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

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

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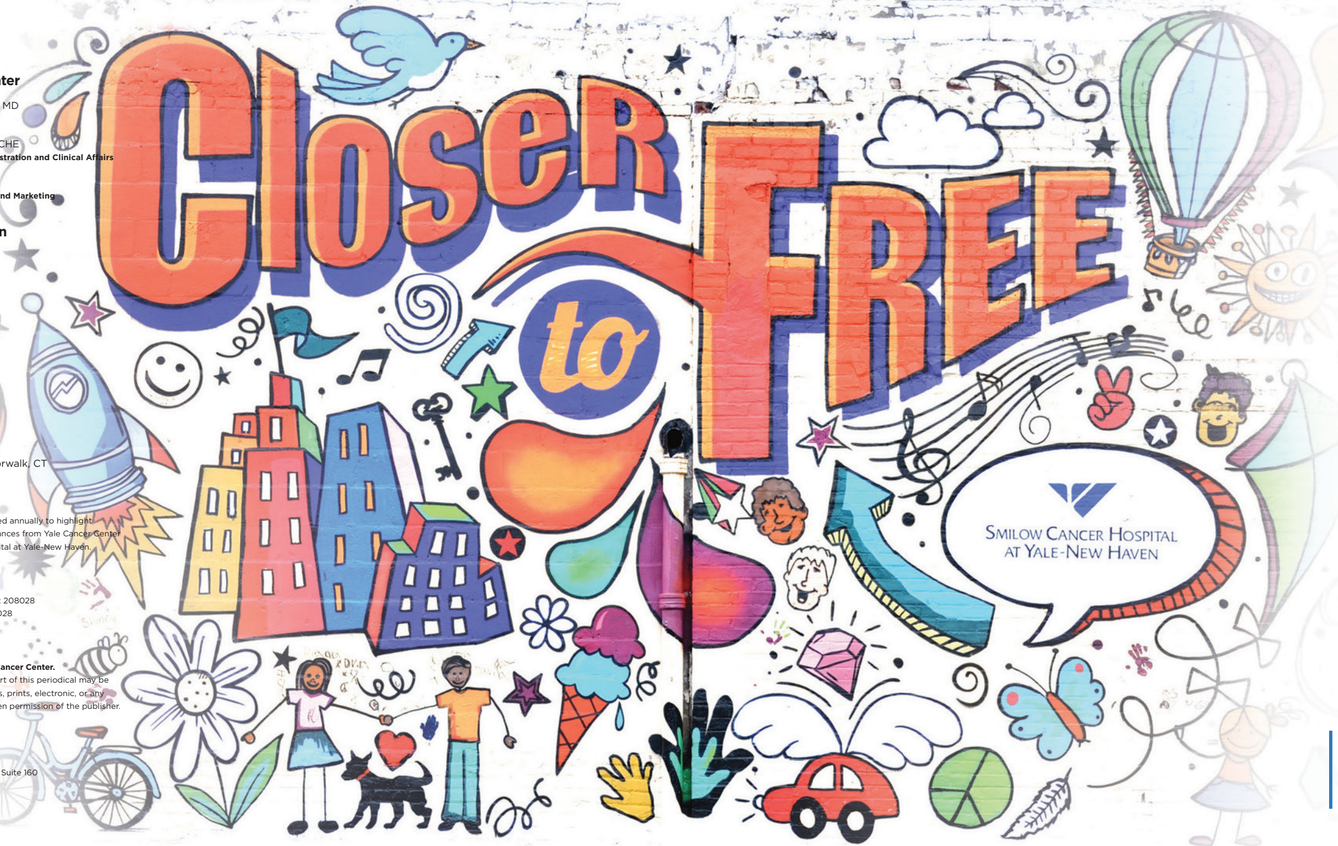
breakthroughs

THE YEAR IN REVIEW



yale cancer center

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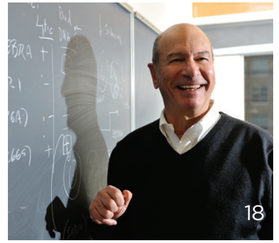
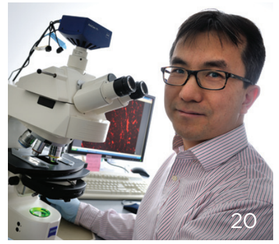
On October 17, 2013, dozens of cancer survivors from Smilow Cancer Hospital, along with family, friends and caregivers, gathered on Water Street in New Haven. The project they participated in was the painting of a Closer to Free wall mural. The message they sent on that day was that cancer can be beaten. And that the world is closer to free.





