breakthroughs

YALE CANCER CENTER
SMILOW CANCER HOSPITAL | THE YEAR IN REVIEW

yale cancer center

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

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2018 was a tremendous year for Yale Cancer Center and Smilow Cancer Hospital. Our community of dedicated faculty and staff collaborated to ensure we offer the very best in cancer care to our patients and families at Smilow Cancer Hospital and at our Care Centers throughout the state of Connecticut, while making innovative discoveries in cancer research and treatment. The incredible breakthroughs reported from our laboratories and clinics are impacting cancer treatment and care globally.

Dr. Alessandro Santin's long determination to change the course of treatment and outcomes for women with aggressive type 2 endometrial cancer led to nearly a decade of research to support his theory that the women would respond to trastuzumab. A subsequent trial proved his hypothesis and improved outcomes, leading to rapid changes in the National Comprehensive Cancer Network (NCCN) guidelines to treat the disease.

Similar persistence has helped Dr. Scott Gettinger's patients with advanced lung cancer find new options. Through multiple biopsies and advanced testing to understand how and when tumor cells become resistant to therapy, he and his colleagues are now able to personalize treatment with new therapies to target the newly mutated tumors.

One highlight of 2018 was the successful renewal of our Cancer Center Support Grant, with an unprecedented 73% increase in funding from the National Cancer Institute. And while our research efforts will continue to expand and thrive in 2019, with total research funding of more than $125 million, our clinical services continue to grow as well.

In 2018, our physicians completed over 232,000 office visits and 92,000 infusion visits at Smilow Cancer Hospital and at our Smilow Cancer Hospital Care Centers. In addition, clinical trial enrollment reached a new high, with nearly 950 patients enrolled, of which 22% were enrolled by our Care Centers. The combined efforts of all our physicians, clinicians, and staff continue to ensure Smilow Cancer Hospital is the leading provider of exceptional, compassionate, innovative patient-focused care in our state.

Looking ahead, our leadership team is committed to further expanding the breadth and impact of our clinical, research, and educational missions in the years to come.

One highlight of 2018 was the successful renewal of our Cancer Center Support Grant, with an unprecedented 73% increase in funding from the National Cancer Institute.

This issue of *Breakthroughs* features some of the many advances from our clinics and laboratories, and I look forward to sharing more from Yale Cancer Center and Smilow Cancer Hospital.

Sincerely,

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

FIGHTING FOR THE RIGHT TREATMENT *FOR A RARE REPRODUCTIVE CANCER*

Paula Derrow writer

In 2012, Mary Di Gioia, a grandmother of four was working as a social worker when she began experiencing abdominal pain. "I ignored it for a while," said Ms. Di Gioia, who has since retired. But when the discomfort persisted, she went for an ultrasound and was eventually diagnosed with endometrial cancer.

Her prognosis was not good. Endometrial cancer is the most common gynecological cancer in the U.S.—more than 60,000 women will develop it this year alone and more than 10,000 will die—"but the majority of tumors are curable," said Alessandro Santin, MD, Professor of Obstetrics, Gynecology, & Reproductive Sciences and Co-Leader of Smilow Cancer Hospital's Gynecologic Oncology Program.

Ms. Di Gioia's cancer, however, was a different type of endometrial cancer known as uterine serous carcinoma (USC), which Dr. Santin describes as a "biologically aggressive, type 2 endometrial cancer." How aggressive? While USC comprises only 10 percent of endometrial cancers, it ends up killing more than 40 percent of patients.

Mary Di Gioia, however, is thriving, and is now well into her sixth year since her diagnosis, enjoying her husband, children, and four grandchildren, going to the gym, and happy to be alive. "She is a lucky woman," said Dr. Santin. "I call her my miracle lady."

Yet Ms. Di Gioia's survival had little to do with miracles, and everything to do with a novel treatment regimen developed by Dr. Santin at Smilow Cancer Hospital, a regimen that nearly didn't see the light of day.

In 2002, Dr. Santin and his team were the first to identify a striking characteristic in USC tumors: They showed a very high expression of a gene known as human epidermal growth factor receptor 2, more commonly known as HER2/neu. This was still in the relatively early days of immunotherapy treatment for cancer, but HER2/neu was already known in breast cancer. About 15 percent of women with breast cancer test positive for tumors with HER2/neu. These women did better, it seemed, when given a combination of chemotherapy and an antibody known as trastuzumab—also known as Herceptin. Herceptin is an antibody, much like the antibodies we produce to defend ourselves against infection. When everything is

functioning well, antibodies can recognize a virus, bind to it, and destroy it. In the same way, Herceptin was developed as a targeted therapy to specifically recognize HER2/neu, a protein that conveniently exists at high levels only in some cancer tumors and not in normal cells. Herceptin enables the immune system to bind to HER2/neu tumors and obliterate them like

heat-seeking missiles, while not harming normal cells. "This discovery completely changed the way we deal with breast cancer," explained Dr. Santin. "You give women with HER2-positive breast cancer Herceptin and they respond."

When Dr. Santin discovered that there was also an amplification of the HER2/neu gene in uterine serous carcinoma, "I proposed a new paradigm in the treatment of the disease—that we consider treating it with chemotherapy plus Herceptin, just like we do with breast cancer. We already had a targeted therapy that worked, so it made sense."

The trouble is, the National Cancer Institute and the Gynecologic Oncology Group had already done clinical trials using Herceptin in patients with endometrial and ovarian cancers, with lackluster results.

Yet, Dr. Santin was unfazed. "I knew about the results, but I believed the studies hadn't been well designed, mostly because they weren't selecting the right patients," he said.

Dr. Santin was certain that he could design a better study, one that might offer a more effective treatment for women with USC. The medical community, to put it mildly, was skeptical. "I was attacked," he recalled. "People accused me of having a strong imagination." But, Dr. Santin persisted. His theory was that in the previous studies, many patients didn't have a high enough expression of the HER2/neu protein. Prior studies had also used Herceptin alone to treat USC, rather than combining it with chemotherapy, which was ineffective. "In our lab, we found that uterine serous carcinoma was characterized by tumors that were highly heterogeneous—that is, they contained tumor cells expressing HER2/neu but also tumor cells without high expression of the HER2/neu gene that Herceptin couldn't destroy," he explained. As a result, those tumors continued to grow. Dr. Santin believed that using both Herceptin and chemotherapy (specifically carboplatin-paclitaxel) would target both the HER2/neu tumors and the non-HER2/neu tumors, increasing patients' chances of long-term survival.

It wasn't until August 2011 that Dr. Santin, with a small grant from Genentech Roche, the manufacturer of Herceptin, was able to launch an investigator initiated prospective randomized phase II trial comparing the effectiveness of using only the standard chemotherapy for USC versus a combination of chemotherapy and Herceptin in patients with advanced or recurrent USC who tested positive for amplified HER2/neu. "With all the information produced in my research lab studying these aggressive endometrial cancers, I was finally able to show why the earlier studies had failed—they had treated the disease without knowing the underlying biology," he explained. "I suspected that with a different study design, we could succeed."

The study, done at Smilow Cancer Hospital from 2011 to 2016 and led nationally by Dr. Santin, involved 15 academic institutions in the U.S., eventually enrolling 61 women over the course of the six years. Mary Di Gioia was one of those women. "Dr. Santin did gene sequencing on my tumor, which is routine now, but wasn't back then," she said. Her tumor fit the profile that Dr. Santin was looking for: significant amplification of the HER2/neu gene or, a measure of 3+ for HER2/neu.

Initially, however, Ms. Di Gioia was randomized to the control group of the study. She would receive only chemotherapy. "That was disappointing, but Dr. Santin reassured me that if things didn't go well, he would include me in the arm of the trial that included Herceptin," she said.

Things did go well, at least, at first. Ms. Di Gioia did six courses of chemo, followed by vaginal radiation. "I felt great. I exercised every day, and led a completely normal life," she said. Then, in 2015, a follow up PET scan indicated that her cancer had returned, this time in her colon. Optimistic, she had surgery, and, she said, "I went on with my life." Within a year, however, a CAT scan revealed yet another tumor, also in her colon. "That was the point when Dr. Santin said it was time for Plan B," she recalled. "Instead of treating me with just chemo again, we began infusions of Herceptin every 3 weeks."

That was a year-and-a-half ago. Ms. Di Gioia is now going strong, her tumor hasn't grown, and her health remains stable. "I'm a very blessed lady, and that's the truth," she said. Indeed, only about 5 percent of patients with Ms. Di Gioia's advanced stage of USC—classified as 4B—are alive after five years.

Other women who received both chemotherapy and Herceptin in Dr. Santin's study did well, too, living significantly longer than women in the control group without their cancer progressing. After Dr. Santin's results were published in the July 2018 issue of the *Journal of Clinical Oncology*, the medical world took notice. The National Comprehensive Cancer Network (NCCN) guidelines, which are the recognized standard for clinical policy in cancer care, were revised for women with advanced and recurrent HER2/neu-positive USC to chemotherapy plus Herceptin. "I have patients who have been taking Herceptin for three and four years now," said Dr. Santin. "They don't want to stop. They feel great, and they are able to tolerate it in a fantastic way."

That is certainly true for Mary Di Gioia, who says she feels wonderful, both physically and emotionally. "I can't say that I'm thrilled to have gotten cancer, but I have grown from the experience," she said. "I credit Dr. Santin with that. He has taught me how to live with cancer, with the emphasis on the word 'live' rather than on 'cancer.' For that, I'm eternally grateful."

"With all the information produced in my research lab studying these aggressive endometrial cancers, I was finally able to show why the earlier studies had failed—they had treated the disease without knowing the underlying biology. I suspected that with a different study design, we could succeed."

