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Smilow's First Top Nurse Retires

Catherine Lyons, RN, MS, Vice President of Patient Services and Chief Nursing Officer at Smilow, retired at the end of 2018, leaving behind a legacy of extraordinary patient care standards and a model for oncology nursing at Smilow.
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 900 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, interventional 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
In 2012, Mary Di Gioia, a grandmother of four who works as a social worker, 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.” While USC comprises only 10 percent of endometrial cancers, it ends up killing more than 60 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 initially shone the light of hope for USC.

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 HER2/neu. This was still in the relatively early days of immunotherapy treatment for cancer, but HER2/neu was already known in breast cancer. A few years later, Dr. Santin and his team identified a group of women with breast cancer who respond to treatment 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 infections. When everything is

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Paula Derrow | writer

FOR A RARE REPRODUCTIVE CANCER

FOR THE RIGHT TREATMENT

Art direction by Emily Carter

Yale Cancer Center 2018
When Dr. Santin discovered that there was also an amplification of the HER2 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 had already targeted that therapy, but 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 trouble, 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 gene protein. Prior studies had also used Herceptin alone to treat USC, rather than combining it with chemotherapy, which was ineffective. “In our era, we found that uterine serous carcinoma was characterized by tumors that were highly heterogeneous—that is, they contained tumor cells expressing HER2 but also tumor cells without high expression of the HER2 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 could target both the HER2-positive tumors and the non-HER2-positive 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.

With all the information produced in my research lab studying the underlying biology, Dr. Santin believed that using both Herceptin and chemotherapy would allow them to succeed. “In that respect, I suspected that with a different study design, we could succeed.”

The study, done at Sunnybrook 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 was 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 gene or a mutation of the HER2 gene. Finally, however, Ms. Di Gioia was randomized to the control group of the study: she would receive only chemotherapy. ‘That was disappointing,’ said Dr. Santin. ‘But it also showed me that if things didn’t go well, I would include it in the arm of the trial that included Herceptin.’”

Frustrated yet, Ms. Di Gioia did six courses of chemotherapy, 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 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 chemotherapy again, we began infusions of Herceptin every three weeks.’

That was a year and a half ago. Ms. Di Gioia, now going strong, her tumor hasn’t grown, and her health remains stable. ‘I am a very blessed lady, and that’s the truth,’ she said. Indeed, only about 5 percent of patients with USC who have tested positive for amplified HER2 have lived for clinical policy in cancer care, were revised for women (NCCN) guidelines, which are the recognized standard with advanced and recurrent HER2-positive USC: 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 said, ‘I could do worse,’ she said. Dr. Santin with that. He has taught me how to live with cancer, with the emphasis on the word ‘live’ rather than ‘cancer.’ For that, I am 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
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., M.D., Smilow’s first 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. But in Buffalo, she had spent the first 24 years of her oncology career in that city’s Roswell Park Cancer Center before moving on to 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 wanting 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.

“At the time, there was a lot of pushback from nurses who had been doing it the way they had for years,” said Ms. Lyons. “But Cathy didn’t listen to that. She was very clear about what she wanted and told the nurses that they had to do it her way.”

“Cathy is an extraordinary leader—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 operational 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 rededicated care to the cancer patient and established a level of respect for oncology nursing that I had not seen anywhere else,” Ms. Lyons 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 cancer opportunity in 2015, Ms. Lyons 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
Yale Cancer Center has launched a 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 now 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, Medical Oncologist. Dr. Seropian specializes in lymphomas and stem cell transplants. Dr. Isufi is a Pediatric Hematologist and Oncologist. Dr. Seropian is known as “a leader in the science of immune cells to empower the immune system to fight certain cancers,” said Dr. Isufi. Chimeric Antigen Receptor (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. “That produces a new receptor with a different external protein that recognizes whatever you want it to recognize,” he said.

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 into an instrument. Before that instrument stimulates the cells to produce new receptor proteins called chimeric antigen receptors (CARs). The lab basically inserts a gene into the T-cell genome, explained Dr. Seropian.

“Once these cells are put back into the body,” said Dr. Seropian, “they really take off. The therapy can put someone into remission almost immediately in weeks.”

The immune response, however, can be also adverse: immune-related adverse effects are the T-cells’ problem and the patient’s. “The therapy is very effective,” said Dr. Isufi, but it is also potentially very toxic. To kill cancer cells, the T-cells unleash 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 liver and kidney toxicity. Sometimes these side effects, though usually brief and temporary, are dangerous, and are the reason the program at Smilow opened in the spring of 2019 where the team will test new types of CAR T-cells.”

“The treatment’s advantages far outweigh its risks, especially for patients who have run out of options,” said Dr. Seropian. “And we have tremendous potential to improve the therapy and reduce the side effects as research advances.”

Another clinical trial planned for patients with multiple myeloma will test a new method of introducing the antigen receptor into T-cells. This method, transient rather than permanently, should potentially reduce 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.
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 block 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 in 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. Two 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 used to treat 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.

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“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.”

“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.”

Dr. Scott Gettinger, MD

Yale Cancer Center

Yalecancercenter.org – Scott Gettinger, MD

Yale Cancer Center
Breakthrough?

Another Transformational Breakthrough?

He may have done it again. Lieping Chen, MD, PhD, United Technologies Corporation Professor in Cancer Research, Professor of Immunology, 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 original twenty years when Dr. Chen discovered that cancer cells signal pathways that make the immune system shut 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 that pathway with an antibody, the T-cells in the tumor regained and started killing cancer cells.

