Director of the Clinical Trials Office*

Roy H. Decker, MD, PhD

*Special Advisor, Clinical Trials Office*

Nirmala Thevathasan, MPH

*Interim Administrative Director, Clinical Trials Office*

Stacey Stein, MD

*Assistant Director, Clinical Trials Office*

Neal Fischbach, MD

*Assistant Director, Care Centers*

Stephanie Halene, MD, PhD

*Assistant Director, Clinical Research Support Laboratory*

#### Flow Cytometry

Ann Haberman, 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



## Smilow Cancer Hospital

Eric P. Winer, MD

### Physician-in-Chief

Lori Pickens, MHA

### Senior Vice President and Executive Director

Kevin G. Billingsley, MD, MBA, FACS

### Chief Medical Officer

Kim Slusser, MSN, RN, CHPN, NEA-BC

### Vice President, Patient Services

Kevin Vest, MBA, FACHE

### Vice President, Disease Centers

Kerin B. Adelson, MD

### Chief Quality Officer

### Deputy Chief Medical Officer

Anne Chiang, MD, PhD

### Chief Integration Officer

### Deputy Chief Medical Officer

Marcella Nunez-Smith, MD, MHS

### Chief Health Equity Officer

### Deputy Chief Medical Officer

Mehra Golshan, MD, MBA, FACS

### Deputy Chief Medical Officer

### for Surgical Services

Lynn Wilson, MD, MPH, FASTRO

### Deputy Chief Medical Officer

### for Therapeutic Radiology

Jeremy Kortmansky, MD

### Chief Network Officer

### Associate Chief Medical Officer

Sarah S. Mougalian, MD

### Chief Ambulatory Officer

Tara B. Sanft, MD

### Chief Patient Experience Officer

Sonia Grizzle

### Executive Director, Administration

## Multidisciplinary Clinical Centers

### Chênevert Family Brain Tumor Center

Ranjit Bindra, MD, PhD

Jennifer Moliterno, MD

Antonio Omuro, MD

### Center for Breast Cancer

Mehra Golshan, MD, MBA

Maryam Lustberg, MD

### Cellular Therapies

Michael Hurwitz, PhD, MD

Iris Isufi, MD

### Endocrine Cancers

Jennifer Ogilvie, MD

### Center for Gastrointestinal Cancers

Pamela Kunz, MD

### Gynecologic Oncology

Elena Ratner, MD

Alessandro D. Santin, MD

### Head and Neck Cancers

Barbara A. Burtness, MD

Benjamin L. Judson, MD

### Hematology

Stephanie Halene, MD, PhD

### Liver Cancer

Mario Strazzabosco, MD, PhD

### Melanoma

Mario Sznol, MD

### Phase I

Patricia M. LoRusso, DO

### Prostate and Urologic Cancers

Michael Leapman, MD

Daniel P. Petrylak, MD

### Sarcoma

Dieter M. Lindskog, MD

### Therapeutic Radiology

Lynn D. Wilson, MD, MPH

### Center for Thoracic Cancers

Roy S. Herbst, MD, PhD

## Specialty Programs

### Cancer Genetics and Prevention

Xavier Llor, MD, PhD

### Screening and Prevention

Xavier Llor, MD, PhD

### Cardio-Oncology

Lauren A. Baldassarre, MD

### Integrative Medicine

Gary Soffer, MD

### Interventional Oncology

David C. Madoff, MD

### Ocular Oncology

Renelle Lim, MD

### Onco-dermatology

Jonathan Leventhal, MD

### Pain Medicine

Donna-Ann Thomas, MD

### Palliative Care

Jennifer Kapo, MD

### Psycho-Oncology

Jennifer Kilkus, PhD, ABPP

### Sexuality and Intimacy

Elena Ratner, MD

Stanton Honig, MD

### Spine Oncology

Ehud Mendel, MD, MBA

### Cancer Survivorship

Tara Sanft, MD

### Tobacco Treatment

Lisa M. Fucito, PhD

## Yale Cancer Center Membership

### Cancer Immunology

Stephan Ariyan  
Philip Askenase  
Jeffrey Bender  
Marcus Bosenberg  
Alfred Bothwell  
David Braun  
Richard Bucala  
Grace Chen  
Lieping Chen  
Joseph Craft  
Peter Cresswell  
William Damsky

Richard Edelson  
Brinda Emu  
Richard Flavell  
Francine Foss  
Jorge Galan  
Michael Girardi  
Earl Glusac  
Ann Haberman  
David Hafler  
Douglas Hanlon  
Stavroula Hatzios  
Jeanne Hendrickson