– Dr. Alessandro Santin

Catherine Lyons, RN, MS

Smilow's first top nurse retires

Steve Kemper writer

An era ended on December 31 with the retirement of Catherine Lyons, RN, MS, Vice President of Patient Services and Chief Nursing Officer at Smilow Cancer Hospital. She was the last remaining member of the trio generally credited with launching Smilow into a nationally-renowned cancer hospital, the other two being Thomas Lynch, Jr., MD, Smilow's inaugural Physician-in-Chief, and Abe Lopman, the first Executive Director.

"Cathy is an extraordinary leader who has taught us the meaning of world-class, patient- and family-centered care. Her impact on the culture in Smilow is immeasurable," said Charles Fuchs, MD, MPH, Physician-in-Chief of Smilow.

She almost didn't come. When a recruiter called in 2009 about the top nursing job at a brand-new cancer hospital in New Haven, she wasn't interested. She liked her job as associate director of clinical services and nursing at the James P. Wilmot Cancer Center at the University of Rochester. Born in Buffalo, she had spent the first 25 years of her oncology career in that city at the Roswell Park Cancer Center before moving on to stints at a medical center in Maryland and the National Cancer Institute (NCI). She was happy to be back in western New York, near her family, and in a prestigious job.

The recruiter persuaded her to at least meet with Dr. Lynch and Mr. Lopman. "They articulated a vision that was pretty compelling," said Ms. Lyons, "about working to build a world-class cancer facility and a program that would be a destination for patients and a leader in cancer research. We also hit it off personally. I remember telling somebody that these were the kind of guys you could have a beer with and immediately felt like best friends because we thought so much alike."

Nevertheless, she said no. Nevertheless, Dr. Lynch and Mr. Lopman kept asking her to come back and talk, just once more. She reluctantly agreed. "The two of them had so much energy around what they wanted to create here that eventually I wanted to be a part of it," explained Ms. Lyons, who finally arrived at Smilow in 2010.

To create the cancer hospital they envisioned, the three worked with their staff to change the existing culture. They established new models of medical practice and patient care. Big changes always meet resistance. For the first six months, Ms. Lyons kept her belongings packed because she wasn't sure the vision would survive.

"Cathy is a spectacular clinician—a nurses' nurse who practices at the top of her craft," said Dr. Lynch. "That was essential for her to have the credibility of the nursing staff to set the culture that she knew Smilow needed to succeed."

They pushed for staffing at what they considered appropriate levels for the cancer hospital they intended to build and drew their aspirational standards from NCI-designated cancer centers such as Memorial Sloan Kettering and MD Anderson. The nursing staff grew sharply. The number of advanced practice providers (APPs), for instance, went from 12 to 60.

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>
> **– Dr. Charles Fuchs**

They also changed how care was delivered in the outpatient areas, which Ms. Lyons calls "the lifeblood of any cancer program" because that's where most patients receive their treatment, not in hospital rooms. "Our challenge was to create an environment that was not only safer and more efficient, but also more compassionate."

The cultural change that grew out of all this is what makes Ms. Lyons most proud. Asked to describe it, she said, "A relentless pursuit of excellence and compassionate care. On the day that patients come for their physician visit, or surgery, or radiation, or chemotherapy, we want them to feel like they are the most important thing to us. To do that, everybody has to be aligned and focused and really give everything of themselves. It takes a lot of courage and commitment to be in oncology. It's almost like a vocation, not just a job."

The key was hiring staff who felt that way. Ms. Lyons looked for people drawn to the field because of a personal story. Perhaps a beloved grandfather had died of cancer, or maybe a mother's cancer nurse had inspired the person to enter nursing school. Ms. Lyons's story starts with an aunt who died young from breast cancer, leaving five children. Like most families back then, no one talked about the diagnosis, so the death shocked Ms. Lyons and made her want to do something that could help families experience cancer differently. She became an oncology nurse in 1975 and has never left the field.

"I always tell our nurses, our patients have just been given a devastating diagnosis, and you have an opportunity to make that an easier process," she said. "No one ever forgets the oncology nurses who took care of them. I validated that almost 40 years later, because I am a cancer survivor myself." She was diagnosed with breast cancer five years ago and was successfully treated at Smilow.

Tracy Carafeno, RN, MS, Clinical Program Director, Smilow Inpatient Operations, was at Yale New Haven when Ms. Lyons arrived. "I think Cathy was the perfect person to take this nursing leadership role as Smilow opened," she said. "Cathy always says, 'Put the patient first and you'll always be OK.' That's been huge to get us where we are. She sets very high standards, but she provides the support to make that happen."

Ms. Lyons championed nurses, added Ms. Carafeno, starting with staffing levels, and she also built extensive programs to give nurses opportunities for continuing education and advancement.

"Cathy will leave a legacy that will, for many years, be hard to match. She redefined care to the cancer patient and established a level of respect for oncology nursing that I had not seen anywhere else," Mr. Lopman said.

In 2014, just four years after Ms. Lyons arrived, the American Nurses Credentialing Center conferred Magnet status on Yale New Haven Health—including Smilow, signifying the outstanding nursing care. Dr. Lynch left for another career opportunity in 2015, Mr. Lopman retired in October 2018. Now, after nearly 45 years in oncology, Ms. Lyons is going home to Buffalo to be near family again.

"It is rare that we get to thank our mentors who did so much to make us the people and leaders that we become. Cathy and Abe's retirement gives me a chance to do that. At the end of our careers, I think we will all look back on this unique time at Yale and be very proud. Smilow is an exceptional place and is well positioned to continue to grow as one of America's finest cancer hospitals," Dr. Lynch said.

"Our new leaders Charlie Fuchs and Lori Pickens, are the best," Cathy said. "They honor the work that's been done here in the last 10 years and they know it's important to preserve that culture. I have every confidence that they will move this organization forward to even better things."

new IMMUNOTHERAPY for Blood Cancers

Steve Kemper writer

In late 2018, after nearly a year of preparation, Yale Cancer Center and Smilow Cancer Hospital launched an innovative new immunotherapy program for patients with certain blood cancers. Chimeric Antigen Receptor (CAR) T-cell therapy, reprograms a patient's own T-cells to target tumor antigens. CAR T-cell therapy has shown complete remission rates of 80 to 90 percent in patients with B-cell acute lymphoblastic leukemia and multiple myeloma, and 40 percent in patients with aggressive B-cell non-Hodgkin's lymphomas who have failed multiple prior lines of treatment. The therapy is new and currently available in only a handful of leading cancer centers. No other hospital in Connecticut offers it.

The program's Co-Directors are Stuart Seropian, MD, Associate Professor of Medicine, and Iris Isufi, MD, Assistant Professor of Medicine. Dr. Seropian runs Smilow Cancer Hospital's Stem Cell Transplant Program. Dr. Isufi specializes in lymphomas and stem cell transplants.

"CAR T-cell therapy uses advances in our knowledge of genetics and in the science of immune cells to empower the immune system to fight certain cancers," said Dr. Seropian. "It's the next big success story in treating B-cell lymphomas and B-cell leukemias."

For the moment, the therapy is FDA-approved only for patients with either childhood acute lymphoblastic leukemia, the most common cancer in children, or adult B-cell non-Hodgkin's lymphoma. To be eligible, patients must have failed two forms of standard treatment. The Yale program will offer both of the FDA-approved treatments while also conducting clinical trials to test new CAR T-cells against other cancers. Currently available for adults, the pediatric program will launch for children with acute lymphoblastic leukemia under the direction of Dr. Niketa Shah in the spring of 2019.

CAR T-cell therapy has shown complete remission rates of 80 to 90 percent in patients with B-cell acute lymphoblastic leukemia and multiple myeloma.

The science behind the therapy is fascinating. Blood is drawn from the patient so that T-cells, the workhorses of the immune system, can be filtered out and collected. These cells are sent to a lab where they are genetically engineered by introducing a disarmed virus that stimulates the cells to produce new surface receptors called chimeric antigen receptors (CARs). "The lab basically inserts a code into the T-cell's genome," explained Dr. Seropian. "That produces a new receptor with a different external portion, an antibody that targets whatever you want it to target." In the therapies approved by the FDA so far, CAR T-cells target an antigen called CD19, which is common on lymphomas and leukemias.

Next the lab grows these genetically-modified T-cells into an army of millions, which takes several weeks. This mass of cells is frozen and returned to the patient's treatment center. Typically the patient will receive chemotherapy to increase the effectiveness of the next step: infusion of the CAR T-cells.

"Once these cells are put back into the body," said Dr. Seropian, "if they're going to work, they really take off. The therapy can put someone into remission almost immediately or within weeks."

This intense response, however, can be also accompanied by intense side effects as the T-cells proliferate and expand in the body. "The therapy is very effective," said Dr. Isufi, "but it is also potentially very toxic." One of the main toxicities is called cytokine release syndrome (CRS). As T-cells do their work, they release cytokines to excite the immune system. When millions of CAR T-cells are suddenly infused into the bloodstream, they produce a torrent of cytokines.

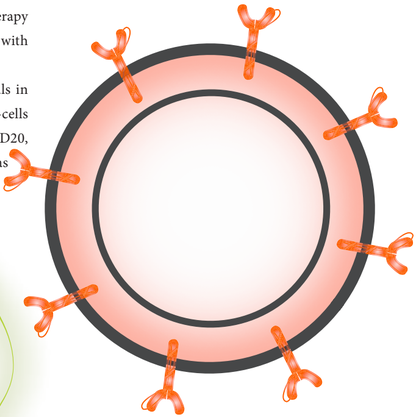
"The patient's blood pressure drops," said Dr. Isufi, "and they can develop high fever and respiratory issues and require intensive care." The other main side effect is neurologic toxicity, manifested by mental confusion and even seizures. These side effects, though usually brief and temporary, are dangerous, and are the reason the program at Smilow took a year to begin.