The year 2013 was a spectacular one for Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. We continued our strong momentum with important breakthroughs from our basic, population, and clinical research teams, and outstanding growth in our clinical care enterprise. We celebrated the successful completion and renewal of our National Cancer Institute Cancer Center Support Grant in 2013, along with a newly approved National Clinical Trials Network – Network Lead Academic Participating Site.

Molecular profiling and expansion of tumor sequencing continues to propel treatment options for our patients. Yale Cancer Center implemented a weekly Precision Medicine Tumor Board in 2013 to ensure our patients benefit from the combined expertise of leaders in oncology, genetics, pathology, and radiology to review their tumor profiling results, and to determine the best treatment plan for each patient. Equally significant, tumor sequencing data from our patients is enriching our laboratory research and giving our research teams new access to information on tumor types and response to treatment.

I am extremely proud of our physicians and nurses who continually go above and beyond to care for our patients. Their dedication is evident in our 2013 Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, the first national standardized survey to measure patients' perspectives of their hospital experience. In fiscal year 2013, Smilow Cancer Hospital exceeded the 50th percentile ranking in 30/32 domains, and two of those domains exceeded the 90th percentile ranking. In our outpatient areas, Smilow achieved the highest overall satisfaction score when compared to 15 of our NCI-designated Comprehensive Cancer Center peer institutions.

Yale Cancer Center and Smilow Cancer Hospital continue to focus on recruiting the very best clinicians and scientists to our team. In 2013, we welcomed Steven Gore, MD, Director of Hematologic Malignancies, Laura Morrison, MD, Director of the Hospice and Palliative Medicine Fellowship, and Daniel Petrylak, MD, Clinical Research Program Leader for Prostate and Urologic Cancers, and I am pleased to announce that Barbara Burtness, MD will return to Yale this spring as Clinical Research Program Leader for Head and Neck Cancers. We also welcomed several new clinicians throughout the hospital, including Caroline Cromwell, MD, James Farrell, MD, Jennifer Moliterno Gunel, MD, Sajid Khan, MD, Asher Marks, MD, and Saral Mehra, MD.

As we move into the New Year, we will continue to expand our presence in Connecticut through our 8 Cancer Care Centers and offer more innovative clinical trial opportunities to our patients. I look forward to sharing new research advances and outcomes from our laboratories and clinics with you in 2014.

"We continued our strong momentum with important breakthroughs from our basic, population, and clinical research teams, and outstanding growth in our clinical care enterprise."

Sincerely,

Thomas J. Lynch, Jr., MD
Director, Yale Cancer Center
Physician-in-Chief, Smilow Cancer Hospital
Jonathan and Richard Sackler Professor of Medicine

MOLECULAR PROFILING GOES REAL TIME

Sequence analysis of genomic DNA is revolutionizing science's understanding of cancer. One application of DNA sequencing – molecular profiling – is enhancing the treatment of cancer patients. Yale Cancer Center is at the forefront of both molecular profiling of tumor DNA and its translation into cancer treatment for patients.

"For the first time, we have developed the clinical ability to look at cancers and to determine, in many cases, what genes are driving the malignancy. And we can now do that in real time – it used to take months – so it influences patient-care decisions. This is part of our effort toward personalized medicine, to link the right drug to the right patient at the right time," Thomas J. Lynch, Jr., MD, Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital at Yale-New Haven, said.

This effort became more focused earlier this year with the formation of a Precision Medicine Tumor Board. The board was the brainchild of several people at Yale: Roy S. Herbst, MD, PhD, Chief of Medical Oncology, Ensign Professor of Medicine, and Associate Director for Translational Research; Murat Günel, MD, FACS, FAHA, Nixdorff-German Professor of Neurosurgery, Professor of Genetics and Neurobiology and Director of the Yale Program in Brain Tumor Research, and Julie Boyer, PhD.