Kevan Herold  
Ya-Chi Ho  
John Hwa  
Jeffrey Ishizuka  
Akiko Iwasaki  
Nikhil Joshi  
Paula Kavathas  
Steven Kleinstein  
Smita Krishnaswamy  
Priti Kumar  
Jonathan Leventhal  
Carrie Lucas

Stacy Malaker  
Mark Mamula  
Jennifer McNiff  
Ruslan Medzhitov  
Eric Meffre  
Kathryn Miller-Jensen  
Ruth Montgomery  
Walther Mothes  
Markus Müschen  
Kelly Olino  
Noah Palm  
Zenggang Pan

Tristen Park  
Joao Pereira  
Jordan Pober  
Anna Marie Pyle  
Aaron Ring  
Carla Rothlin  
Nancy Ruddle  
Kurt Schalper  
David Schatz  
Stuart Seropian  
Brian Smith  
Edward Snyder

Xiaolei Su  
Mario Sznol  
Peter Tattersall  
Robert Tigelaar  
Mary Tomayko  
Thuy Tran  
Juan Vasquez  
Xiong Yong  
Tianxiang Zhang

### Cancer Prevention and Control

Kerin Adelson  
Kathleen Akgun  
Prasanna Ananth  
Harry Aslanian  
Brett Bade  
Elizabeth Berger  
Kevin Billingsley  
Susan Busch  
Brenda Cartmel  
Anees Chagpar  
Elizabeth Claus  
Nicole Deziel  
Michaela Dinan

Leah Ferrucci  
Charles Fuchs  
Lisa Fucito  
Courtney Gibson  
Mehra Golshan  
Cary Gross  
Raul Hernandez-Ramirez  
Yuan Huang  
Scott Huntington  
Melinda Irwin  
Sofia Jakab  
Ania Jastreboff  
Caroline Johnson

Beth Jones  
Benjamin Judson  
Amy Justice  
Manisha Juthani-Mehta  
Jennifer Kapo  
Mary Knobf  
Grace Kong  
Suchitra Krishnan-Sarin  
Donald Lannin  
Michael Leapman  
Ira Leeds  
Lingeng Lu  
Maryam Lustberg

Shuangge Ma  
Xiaomei Ma  
Asher Marks  
Sherry McKee  
Sara Mehra  
Rajni Mehta  
Anne Mongiu  
Sarah Mougalian  
Linda Niccolai  
Marcella Nunez-Smith  
Stephanie O'Malley  
Jennifer Ogilvie  
Elijah Paintsil

Bohdan Pomahac  
Elizabeth Prsic  
Jonathan Puchalski  
Elena Ratner  
Ilana Richman  
Harvey Risch  
Joseph Ross  
Peter Salovey  
Tara Sanft  
David Sells  
Sangini Sheth  
Andrea Silber  
Dorothy Sippo

Mehmet Sofuoglu  
Donna Spiegelman  
Sakinah Suttiratana  
Tamar Taddei  
Jamie Tam  
Alla Vash-Margita  
Sten Vermund  
Shi-Yi Wang  
Wei Wei  
Xiao Xu  
Yong Zhu

### Cancer Signaling Networks

Anna Arnal Estape  
Anton Bennett  
Titus Boggon  
David Breslow  
Guoping Cai  
David Calderwood  
Gary Desir  
Michael DiGiovanna  
Rong Fan  
Kathryn Ferguson  
Carlos Fernandez-Hernando  
Clare Flannery

Ellen Foxman  
John Geibel  
Sourav Ghosh  
Valentina Greco  
Julie Hens  
Mark Hochstrasser  
Robert Homer  
Valerie Horsley  
Won Jae Huh  
Peter Humphrey  
Michael Hurwitz  
Karl Insogna

Richard Kibbey  
Isaac Kim  
Joseph Kim  
Daryl Klein  
Anthony Kolesko  
Shalin Kothari  
TuKiet Lam  
Francis Lee  
Mark Lemmon  
Andre Levchenko  
Yansheng Liu  
Michael Mak

Darryl Martin  
Jon Morrow  
Peggy Myung  
Michael Nathanson  
Don Nguyen  
Rachel Perry  
Daniel Petrylak  
Katerina Politi  
David Rimm  
Jesse Rinehart  
Matthew Rodeheffer  
Harold Sanchez