"A lot of effort has gone into hiring and training personnel in the lymphoma and transplant teams," said Dr. Isufi, "but also the medical intensive care unit team, critical care physicians, pharmacists, neuro-oncologists, and the epilepsy team are involved in the management of the patients, so we were sure to train and include them. And of course we had to train all the nursing staff and the hospitalists and the fellows who might be caring for the patients on the floor at night, because patients can get sick very quickly, and early identification of the toxicities is crucial so that the interventions can be given. It's been a multidisciplinary, hospital-wide educational effort. Everyone who could potentially touch the patient, at every level, needed to become familiar with the therapy and how to manage the toxicities."

Patients generally are discharged within two weeks after infusion, but the risk of side effects continues, so for the first month, CAR T-cell patients must stay within two hours of the cancer center in case they need specialized care. That's another reason Drs. Seropian and Isufi are so pleased that Yale now offers the therapy, so their patients don't have to leave the state to receive it elsewhere.

The treatment's advantages far outweigh its risks, especially for patients who have run out of options. Aside from the strong possibility of remission, which in the majority of patients seems durable, the therapy is also relatively brief compared to the standard regimen for blood cancer—six months of chemotherapy. Dr. Seropian mentions that CAR T-cell therapy may function as a bridge treatment for some patients, putting them in remission long enough to qualify for a stem cell transplant that could cure them. Dr. Isufi adds that CAR T-cell therapy may even cure some patients, making a transplant, with all its attendant dangers, unnecessary.

They expect to start several related clinical trials in 2019 where the team will test new types of CAR T-cells that target antigens beyond CD19, in particular CD20, found in certain lymphomas and leukemias, as well as BCMA, common in multiple myeloma. They are also participating in a trial to test a chimeric T-cell receptor that binds to an antibody instead of targeting one protein on the surface of a cancer cell. They will test this antigen on solid tumors as well, an area where existing CAR T-cells have been disappointing so far, perhaps because such tumors are more complex and difficult to penetrate.



Another clinical trial planned for patients with multiple myeloma will test a new method of introducing the chimeric antigen receptor into the T-cells transiently rather than permanently, thereby potentially reducing the risk of cytokine release and neurologic toxicity.

As research advances, Drs. Seropian and Isufi expect CAR T-cell therapies to be approved for a wider array of lymphomas and leukemias, and expanded to include all age groups. They also expect that new varieties of CAR T-cells will target multiple antigens and will be used in combination with each other as well as with other therapies to give patients with blood cancer more ways to achieve remission.

Making Waves AGAINST LUNG CANCER

Paula Derrow writer

By the time Anita Adler made her way to Smilow Cancer Hospital in July of 2013 with stage IV non-small cell lung cancer (NSCLC), she had already heard the words every patient dreads. "My doctor told me there was nothing more they could do," Mrs. Adler said, now 80, a substitute teacher and mother of four who has been married to her husband Russ for 61 years. Mrs. Adler had always been physically strong. Even in her 70s, she was an avid swimmer who religiously did laps in her local pool in winter and swam in the Long Island Sound during the summer. But in the fall of 2013, she was exhausted from several rounds of chemotherapy and radiation, frail, in need of oxygen, and fighting a chronic cough. "I had every side effect from chemo listed," she explained. "And I couldn't bring myself to eat much. The silly thing is, like many women, I spent so much time trying to lose weight, then with the cancer, I lost 40 pounds in one month."

Mrs. Adler had one thing in her favor, however: Her doctor referred her to Scott Gettinger, MD, Associate Professor of Medicine (Medical Oncology) at Yale Cancer Center and the Disease Aligned Research Team Leader for the Thoracic Oncology Program at Smilow Cancer Hospital.

Dr. Gettinger is used to tough cases. Since 2009, he has been investigating the effectiveness of immunotherapy drugs against lung cancer. "There was pessimism about using immunotherapy for lung cancer back then, with several clinical trials failing to demonstrate effectiveness. Most had given up on this approach," said Dr. Gettinger.

When Dr. Gettinger decided to try using checkpoint inhibitors to treat patients with advanced lung cancer, his colleagues were skeptical. Simply put, checkpoint inhibitors relieve brakes put on the body's immune system by cancer, thereby allowing immune cells to do what they were meant to do–attack cancer. "No one thought they would work for lung cancer," he admitted. But in 2009, he started enrolling select patients to a trial evaluating the checkpoint inhibitor drug Nivolumab. He was at first impressed by the tolerability of Nivolumab, with most patients experiencing little or no side effects. Then, he saw the responses. "Prognosis for these patients was on the order of 3-6 months, with few patients expected to live beyond a year. Five years later though, 16 percent of patients were alive. I am still following some of these patients today."

Flash forward to 2018: The treatment Dr. Gettinger

"Anita's contribution has paved the way to new discoveries that will benefit many. Seeing her enjoying life is an indescribable reward that pushes us to do more."

— Scott Gettinger, MD

"I am very lucky to have been sent to Yale. I'm grateful to the doctors, and I feel good about what I'm doing for them. But I feel twice as good about what they have done for me."

pioneered is now available as a first line therapy option for lung cancer. "The success of these medications has radically changed the treatment paradigm for lung cancer," he said.

That was good news for Anita Adler, who, despite her weakened physical state, says she felt more optimistic the moment she came to Smilow Cancer Hospital. "Everyone was just wonderful. I drew confidence from the environment," she said. Dr. Gettinger started her on a trial randomizing patients to standard salvage chemotherapy or immunotherapy. Mrs. Adler was randomized to chemotherapy. After that failed, Dr. Gettinger told Mrs. Adler that it was time to consider another clinical trial that was testing a combination of two immunotherapy drugs. Instead of chemotherapy, she would get an infusion of an immunotherapy regimen every three weeks.

Soon after beginning the new treatment in early 2014, Mrs. Adler's appetite returned. Shortly after that, she was out of her wheelchair, off oxygen, teaching again—and more. "I'll never forget when Anita's son showed me a video of Anita during one of her treatment visits-there she was, swimming in the Long Island Sound!" Dr. Gettinger recalled.

That was memorable for Mrs. Adler, too. "Every August, we have a family beach day, when everyone comes home," said Mrs. Adler. "My son always takes pictures of me swimming!"

Within a few months, Mrs. Adler's cancer was totally gone. "Dr. Gettinger called me at 8:30 one night after a CT scan, and said he couldn't believe what he was seeing," she recalled.

But Mrs. Adler's cancer would not be vanquished so easily. Four or five months into her treatment, a PET scan turned up signs of cancer in a lymph node. "I could always tell when the cancer was returning because I'd feel that exhaustion," she explained. Surgery to remove the affected and surrounding lymph nodes left her without evidence of disease, and after a year of continued immunotherapy and no sign of cancer, Mrs. Adler went off the treatment, as the trial required.

Yet, less than a year later, the cancer again returned in her lymph nodes. Once again, the immunotherapy beat it back.

Along the way, Dr. Gettinger was taking samples of Mrs. Adler's tumor—at the beginning of treatment, and each time her cancer returned. His goal: to understand why certain tumors seemed to acquire resistance to the immunotherapy. "Like Anita, most patients with response to these therapies inevitably develop resistance when cancer recurs," explained Dr. Gettinger. "We want to understand why."

To do that, Dr. Gettinger compared Mrs. Adler's initial tumor to ones that appeared later, after periods of successful therapy. "By comparing the specimens we can see what has changed that might be rendering the cancer resistant," he explained.

His team is also studying cells from tumors of patients who don't respond to immunotherapy at all, as well as from patients who seem to respond robustly and indefinitely. "We've collected a cohort of what we call 'exceptional responders,' who show no evidence of active disease at least three years after starting treatment. We are tracking 30 or so patients in this group to see what's unique about their tumors."

By 2017, Mrs. Adler's cancer had recurred again. The good news was that Dr. Gettinger and his team, who had been doing biopsies of Mrs. Adler's tumors all along, now had more information about her cancer cells. "We looked at the tumors on a molecular level, studying changes in DNA and RNA, and additionally at Anita's immune cells within the tumor," Dr. Gettinger explained.

Even more remarkable: Each time Dr. Gettinger and his team biopsied Mrs. Adler's various tumors, they injected samples of that tumor into laboratory mice, creating mice models that now had growing tumors identical to Mrs. Adler's. "We created a litter of mice with Anita's tumors that could be interrogated further, and treated them with different therapies designed to counteract resistance to the immunotherapy Anita received."

Yet one crucial element was missing in that experiment. To truly get a complete picture of how these tumors interacted with the immune system, and learn why some seemed to grow resistant to treatment, Dr. Gettinger's team needed mice that not only had Mrs. Adler's tumors but also had her immune system—what Dr. Gettinger refers to as a humanized mouse model. To do that, he needed to take early progenitor cells from Mrs. Adler's bone marrow to recreate her immune system in the mice.

While Mrs. Adler was happy to contribute pieces of her tumor and submit to biopsies–"If it's going to advance science, I'm excited about it," she said--she was nervous about donating her bone marrow cells. "My sister died from bone cancer, so getting near my bones frightened me," she said. "But in my heart, I knew I wanted to do it."

Once Mrs. Adler gave her consent, Dr. Gettinger and his team aspirated her bone marrow cells during one of her tumor biopsy procedures— "I was under anesthesia; it was all fine," Mrs. Adler recalled—and they could now inject those cells and create a mouse with Mrs. Adler's immune system. "That meant we could replicate how the tumors and the immune system were interacting," said Dr. Gettinger.

When Mrs. Adler's cancer returned, and her tumors looked as if they were now resistant to treatment, Dr. Gettinger went back to the lab and discovered something that had not been described before. "We saw that Anita's tumor was further thwarting her body's immune system, evading detection by altering certain markers on its surface." Normally, when a cancer cell or virus camouflages itself in this way, there are specialized immune cells that can sense the deception, and decimate the altered cancer cells. These extra-alert immune cells are known as natural killer cells. By using flow cytometry on one of the tumor specimens they had collected from her, Dr. Gettinger and his team discovered that Mrs. Adler's tumor was expressing keys on its surface that turned off the natural killer cells, thus explaining their resistance to treatment.