Using drugs to trigger 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 have only worked 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 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 that pathway with an antibody, the T-cells in the tumor regained and started killing cancer cells.

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,” Dr. Chen said. “I’m so proud of this project,” Dr. Herbst said. “It will be helping patients in New Haven when it began as part of our Yale (SPOR) research project and will widely expand to Yale and beyond.”

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.

“With so many potential applications, we can see how much this drug might work,” Dr. Chen said. “This antibody is the first example to prove that we can make these kinds of drugs work. That’s very exciting, almost as exciting as seeing the drug itself.”

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Another Transformational Breakthrough? Lieping Chen, 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 Radiobiology, "so these patients remain uncertain 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 breathing gas dislocated from scanning it is because of a check-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.

"But with immunotherapy," said Dr. Patel, "the biomarkers will be evident, sometimes even months. And sometimes it’s evident on a scan because it is shrinking. That can be confusing. Do we wait another month or two to see if it shrinks? The scans aren’t giving us clear-cut data to do the 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 biomarkers that could. They settled on circulating tumor DNA (ctDNA), a byproduct of dying tumor tissue that Dr. Patel 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 the 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? By comparing the levels of a patient’s ctDNA before and after treatment, clinicians had confirmation, on average, just 24 days after treatment started, compared to 72 days when using scans. In other words, even very early in the treatment, before a scan could detect shrinkage, a patient’s ctDNA was detected, said Dr. Patel, imagining this future, "a day in the future when you could 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 would say, ‘This patient very likely has cancer, and perhaps 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.”

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 Institute 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."

The multidisciplinary group has 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 tests 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 would say, ‘This patient very likely has cancer, and perhaps three most likely cancers are X, Y, or Z,’ then you could do a CT scan or an MRI in further diagnosis. Such early detection could save countless lives.”
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 side effects 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 didn’t have that sensitivity to chemotherapy 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 the 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 24.9 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 no recurrence of their disease. That’s an exceedingly rare event. 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 in combination with chemotherapy in 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 radiation resistance. “We’ve seen complete responses in that setting,” she said. “It seems clear that patients with head and neck cancer soon won’t have to settle for the unpleasant three-drug cocktail.”
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, “so we knew we 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 Charlebois, 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 it’s not clear 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 transport proteins from outside to inside, but rather from one compartment inside the 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 vouchards 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 intriguing possibility of using them to deliver anti-cancer drugs. Dr. DiMaio intends to explore this idea using L2.

“Another possibility would be to step L2 from provoking the endosome membrane in the first place. That would guarantee HPV in its vouchard and prevent infection. Based on our improved understanding of the entry mechanisms,” 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.”
Dr. Wilson did his early research on MTAP at the Broad Institute of MIT and Harvard before coming to Yale in 2018 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 inspired his. Agios has developed a compound that inhibits the PRMT5 pathway: the compound, called AG-278, is designed to deprive MTAP-deficient cancer cells of the PRMT5 activity that they need to survive.

When AG-278 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 and tumor response.

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.”
Can a technology aimed at preventing cancer deaths become so efficient that it causes 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 rates would rise. That didn’t happen.

Dr. 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.

“Sensitization to 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.”

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.

“Mammography has become so entrenched in women’s healthcare that it’s controversial to suggest it’s overused. The social neuralt is that if it would put women at greater risk. Drs. Lannin and Wang point out that overdiagnosis and so overtreatment, carry their own dangers. Detection of small tumors means fill 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 that tumor is biologically unaggressive.

To prevent overtreatment, says Dr. Lannin, oncologists need to recognize which breast cancers are ones likely to be overdiagnosed and then treat them less intrusively. He has this conversation many times a week with worried patients whose mammograms show small tumors. “It’s a low-grade, ER-positive tumor,” he said, “It’s such a good prognosis that I can reassure them that if we didn’t diagnose it on the mammogram, they would have known about it in 15 or 20 years. They have to understand that, they feel better. In general, we still remove the tumor because very few patients want to learn about it, but we don’t plan any additional treatment.”

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Rethinking Mammography

Yale Cancer Center | Year in Review 2018

Donald Lannin, MD, PhD

Shi-Yi Wang, MD, PhD

Cancer Prevention and Control Research Program
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 Yanhong 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 hired here in part by Yale’s offer to furnish his laboratory with the most state-of-the-art 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 10 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 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 also 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 supports that another reason might be genomic volatility among supposedly homogeneous 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 of 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 cell line, he can quantify 5,000 proteins. In a cancer cell line, 6,000 – 8,000 proteins. “DIA can provide unprecedented reproducibility among 100-1000 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—cancer 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 at the Cancer Biology Institute, to perform a study that is underway. With Andre Lesczynski, PhD, John C. Maloney Professor of Biomedical Engineering and Director of the Systems Biology Institute, Dr. Liu is looking at the metastatic features of melanomas in patients and cell lines, in particular protein modifications and turnover.

He is also assisted by Anujey Kikuchi, PhD, a postdoctoral at the Cancer Biology Institute, to perform a study that is monitoring cell signaling mimicked by EGF (epidermal growth factor) or NGF (nerve growth factor) signal, 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 lifetimes, to provide a much deeper understanding of EGF receptor signaling in cancer. “It is quite hard to do clinically-related collaborations with physicians in the Cancer Center,” he said. “We can definitely work together in being better proteomic measurement to perturbative questions in clinical cancer research.”

Yanhong Liu, PhD