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

Min Wu  
John Wysolmerski  
Xiaoyong Yang  
Yang Yang-Hartwich

### Developmental Therapeutics

Karen Anderson  
Masoud Azodi  
Joachim Baehring  
Aarti Bhatia  
Kim Blenman  
Nicholas Blondin  
Ronald Breaker  
Barbara Burtness  
Michael Cecchini  
Herta Chao  
Yung-Chi Cheng  
Anne Chiang  
Zachary Corbin

Jason Crawford  
Craig Crews  
Henk De Feyter  
Hari Deshpande  
Vincent DeVita  
Dan DiMaio  
Joseph Eder  
Barbara Ehrlich  
Jonathan Ellman  
Donald Engelman  
Tarek Fahmy  
James Farrell  
Scott Gettinger

Sarah Goldberg  
Andrew Goodman  
Lohith Gowda  
Ya Ha  
Navid Hafez  
Roy Herbst  
Seth Herzon  
Nina Horowitz  
Iris Isufi  
William Jorgensen  
Patrick Kenney  
Harriet Kluger  
Jeremy Kortmansky

Pamela Kunz  
Jill Lacy  
Alfred Lee  
Grace Lee  
Renelle Lim  
Brett Lindenbach  
Dieter Lindskog  
Elias Lolis  
Patricia LoRusso  
David Madoff  
Scott Miller  
Jennifer Moliterno Gunel  
Natalia Neparidze

Antonio Omuro  
Terri Parker  
Farzana Pashankar  
Joseph Piepmeier  
Nikolai Podoltsev  
Thomas Prebet  
John Roberts  
Michal Rose  
William Mark Saltzman  
Alessandro Santin  
William Sessa  
David Spiegel  
Preston Sprenkle

Stacey Stein  
Mario Strazzabosco  
Richard Sutton  
Seyedtaghi Takyar  
Vasilis Vasiliou  
Sarah Weiss  
Eric Winer  
Amer Zeidan  
Jiangbing Zhou

### Genomics, Genetics, and Epigenetics

Nita Ahuja  
Claudio Alarcon  
Mathieu Bakhoum  
Allen Bale  
Susan Baserga  
Demetrios Braddock  
Sidi Chen  
Keith Choate  
James Clune  
Andrew Dewan  
Nadya Dimitrova  
Mark Gerstein  
Antonio Giraldez

Murat Gunel  
Shangqin Guo  
Ruth Halaban  
Stephanie Halene  
Gloria Huang  
Farren Issacs  
Dhanpat Jain  
Lucia Jilaveanu  
Samuel Katz  
Sajid Khan  
Kenneth Kidd  
Yuval Kluger  
Christine Ko

Diane Krause  
John Kunstman  
David Leffell  
Bluma Lesch  
Morgan Levine  
Peining Li  
Haifan Lin  
Chen Liu  
Xavier Llor  
Jun Lu  
Charles Lusk  
Shrikant Mane  
I George Miller

Binyam Mogessie  
Michael Murray  
Mandar Muzumdar  
Sigrid Nachtergaele  
Karla Neugebauer  
James Noonan  
E. Zeynep Erson Omay  
Manoj Pillai  
Manju Prasad  
Lajos Pusztai  
Ansley Roche  
Mariya Rozenblit  
Peter Schwartz

Emre Seli  
Anup Sharma  
Jason Sheltzer  
Jeffrey Sklar  
Jeffrey Sklar  
Zachary Smith  
Joan Steitz  
Hugh Taylor  
Toma Tebaldi  
Jeffrey Townsend  
Zenta Walther  
Zuoheng Wang  
Sherman Weissman

Craig Wilen  
Frederick Wilson  
Andrew Xiao  
Mina Xu  
Tian Xu  
Qin Yan  
Hongyu Zhao  
Minghao Zhong

### Radiobiology and Radiotherapy

Sanjay Aneja  
Ranjit Bindra  
Justin Blasberg  
Franziska Bleichert  
Daniel Boffa  
Douglas Brash  
Zhengxin Cai  
Richard Carson

Sandy Chang  
Zhe Chen  
Veronica Chiang  
John Colberg  
Daniel Coman  
Joseph Contessa  
Francesco D'Errico  
Shari Damast