Based on those results, Dr. Gettinger tried a combination immunotherapy treatment through a clinical trial. "We were participating in a phase one study evaluating a new medication that could potentially release Anita's natural killer cells from the restraints used by the lung cancer," he explained. In November of 2017, Mrs. Adler began this therapy. "Not only did she respond, but she had a complete response, which is rare," said Dr. Gettinger, still jubilant. "No remaining tumors could be found on imaging studies."

That was more than a year ago. Aside from some skin side effects that are now subsiding, Mrs. Adler is once again swimming laps, teaching, and enjoying her family. Thanks to her generosity and willingness to participate in Dr. Gettinger's research, there is also more hope for all patients with advanced NSCLC. "Anita let us go one step beyond," said Dr. Gettinger. "We learned a great deal from her tumor and immune system, and were able to recommend a therapy based on our discoveries that resulted in clearance of her lung cancer. Anita's contribution has paved the way to new discoveries that will benefit many. Seeing her enjoying life is an indescribable reward that pushes us to do more." Which is why Mrs. Adler gathered with her family this past Thanksgiving, felt especially grateful. "I am very lucky to have been sent to Yale," she said. "I'm grateful to the doctors, and I feel good about what I'm doing for them. But I feel twice as good about what they have done for me."

Another Transformational Breakthrough?

Lieping Chen, MD, PhD

He may have done it again. Lieping Chen, MD, PhD, United Technologies Corporation Professor in Cancer Research, Professor of Immunobiology, Dermatology, and of Medical Oncology, and Co-Director of the Cancer Immunology Program, believes he has found another transformational key to treating cancer.

The first originated twenty years ago when Dr. Chen discovered that cancer cells emit signals that trick the immune system into shutting down. He identified one culprit: a protein named PD-L1 that bound to PD-1 in a tumor's microenvironment, disabling the immune system. When he blocked this pathway with an antibody, the T-cells in the tumor reignited and started killing cancer cells.

Using drugs to incite the body's own immune system against cancer is called immunotherapy, and Dr. Chen is one of its foremost pioneers. Since his original discovery, the FDA has approved six drugs that target the PD-1/PD-L1 pathway to fight more than a dozen different cancers, with more approvals expected soon.

But not every tumor expresses PD-L1, so the drugs that block it are effective in only about 30 percent of cancer patients. That other 70 percent is now Dr. Chen's focus. He knew that in tumors without PD-L1, other molecules must be disrupting the immune system; and so the search began. He and his colleagues used a sophisticated screening assay called a T-cell activity array, which Dr. Chen developed about 10 years ago.

"We ran almost 7,000 molecules through this big assay looking for potential suspects," Dr. Chen said. "Then we started to map which bad molecules shut down T-cell activities, and then we looked for which molecule was responsible for which type of tumor."

One promising candidate was a protein called Siglec-15 (S15). Like PD-1/PD-L1, S15 does its mischief in the tumor microenvironment, but with different tactics. When cancer cells express PD-L1, provoking T-cells to attack, PD-1/PD-L1 counterattacks. "When we found this mechanism," said Dr. Chen, "we were amazed that the tumor can do such things." S15 operates with less belligerence in a tumor's macrophage. When the cancer cells express high levels of S15, drawing an army of T-cells, the S15 molecules don't attack, but somehow soothe them into stillness.

"We're still trying to figure out biochemically what kind of signal this is. Different tumors develop different weapons, so we have to deal with them differently."

The next step was to develop an antibody that blocked S15 to see if that reanimated the immune system. With the PD-1/PD-L1 antibody, Dr. Chen had to wait more than 10 years for the first large clinical trial. His frustration with that long gap led him to explore ways to shorten the trip from lab to clinic. In 2016, he became the scientific founder of a biotech startup called NextCure, which raised $67 million to develop his future breakthroughs on an accelerated schedule.

In October 2018, NextCure's S15 antibody, currently called NC318, received the green light from the FDA and went into trials at several sites, including Smilow Cancer Hospital, less than five years after Dr. Chen's initial insight.

"It's a new model," he said. "We want a smooth transition from discovery to developing the drug to the clinic. I think this drug can save lives, so you want to bring it to the clinic as quickly as you can. This antibody is the first example to prove that we can make this new model work. That's very exciting, almost as exciting as the drug itself."

Dr. Chen is confident the new antibody will work. Like PD-1/PD-L1, S15 is expressed in many types of solid cancers. A preliminary study found it in lung, breast, ovarian, pancreatic, thyroid, and head and neck cancers. Theoretically, an S15 antibody should work against all of them.

"I will predict that it will target another 20 to 30 percent of cancer patients," said Dr. Chen. "So it could be very exciting, and that's why we're excited the phase one trial has started."

At Yale the trial is led by Patricia LoRusso, DO, Professor of Medicine and Associate Director of Experimental Therapeutics. Because the drug has never been used in humans, the trial will start small. "Once we hit the right dose," said Dr. LoRusso, "we'll expand into certain tumors to see whether or not there is a signal of activity. Within 18 or 24 months, we'll have a lot of information."

Roy S. Herbst, MD, PhD, Ensign Professor of Medicine, Professor of Pharmacology, Chief of Medical Oncology, and Associate Director for Translational Research, is so excited by Dr. Chen's research that he spent six months of his recent sabbatical in Dr. Chen's lab. Together, they built a clinical team to work on S15 at Yale.

"I am so proud of this project," Dr. Herbst said. "It will be helping patients here in New Haven where it began as part of our Lung SPORE research project and will surely expand to patients worldwide. Lieping is a proven winner who's already brought us a drug that's treating millions of people. We're very optimistic that this is another drug that will target the engine of tumors and successfully stop cancer."

Mining DNA in Blood for Fast, Specific Information About Tumors


Abhijit Patel, MD, PhD

Immunotherapy may be the most promising development in cancer treatment in the last decade, but so far it is only effective for about 30 percent of patients. Testing for biomarkers can sometimes predict which patients will benefit, but current tests do not provide absolute proof of how a patient will respond.

"While many patients derive remarkable benefit from immunotherapy, it fails to help many others," said Abhijit Patel, MD, PhD, Associate Professor of Therapeutic Radiology, "so these patients waste time when they could have been receiving some other therapy instead. There's a lot of interest in developing biomarkers that can predict response. But the biomarkers we have aren't correct as often as we would like them to be."

The stakes are high. What if a patient for whom immunotherapy could be lifesaving gets disqualified from receiving it because of a falsely negative biomarker test? Or, what if a patient tests positive for the biomarker but doesn't respond to immunotherapy while the tumor continues to grow?

Clearly all of these scenarios are unsatisfactory. Adding to the uncertainty, says Dr. Patel, tumors respond differently to immunotherapy than to other therapies, leading to confusing results on CT scans. With chemotherapy, for instance, CT scans reveal fairly quickly whether a tumor is shrinking.

"But with immunotherapy," said Dr. Patel, "the shrinkage can take time, sometimes many months. And sometimes it looks bigger on a scan before it shrinks, because the immunotherapy can make the tumor swell at first. So on your first scan, maybe a month after your therapy, your tumor can actually look worse. That can be confusing. Do we throw in the towel and say immunotherapy isn't working, or do we wait another month or two to see if it shrinks? The scans aren't giving us clear-cut data as they do for other therapies, so immunotherapy presents a unique challenge in monitoring and predicting response."

Since scans can't reliably detect the early effects of immunotherapy, Dr. Patel and a team of scientists at Yale began looking for blood biomarkers that could. They settled on circulating tumor DNA (ctDNA), a byproduct of dying cells shed by a tumor into the bloodstream. They theorized that measuring changes in ctDNA could provide a quicker and more reliable assessment of immunotherapy efficacy than CT scans because the amount of ctDNA in the blood reflects how many cancer cells are dying. To test this idea, they studied a group of patients with non-small cell lung cancer who were receiving immunotherapy, and published their eye-opening findings last year [2018] in *Clinical Cancer Research*.

Their basic question: Can ctDNA detect whether immunotherapy is working more quickly and reliably than a scan can? By comparing the levels of a patient's ctDNA before and after treatment, clinicians had confirmation, on average, just 24.5 days after treatment started, compared to 72.5 days when using scans. In other words, even very early in the treatment, before a scan could detect shrinkage, a patient's ctDNA showed that immunotherapy was killing the cancer—a clear sign to clinicians and patients to continue the treatment.

"Those patients whose ctDNA levels showed a clear drop shortly after starting immunotherapy also did a lot better in terms of overall survival and progression-free survival," said Dr. Patel. "We eventually saw substantial shrinkage of their tumors on scans, and these patients benefitted from immunotherapy for a much longer duration." Conversely, measuring ctDNA also offered an early indication of when immunotherapy was not working.

In September 2018, Dr. Patel and a multidisciplinary team from Yale, Harvard, Rice, and Microsoft Research received a $2.6 million grant from the National Institutes of Health to develop an assay that will use ctDNA-screening to detect early-stage lung cancer, which kills an estimated 154,000 Americans each year.

"The impact of this, if it works, could be tremendous," said Dr. Patel. "It's widely known that if you detect most types of cancer early, outcomes will improve, because you can surgically remove or eradicate all of the cancer cells and have a higher probability of achieving a cure."

He expects his multidisciplinary group to have made substantial progress toward a lung cancer early detection test within the five-year period of the grant. But his ultimate goal is a "pan-cancer assay" that could detect early-stage cancers of all types through a blood test that looks for ctDNA, sometimes called a "liquid biopsy." The theory is that ctDNA contains evidence of mutations specific to each tumor, evidence not typically found in healthy people. If ctDNA was detected, said Dr. Patel, imagining this future, "You could say, 'This patient very likely has cancer, and the three most likely cancers are X, Y, or Z,' then you could do a CT scan or an MRI to further diagnose. Such early detection could save countless lives."