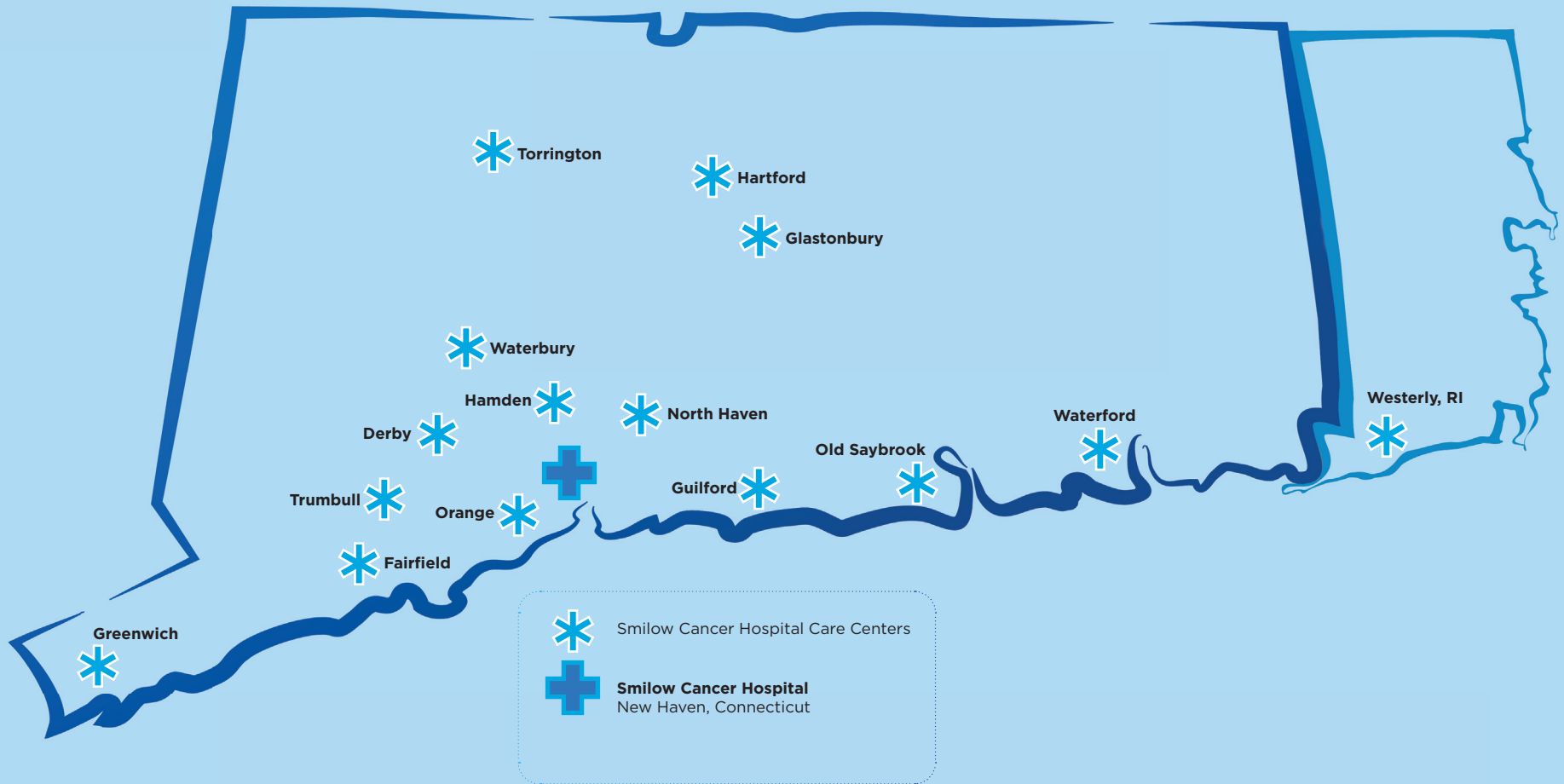
Roy Decker  
Jun Deng  
Frank Detterbeck  
James Duncan  
Luisa Escobar-Hoyos  
Suzanne Evans  
Peter Glazer  
Fanqing Guo

James Hansen  
Thomas Hayman  
Susan Higgins  
D.S. Fahmeed Hyder  
Vikram Jairam  
Ryan Jensen  
Lilian Kabeche  
Megan King