Barbara Burtness, MD

A Big Advance in Treatment of Head and Neck Cancers

The standard treatment for patients whose head and neck cancer has either recurred or metastasized had not improved since 2006. "It's a three-drug cocktail," said Barbara Burtness, MD, Professor of Medicine and Co-Director of the Developmental Therapeutics Research Program. "It's a hard treatment. The response rate is just 35 or 40 percent and the average survival is under 11 months. So we've been looking for something that would work better, to allow patients to live longer and avoid the toxicity of this regimen."

That something might be an immunotherapy drug called pembrolizumab. An earlier trial showed that pembrolizumab was more effective for patients with head and neck cancer who had failed first line chemotherapy than selecting a second chemotherapy. Dr. Burtness wanted to test whether pembrolizumab alone, as a first-line drug, increased survival for patients with biomarkers that predicted a response to pembrolizumab, and whether using it in combination with chemotherapy would be more effective even without the biomarker selection.

Pembrolizumab is an immune checkpoint inhibitor. It blocks the receptor activated by a protein called PD-L1, which allows cancer cells to escape detection by the immune system. When pembrolizumab seeks out the receptor, PD1, the immune system wakes up and starts attacking cancer cells. But many tumors don't express this biomarker, and some express it at low levels.

"We had two hypotheses," explained Dr. Burtness of her trial, named Keynote-048. "One was that if you had enough of the biomarker PD-L1, you were a good candidate for immunotherapy, and that maybe getting immunotherapy alone would be sufficient. The other hypothesis was that combining pembrolizumab with chemotherapy might be beneficial because chemotherapy does lead to response in and of itself, and maybe the cell death caused by chemotherapy would not only help control the disease, but potentially could release proteins that would be targets for the immune system, and thus make patients who weren't that sensitive to immunotherapy more sensitive to it."

Keynote-048 was a large trial involving almost 900 patients. All were tested for their level of PD-L1 expression and then randomly divided into three groups. One group received only pembrolizumab. A second group got pembrolizumab plus platinum-based chemotherapy. The third group was treated with the standard three-drug cocktail.

In October, Dr. Burtness presented interim findings of this phase 3 trial at the annual meeting of the European Society for Medical Oncology (ESMO). For patients with the PD-L1 biomarker, pembrolizumab alone was much more effective than the current standard of care. Patients who took a combination of pembrolizumab and chemotherapy also did better than patients using the standard treatment, even without using a biomarker to select patients.

"The median overall survival is longer, the one-year overall survival is higher, and the two-year overall survival is higher," said Dr. Burtness. In short, patients who receive pembrolizumab live longer than those who don't.

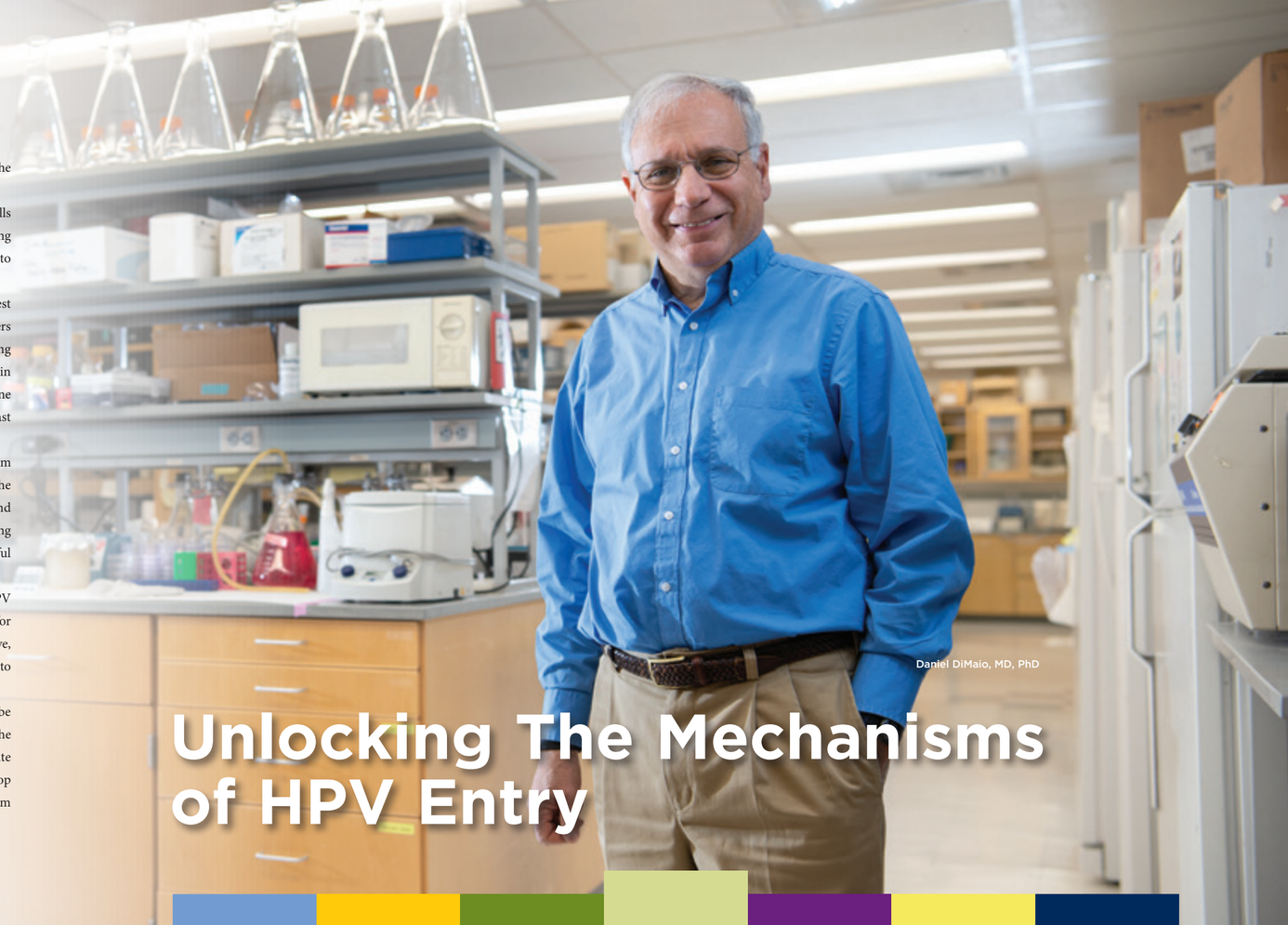
To people outside of cancer research, an improvement in median survival of four months might seem small, but Dr. Burtness calls it substantial. She points out that 14.9 months represents median survival, which means that 50 percent of the patients lived longer than that, sometimes much longer, as demonstrated by the fact that some people had responses that lasted over 21 months.

"And there were some patients who had complete responses," she added. "They were able to stop treatment and have had no recurrence of their disease. That's an exceedingly rare event with the older chemotherapy regimen. Giving pembrolizumab early has the ability to change the natural history of head and neck cancer. That fills us all with hope that moving this treatment into the curative setting will have a profound effect."

Dr. Burtness' results offer strong evidence that pembrolizumab alone or with chemotherapy is superior to the current standard of care for head and neck cancers. She hopes her findings lead to FDA approval of the drug as a first-line treatment. Meanwhile, she and her colleagues are studying how best to use pembrolizumab in patients with earlier stages of the disease who are being treated with chemotherapy and radiation. She is also exploring the drug's use in patients with radiotherapy resistance. "We've seen complete responses in that setting," she said.

It seems clear that patients with head and neck cancers soon won't have to settle for the unpleasant three-drug cocktail.

Unlocking The Mechanisms of HPV Entry



Daniel DiMaio, MD, PhD

Human papillomavirus (HPV) causes almost all cancers of the cervix and anus, and a large percentage of cancers of the vagina, vulva, penis, and the back of the throat. The virus is spread by sexual activity, but vaccination can help prevent infection.

Deciphering how HPV gets into cells is a quest for Daniel DiMaio, MD, PhD, Waldemar Von Zedtwitz Professor of Genetics and Professor of Therapeutic Radiology and of Molecular Biophysics and Biochemistry, and Deputy Director of Yale Cancer Center. Several years ago, he and other researchers discovered that HPV follows an unusual path to the cell nucleus. The virus itself is not covered by a membrane, but as it enters cells it is encapsulated in a membrane-bound vesicle, or sac, called the endosome. Dr. DiMaio and his colleagues also showed that for HPV to successfully complete the entry process, a viral protein named L2 must bind to a protein called retromer inside the cell cytoplasm. The retromer then takes the viral cargo into what's called the retrograde pathway, which transports it to the nucleus.

Dr. DiMaio knew what had to happen for viral infection, but he was puzzled about how it occurred. "It wasn't clear how the virus was able to see the retromer and bind to it," explained Dr. DiMaio, "which we knew was required for proper trafficking of the virus."

Now Dr. DiMaio and his colleagues have solved this conundrum. They published their findings in *Cell* last September [2018]. "We found that L2 has a short sequence of only six amino acids that can actually poke through the endosome membrane into the cytoplasm, so it can bind to retromer," said Dr. DiMaio.

After Dr. DiMaio and his colleagues hypothesized such a mechanism, his lab tested and confirmed it through a novel assay. Most of the experiments in the *Cell* paper were performed by Pengwei Zhang, PhD, a post-doctoral associate in Dr. DiMaio's lab. Other collaborators on this study were Gabriel Monteiro da Silva, MS, Catherine Deatherage, PhD, and Christopher Burd, MS, PhD, Professor of Cell Biology.

In another first, they also discovered that L2 contains a cell-penetrating peptide (CPP). These peptides were discovered in other proteins 30 years ago, but their biological role remained virtually unknown. "This is one of the first times that the normal function of a CPP has been elucidated," said Dr. DiMaio. "People have been studying them for a long time, trying to figure out how they get proteins into cells, but in fact that's not what this one is doing. Rather, it's crossing a membrane that's already inside the cell. It may be a general property of CPPs that they're not used so much to transfer proteins from outside to inside, but rather from one compartment inside a cell to another."

After the probing end of L2 pierces the membrane, it functions as a pipeline into the cell for the HPV particle. The L2 pipeline is the virus's only contact with the cytoplasm. The main body of the virus stays inside the endosome, invisible to the cell.

"Cells have all sorts of mechanisms to halt foreign invaders," said Dr. DiMaio, "and viruses come up with all sorts of strategies to overcome that. HPV's strategy is to stay inside these vesicles and never expose itself to the cellular immune system during entry."

The ability of cell-penetrating peptides to enter cells and deliver cargo raises the tantalizing possibility of using them to deliver anti-cancer drugs. Dr. DiMaio intends to explore this idea using L2.

In the meantime, these recent discoveries suggest new ways of preventing HPV infection and the cancers it causes. If a targeted drug could stop L2 from binding to retromer, the virus couldn't infect. Blocking protein interactions can be tricky, said Dr. DiMaio, but this one only involves three amino acids on L2. "So, it's at least plausible to find a small molecule to prevent that."

Another possibility would be to stop L2 from protruding through the endosome membrane in the first place. That would quarantine HPV in its vesicle and prevent infection. "Based on our improved understanding of the entry mechanism," Dr. DiMaio said, "we're hopeful that we will be able devise ways to prevent infection."

He emphasizes that the current vaccination for HPV is very good and is likely to remain the mainstay for prevention. Yet not everybody responds to it, it's expensive, and some people refuse it. "Having additional approaches to block infection might be very useful," he explained.

"We think these targeted approaches could be applicable to every single HPV type because all the papillomaviruses have L2 sequences that penetrate membranes and bind to retromer. If you could develop a way to prevent the L2 cell-penetrating peptide from working, that would be a general solution."

Frederick Wilson, MD, PhD

Collateral Damage Creates an Opening Against Cancer

Computational biology and bioinformatics are allowing researchers to explore deep within the genome. Some of their discoveries may become weapons against cancer. One such discovery has recently been translated into a clinical trial at Smilow Cancer Hospital and other locations.

Using computational biology and bioinformatics, a group of researchers that includes Frederick Wilson, MD, PhD, Assistant Professor of Medicine (Medical Oncology), learned that certain cancers sustain their growth by eradicating a tumor suppressor gene called CDKN2A. This assault on CDKN2A often wipes out a nearby innocent bystander, a gene named MTAP that sits next to CDKN2A on the genome.

"MTAP seems to be lost as collateral damage due to its proximity to CDKN2A," said Dr. Wilson. "Deletion of MTAP is common in many cancers. When MTAP is deleted, cancer cells become dependent on another gene that encodes a protein called PRMT5."

Dependency means vulnerability, which can be exploited. Dr. Wilson and his colleagues wondered if it was possible to take advantage of this dependency on PRMT5 with a therapeutic strategy. If the answer is yes, the effects could be far-reaching. A phase one clinical trial is now underway at several sites, including Smilow Cancer Hospital, where Dr. Wilson is the principal investigator.

"What's exciting to us," said Dr. Wilson "is that MTAP loss is observed in about 15 percent of all cancers. That's a lot of people. And it's seen at greatest frequency in certain solid tumors that have historically been very challenging to treat."

Dr. Wilson did his early research on MTAP at the Broad Institute of MIT and Harvard before coming to Yale in 2017 to start his own lab. Computer biologists at Broad winnowed their discoveries about MTAP and PRMT5 from two large collections of cancer cell lines, the Cancer Cell Line Encyclopedia and Project Achilles. Using these cell lines, the scientists went through the genome one gene at a time, trying to inactivate or turn off the expression of each gene in order to gauge the effect on other genes. That's how they found subsets of cancer cells that seemed dependent on PRMT5. Next, they looked for a genetic feature that these cells had in common. The answer: cells in which both copies of MTAP were deleted. Dr. Wilson took that insight into the lab and began exploring the mechanistic basis for why the loss of MTAP in cancer cells leads to dependency on PRMT5.

He found that when MTAP is lost, a metabolite called MTA, which is normally broken down by MTAP, builds up in cells that lack MTAP. "It turns out that MTA can inhibit PRMT5." said Dr. Wilson. "Since PRMT5 activity is essential in most cells, inhibition of PRMT5 by high MTA combined with further reduction of PRMT5 function in cancer cells without MTAP impairs growth."

Dr. Wilson and his colleagues published these findings in *Science* in 2016. At the same time, two pharmaceutical companies independently made the same discovery, which confirmed Dr. Wilson's research.

Now, in his Yale lab, Dr. Wilson continues to study how PRMT5 functions in cancer cells where MTAP has been deleted. Additionally, he is working with Agios, one of the pharmaceutical companies whose research on MTAP mirrored his. Agios has developed a compound that inhibits the PRMT5 pathway. The compound, called AG-270, is designed to deprive MTAP-deleted cancer cells of the PRMT5 activity that they need to survive.

When AG-270 was ready for a phase one trial last fall [2018], Dr. Wilson's expertise made Smilow Cancer Hospital and Yale Cancer Center a natural choice as one of the locations. The compound has never been used in humans, so the trial's primary goal is to assess the drug's safety at various dosages.

Finding the right dosage is crucial. The goal is to deliver just enough of the drug to further reduce the level of PRMT5 activity, which is already lowered in MTAP-deleted cancer cells, to a point where the cancer can no longer grow. But most normal cells also rely on PRMT5, so administering too much drug could cause unwanted side effects.

The potential benefits of finding a way to inhibit PRMT5 in cancers that lack MTAP are striking, especially in solid tumors. MTAP is deleted in about 15 percent of all cancers. But in some cancers that figure is even higher—40 percent of glioblastomas and 25 percent of melanomas, urothelial cancers, and pancreatic cancers.

"If this compound has promising activity in patients," said Dr. Wilson, "or if we can identify alternative potential targets in this pathway, the results could be relevant to many patients. What's really exciting is the opportunity to transition from a discovery in the lab to a therapeutic strategy, and to bring that therapy into the clinic for the benefit of our patients."

Rethinking Mammography

Can a technology aimed at preventing cancer deaths become so efficient that it creates other problems? The counterintuitive answer is yes. Studies suggest that 20 to 40 percent of breast tumors found by mammography are overdiagnosed, meaning that the detected tumors would not have become clinically noticeable or dangerous during the patients' lifetimes.

Donald Lannin, MD, Professor of Surgery, and Shi-Yi Wang, MD, PhD, Associate Professor of Epidemiology, have added to this growing body of research by investigating the mechanisms behind overdiagnosis using mammography. Dr. Lannin, whose specialty is breast surgery, noticed that studies showed a dramatic increase in the incidence of small breast cancers due to mammography screening, but no corresponding dramatic drop in breast cancer fatalities.

They published their findings in *The New England Journal of Medicine* under the intriguing title, "Are Small Breast Cancers Good Because They Are Small Or Small Because They Are Good?" A key factor in their analysis is "lead time," the period between when a mammogram can detect a breast tumor and when the tumor would become clinically apparent without screening.

"In general we thought that the lead time before breast cancer diagnosis was three or four years," said Dr. Wang. "But based on our simulation modeling—and we are the first paper to say this—we found that the lead time differs by tumor characteristics. For aggressive, unfavorable breast cancers, the lead time could be as short as two years. But for small tumors with favorable characteristics, the lead time could be as long as 15 or 20 years."

"Shi-Yi has given us a better picture of who is being overdiagnosed based on the biology of the tumor and the age of the patient," added Dr. Lannin. "That's quite a conceptual advance in understanding overdiagnosis."

When mammography came into wide use around 40 years ago, scientists incorrectly assumed that all breast cancers were the same. The new technology was expected to drastically cut the death rate. The logic was sound—if breast cancers could be detected early, while they were still small, the survival rate would soar. That didn't happen.

Drs. Lannin and Wang found that mammography is great at finding small tumors, which tend to have excellent prognoses—not because the tumors are found early, but because they are biologically unaggressive and grow so slowly. Mammography is less successful at early detection of the aggressive breast cancers that really endanger a woman's life. These cancers grow so quickly that by the time the woman gets her next screening, they have spread.

Drs. Lannin and Wang note that mammography can be critical, especially for women at high-risk for breast cancer. Screenings have cut breast cancer mortality by about 19 percent, notes Dr. Lannin, then he added, "But on the other hand, that's not the 75 percent to 90 percent that we once expected and that many people still assume. Our data is very consistent with big trials on screening mammography that show a small benefit. Now, I think we understand a little bit better why it's fairly small."