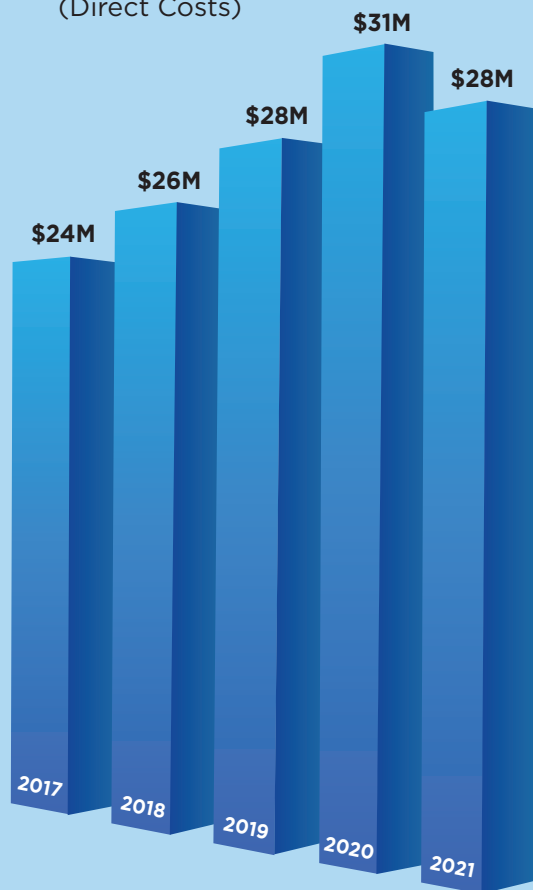
Bernadette Marquez-Nostra  
Meena Moran  
Evan Morris  
Rosa Munoz Xicola  
Henry Park  
Abhijit Patel  
Kenneth Roberts  
Faye Rogers

Christian Schlieker  
David Stitelman  
Christopher Tien  
Lynn Wilson  
James Yu

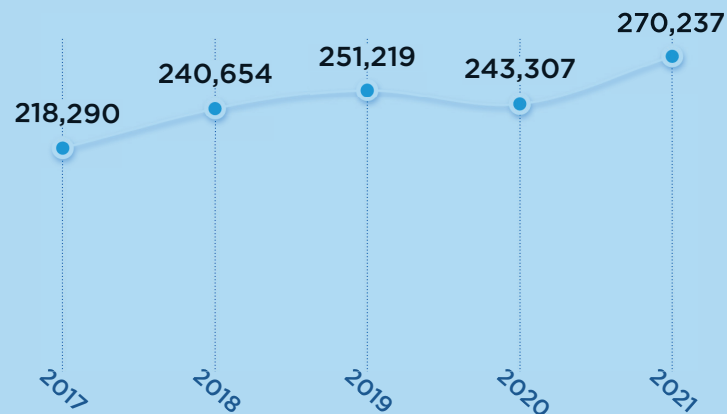
# Yale Cancer Center and Smilow Cancer Hospital Data



## Total NCI Funding (Direct Costs)



## Clinical Volume



Office Visits by Year

## 2020 Top Ten Cancer Types at Smilow Cancer Hospital

	MALE	FEMALE	
PROSTATE	15.8%	470	BREAST
LUNG & BRONCHUS	12.1%	359	LUNG & BRONCHUS
MELANOMA	8.7%	259	CORPUS & UTERUS
COLORECTAL	5.8%	172	BRAIN & CNS
NON HODGKIN'S LYMPHOMA	5.6%	168	MELANOMA
URINARY BLADDER	5.5%	164	COLORECTAL
BRAIN & CNS	5.4%	162	NON HODGKIN'S LYMPHOMA
ORAL CAVITY & PHARYNX	5.4%	160	THYROID
PANCREAS	4.6%	137	PANCREAS
LEUKEMIA	4.6%	136	ORAL CAVITY & PHARYNX
OTHER	26.6%	792	OTHER
<b>TOTAL:</b>	<b>2,979</b>	<b>3,442</b>	<b>TOTAL:</b>

## Publications

from Yale Cancer Center Members

June 30, 2020 – July 1, 2021

### 793 PUBLICATIONS

228 High Impact Publications  
IF > 10, including:

- 48 - Nature/Nature Specialty
- 22 - Clinical Cancer Research
- 15 - Journal of Clinical Oncology
- 13 - Science/Science Specialty
- 12 - Cell/Cell Specialty
- 10 - Journal of National Cancer Institute
- 9 - JAMA/JAMA Oncology
- 7 - Molecular Cell
- 6 - Lancet/Lancet Oncology
- 6 - Cancer Discovery
- 4 - New England Journal of Medicine



We're a group of basic scientists and physician-scientists who are studying the fundamentals of biology with more than half an eye on the clinical applications—so we can understand how to fix it when it has gone wrong in cancer.”

— MARK LEMMON, PHD, FRS





YaleNewHaven**Health**  
Smilow Cancer Hospital

Yale CANCER  
CENTER  
A Comprehensive Cancer Center Designated  
by the National Cancer Institute

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