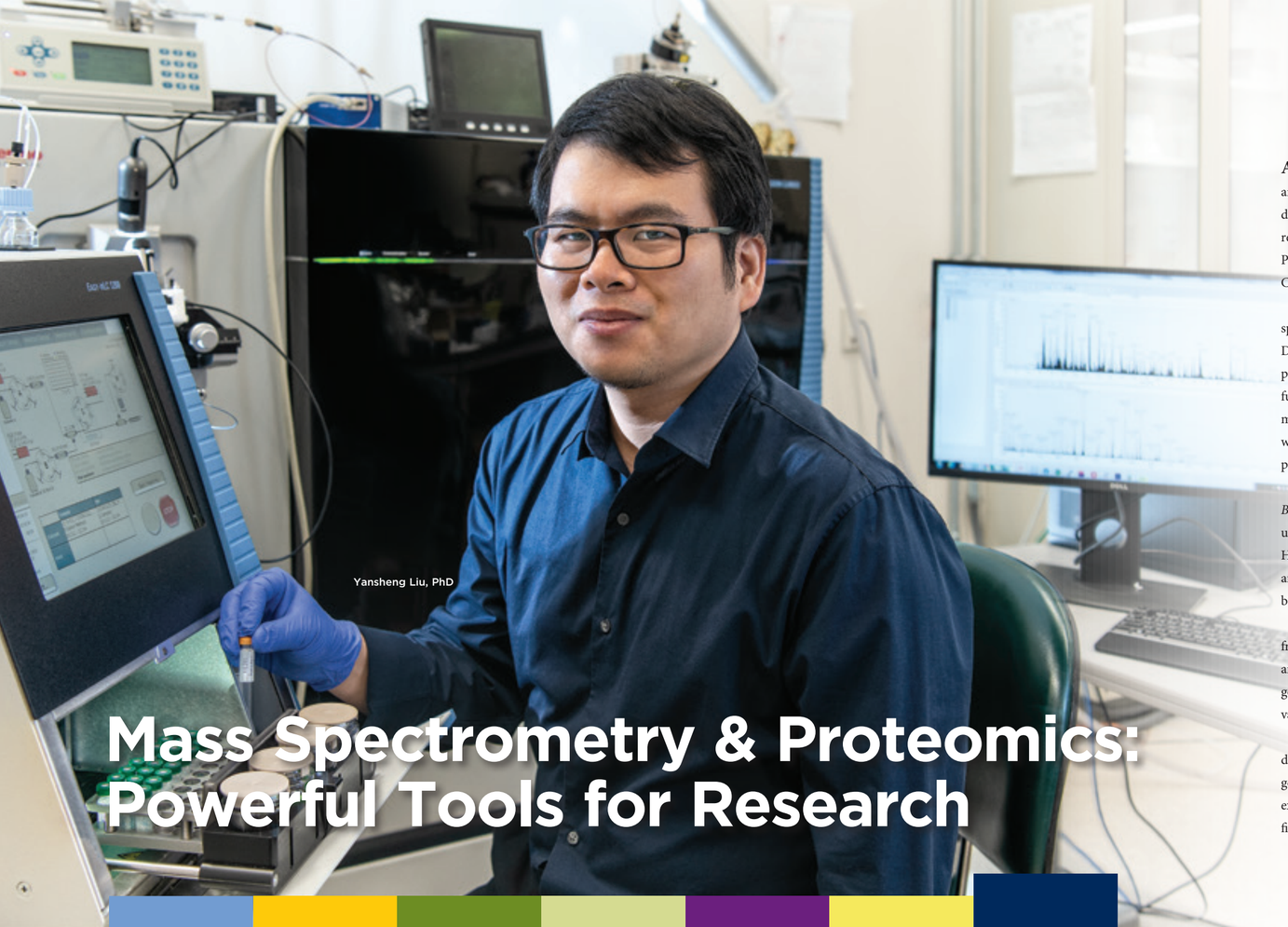
"We need to rethink this issue," said Dr. Wang, "especially now when healthcare costs are so prohibitive."

Mammography has become so entrenched in women's healthcare that it's controversial to suggest it's overused. The usual rebuttal is that limiting it would put women at greater risk. Drs. Lannin and Wang point out that overdiagnosis and its corollary, overtreatment, carry their own dangers. Detection of a small tumor on a mammogram fills a woman with fear, which can drive her to get a sentinel node biopsy, radiation, chemotherapy, or even surgery—pain, risk, and expense that could be avoided if her cancer is biologically unaggressive.

To prevent overtreatment, says Dr. Lannin, oncologists need to recognize which breast cancers are more likely to be overdiagnosed and then treat them less intrusively. He has this conversation many times each week with worried patients whose mammograms show a small tumor.

"If it's a low-grade ER-positive tumor," he said, "it has such a good prognosis that I can reassure them that if we hadn't diagnosed it on the mammogram, they wouldn't have known about it for 10 or 15 years. Once they understand that, they feel better. In general, we still remove the tumor because very few patients want to leave it alone, but we don't plan any additional treatment."

They point out that this idea isn't new or radical. When the screening test with prostate-specific antigen (PSA) was new, it created a spike in diagnoses of prostate cancer, leading to overtreatment. Oncologists now understand that many prostate cancers are slow-growing and nonthreatening, so the current treatment strategy is monitoring. Something similar–monitoring after a lumpectomy, say Drs. Lannin and Wang, is appropriate for many breast cancers.



Yansheng Liu, PhD

Mass Spectrometry & Proteomics: Powerful Tools for Research

Advances in mass spectrometry and proteomics are giving researchers new ways to better understand, detect, diagnose, and treat cancer. A year ago, Yale recruited Yansheng Liu, PhD, Assistant Professor of Pharmacology, to bring these innovative tools to the Cancer Biology Institute.

Dr. Liu arrived from Zurich, Switzerland, where he spent more than six years in the Proteomics Lab of Dr. Ruedi Aebersold, a world-renowned pioneer in proteomics. He was lured here in part by Yale's offer to furnish his laboratory with the fastest and most versatile mass spectrometer available, an Orbitrap Fusion Lumos, which Dr. Liu calls essential for his next-generation proteomics research.

One example of that research is now in press at *Nature Biotechnology*. "The paper presents something quite unexpected and surprising about HeLa cells," said Dr. Liu. HeLa is a line of human cancer cells that can be cloned and cultured, and may be the most widely-used cell line in biological and biomedical research.

Dr. Liu and his colleagues collected 14 HeLa samples from 13 labs in six countries, cultured them, and then analyzed them using mass spectrometry (MS), proteomics, genomics, and transcriptomics. They found significant variation between HeLa variants.

Equally surprising, the scientists often found progressive divergence even within a specific variant. "After just 50 generations," explained Dr. Liu, "if we compare the gene expression of one HeLa cell line from beginning to end, we find six percent of the genome is significantly different."

The implications are important, he added. Researchers assume that their HeLa cell lines are homogenous and that research based on them can be independently verified—a crucial aspect of science. But if the HeLa cells vary across and even within strains, that can change results and thwart verification. Dr. Liu's paper cites a survey conducted by *Nature* in 2016 in which more than half of the participating researchers agreed that there is a "reproducibility crisis" in the life sciences, which has been blamed on factors such as contamination, statistical error, incompetence, fraud, and misidentification of cell lines. Dr. Liu's research suggests that another reason might be genomic volatility among supposedly homogenous cell lines. He believes that MS and proteomics can help solve the reproducibility crisis by providing another way to do cell line authentication, measuring steady-state gene expression at the transcript and proteome levels.

He is certain that MS and proteomics are even more valuable when applied broadly in cancer research. These tools and experimental strategies can capture and characterize not only protein expression but protein modifications such as phosphorylation and ubiquitination, protein turnover, and protein localization. "All of these are quite relevant for cancer research," he said.

For instance, MS and proteomics are incredibly powerful for identifying and characterizing molecular elements. With a new MS method called Data-Independent Acquisition (DIA), Dr. Liu can quantify almost 800 proteins in plasma in just two hours. In one microgram of cancer tissue, he can quantify 5,000 proteins. In a cancer cell line, 6,000 - 8,000 proteins. "DIA can provide unprecedented reproducibility among 100-1000s samples. This gives us bigger opportunities to understand more deeply what is going on at the proteome level," said Dr. Liu.

Dr. Liu is also enthusiastic about using MS and proteomics to study protein localization. If proteins get localized aberrantly—put into the wrong cellular compartments—disease can result, including cancer. "We have a very cool technique," explained Dr. Liu, "where we can assign a protein or a modified protein into an organelle."

He is eager to use these technologies to advance research across Yale Cancer Center, and has some collaborations underway. With Andre Levchenko, PhD, John C. Malone Professor of Biomedical Engineering and Director of the Systems Biology Institute, Dr. Liu is looking at the metastatic features of melanoma in patients and cell lines, in particular protein modification and turnover.

He is also assisted by Anatoly Kiyatkin, PhD, a postdoc at the Cancer Biology Institute, to perform a study that is monitoring cell signaling stimulated by EGF (epidermal growth factor) or NGF (nerve growth factor) ligand, a process implicated in many cancers. Using DIA-MS, Dr. Liu can measure changes instantaneously and periodically in both the protein's abundance and its phosphorylation, and their respective lifetime, to provide a much better understanding of EGF receptor signaling in cancer.

"I look forward to more clinically-related collaborations with physicians in the Cancer Center," he said. "We can definitely work together to bring better proteomic measurement to particular questions in clinical cancer research."

Yale Cancer Center Leadership

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Assistant Director, Surgery

Andrea Silber, MD
Assistant Clinical Director, Diversity and Health Equity

Edward Snyder, MD
Assistant Director, Membership

Yale Cancer Center Research Programs

Cancer Immunology
Lieping Chen, MD, PhD
Mario Sznol, MD

Cancer Prevention and Control
Melinda Irwin, PhD, MPH
Xiaomei Ma, 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
Joann B. Sweasy, PhD

Virus and Other Infection-associated Cancers
Amy Justice, MD, PhD
Walther H. Mothes, PhD

Signal Transduction
Mark A. Lemmon, PhD, FRS
Daniel P. Petrylak, MD
David F. Stern, PhD

Yale Cancer Center Shared Resources

Biostatistics and Bioinformatics
Shuangge Steven Ma, PhD

Cesium Irradiator
Ravinder Nath, PhD

Clinical Research Services
Charles S. Fuchs, MD, MPH, *Interim Director*
Stephanie Halene, MD, PhD, *Assistant Director, Clinical Research Support Laboratory*
Thomas Prebet, MD, PhD, *Assistant Director, Clinical Trials Office, Hematology Trials*
Scott Gettinger, MD, *Assistant Director, Clinical Trials Office, Medical Oncology Trials*

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

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

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
Medical Director, Ambulatory Clinics
Deputy Chief Medical Officer

Sonia Grizzle
Director, Financial Operations

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

Endocrine Cancers
Clinical Program and Disease Aligned Research Team Leader:
Tobias Carling, MD, PhD

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

Pediatric Oncology and Hematology
Clinical Program and Disease Aligned Research Team Leader:
Gary Kupfer, 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

Radiobiology and Radiotherapy

Sanjay Aneja
Ranjit Bindra
Justin Blasberg
Daniel Boffa
Douglas Brash
Jason Cai
David Carlson
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
Hoby Hetherington
Susan Higgins
D.S. Fahmeed Hyder
Ryan Jensen
Megan King
Gary Kupfer
Patty Lee
Wu Liu
Bernadette Marquez-Nostra
Meena Moran
Evan Morris
Rosa Munoz Xicola
Ravinder Nath
Henry Park
Abhijit Patel
Kenneth Roberts
Faye Rogers
Peter Schulam
Patrick Sung
Joann Sweasy
Lynn Wilson

Genomics, Genetics, and Epigenetics

Nita Ahuja
Claudio Alarcon
Allen Bale
Linda Bartoshuk
Susan Baserga
Jean Bolognia
Marcus Bosenberg
Demetrios Braddock
Tobias Carling
Nancy Carrasco
Sidi Chen
Keith Choate
Lynn Cooley
Jose Costa
Andrew Dewan
Nadya Dimitrova
Mark Gerstein
Antonio Giraldez
Murat Gunel
Shangqin Guo
Ruth Halaban
Stephanie Halene
Shilpa Hattangadi
Erin Hofstatter
Natalia Ivanova
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
Janina Longtine
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
Scott Weatherbee
Sherman Weissman
Frederick Wilson
Andrew Xiao
Mina Xu
Tian Xu
Qin Yan
Hongyu Zhao

Virus and Other Infection-associated Cancers

Kathleen Akgun
Daniel DiMaio
Ayman El-Guindy
Ellen Foxman
Jorge Galan
Andrew Goodman
Stavroula Hatzios
Ya-Chi Ho
Stanley David 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
Heather Osborn
Elijah Paintsil
Noah Palm
Anna Marie Pyle
John Rose
Christian Schlieker
Joan Steitz
Richard Sutton
Tamar Taddei
Peter Tattersall
Anthony Van den Pol
Sten Vermund
Craig Wilen

Cancer Immunology

Stephan Ariyan
Philip Askenase
Kevin Becker
Jeffrey Bender
Alfred Bothwell
Richard Bucala
Lieping Chen
Oscar Colegio
Joseph Craft
Peter Cresswell
Richard Edelson
Brinda Emu
Richard Flavell
Francine Foss
Michael Girardi
Earl Glusac
Ann Haberman
David Hafler
Douglas Hanlon
Kevan Herold
John Hwa
Nikhil Joshi
Paula Kavathas
Tae Kon Kim
Steven Kleinstein
Smita Krishnaswamy
Carrie Lucas
Mark Mamula
Jennifer McNiff
Ruslan Medzhitov
Eric Meffre
Kelly Olino
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

Developmental Therapeutics

Karen Anderson
Masoud Azodi
Joachim Baehring
Aarti Bhatia
Debra Brandt
Ronald Breaker
Barbara Burtness
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
Gigi Galiana
Scott Gettinger
Sarah Goldberg
Steven Gore
Lohith Gowda
Ya Ha
Roy S. Herbst
Seth Herzon
Nina Horowitz
Iris Isufi
William Jorgensen
Patrick Kenney
Kevin Kim
Harriet Kluger
Jaseok Koo
Jill Lacy
Rogerio Lilenbaum
Renelle Lim
Dieter Lindskog
Elias Lolis
Patricia LoRusso
Scott Miller
Jennifer Moliterno
Gil Mor
Bryce Nelson
Natalia Neparidze
Terri Parker
Farzana Pashankar
Pasquale Patrizio
Peter Peduzzi
Joseph Piepmeier
Nikolai Podoltsev
Thomas Prebet
John Roberts
Michal Rose
W. Mark Saltzman
Alessandro Santin
Clarence Sasaki
Alanna Schepartz
William Sessa
David Spiegel
Preston Sprenkle
Stacey Stein
Mario Strazzabosco
Seyedtaghi Takyar
Vasilis Vasiliou
Sarah Weiss
Amer Zeidan
Daniel Zelterman
Jiangbing Zhou

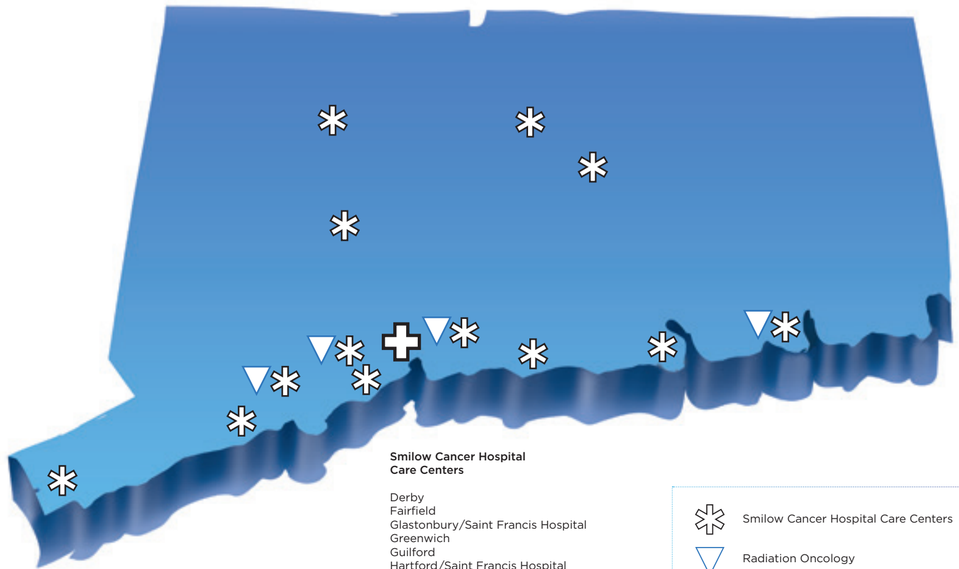
Signal Transduction

Anna Arnal Estape
Anton Bennett
Titus Boggon
David Breslow
David Calderwood
Toby Chai
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
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
Joseph Schlessinger
Martin Schwartz
David Stern
Yajaira Suarez
Derek Toomre
Benjamin Turk
Narendra Wajapeyee
Robert Weiss

Cancer Prevention and Control

Kerin Adelson
Prasanna Ananth
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
Beth Jones
Manisha Juthani-Mehta
Nina Kadan-Lottick
Jennifer Kapo
Brigid Killelea
Mary Knobf
Suchitra Krishnan-Sarin
Donald Lannin
James Lazenby
Michael Leapman
Haiqun Lin
Lingeng Lu
Shuangge Steven Ma
Xiaomei Ma
Asher Marks
Ruth McCorkle
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 Smith
Mehmet Sofuoglu
Donna Spiegelman
Sakinah Suttiratana
Shi-Yi Wang

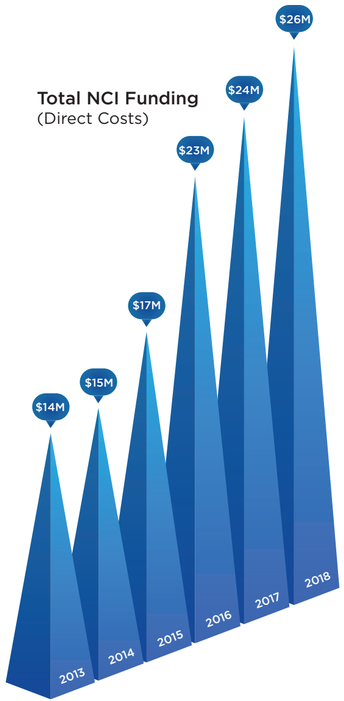
Yale Cancer Center and Smilow Cancer Hospital Data



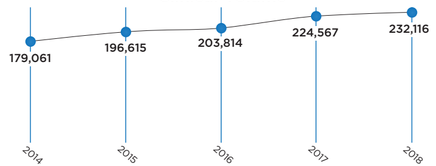
Smilow Cancer Hospital Care Centers

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

Total NCI Funding
(Direct Costs)



Clinical Volume



Office Visits by Year

2017 Top Ten Cancer Sites
at Smilow Cancer Hospital

MALE			FEMALE		
PROSTATE	14.7%	473	1206	31.1%	BREAST
LUNG & BRONCHUS	12.9%	414	454	11.7%	LUNG & BRONCHUS
MELANOMA	8.5%	275	239	6.2%	CORPUS & UTERUS
COLORECTAL	6.4%	207	215	5.5%	MELANOMA
NON HODGKIN'S LYMPHOMA	5.8%	186	208	5.4%	THYROID
ORAL CAVITY & PHARYNX	5.2%	169	182	4.7%	BRAIN & CNS
KIDNEY & RENAL PELVIS	4.7%	150	166	4.3%	COLORECTAL
URINARY BLADDER	4.4%	142	126	3.2%	NON HODGKIN'S LYMPHOMA
LEUKEMIA	4.3%	140	126	3.2%	LEUKEMIA
BRAIN & CNS	4.1%	132	115	3.0%	PANCREAS
OTHER	28.9%	932	846	21.8%	OTHER
		TOTAL: 3,220	3,883: TOTAL		

Publications
from Yale Cancer Center Members

June 1, 2017 – July 31, 2018

889 PUBLICATIONS

193 High Impact Publications
IF > 10, including:

- 36 – Nature/Nature Specialty
- 25 – Journal of Clinical Oncology
- 17 – JAMA/JAMA Oncology
- 8 – Cell/Cell Specialty
- 8 – Cancer Discovery
- 8 – Blood
- 7 – Science/Science Specialty
- 5 – Angewandte Chemie
- 4 – Lancet/Lancet Oncology
- 3 – Journal of Clinical Investigation
- 2 – New England Journal of Medicine
- 1 – Advanced Materials
- 1 – Nano Letters
- 1 – Genes & Development

YaleNewHavenHealth
Smilow Cancer Hospital

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

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