Others quickly became deeply involved, including Jeffrey L. Sklar, MD, PhD, Director of the Molecular Tumor Profiling Laboratory and of the Molecular Diagnostics Program; and Paul Eder, MD, Director of Experimental Therapeutics and the Phase I Research Group.

"This was a dream that Tom Lynch and I had for several years," Dr. Herbst said, "to use the technology of genomic sequencing to have a strong impact on clinical care. This year we've seen the merging of our clinical and research interests in a way that's hopefully providing better care for patients, which is our fundamental goal."

The board meets every Thursday to discuss the best course of treatment for several cancer patients. Yale's full range of multidisciplinary expertise is brought to bear on each case. Participants include medical oncologists, hematologists, pathologists, radiation oncologists, surgeons, radiologists, nurses, and basic scientists, and sometimes individuals from the Law School to represent ethical issues.

"We are bringing the scientists and the clinicians together in one room," Dr. Herbst said, "so that we can do our best in real time to figure out what's driving each tumor, and to choose the right drug or clinical trial."

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Before a patient's case reaches the board, the tumor must be molecularly profiled. The process begins with a biopsy. "We extract DNA from the tumor and interrogate its genes," explained Dr. Sklar, "to see if it has mutations that can be treated by a drug that targets that mutation. There's a rapidly expanding arsenal of these drugs."

The profiling process has changed drastically and quickly. Three years ago Dr. Sklar was testing for about 72 mutations in eight genes. Two years ago he began using a technology that tests 50 genes. In early 2013, he started running tests with the next generation of that technology, which analyzes 409 genes.

In addition to targeted sequencing, Yale was one of two centers that pioneered the 'exome sequencing' technology, which allows for the profiling of 22,000 genes – essentially every gene in the entire genome. The invention of this technology in 2010 was considered to be one of the 10 scientific breakthroughs of the year by Science magazine. Although only initially applicable for the discovery of inherited mutations, this technology is now being used in real time for cancer genome sequencing. "Currently the technology is so advanced that, when a cancer progresses or recurs, we can use it to compare the genomic profile of the progressed sample to the original tumor, determining why the cancer advanced," Dr. Günel explained. Yale researchers can now even extract the genetic information from formalin fixed tumor samples, including small needle biopsy specimens, archived for several decades, determining the exact changes that caused a cancer to progress or recur and precisely targeting these changes for treatment.

Whether these tests are targeted or based on exome sequencing, they are aimed at detecting genomic abnormalities that cause cancer, starting with "point mutations" – or small abnormalities in DNA. "The structure of DNA is like beads on a string," explained Dr. Sklar, "with maybe 10,000 beads making up a gene. We look for a change in a single bead, or in a couple of beads, insertion of beads, or maybe the deletion of a couple of beads – but most often the substitution of one bead for another."

In another kind of mutation seen in tumors, segments within DNA rearrange themselves, by breaking, flipping, and reduplicating variable numbers of times, sometimes exchanging position with other fragments of DNA, and then fusing together to create a new sequence at the sites of fusion. These so-called rearrangements are detected through another technology for molecular profiling called fluorescence in situ hybridization (FISH), which was pioneered at Yale in the 1980s.

Several of these mutations can be treated with drugs aimed precisely at them. For instance, if the profile of a lung cancer reveals that a segment of the ALK gene has inverted in the DNA of a lung tumor, the patient will receive a drug called crizotinib that targets that specific mutation. After receiving the right treatment, "patient's large tumors often just melt," Dr. Sklar said. Similarly, lung cancer patients whose profile reveals a mutation in the EGFR gene can be treated with a targeted drug called erlotinib. Breast cancer patients whose profiles show an amplification of the gene called HER2 receive the targeted drug trastuzumab. If the molecular profile of someone with chronic myeloid leukemia (CML) reveals a fusion of the genes BCR and ABL, they can be treated with imatinib.

"The drugs are very effective because they exactly hit the drivers of the cancer, but they have relatively few side effects. That's why they're referred to as targeted, as opposed to chemotherapy which is like a blunderbuss. These new drugs are not quite magic bullets," he added, "but they're the closest thing we have, and in the case of CML and possibly other cancers, there are patients who are likely cured."

For these cancer patients, the benefits of molecular profiling are clear. But currently, there are far more known mutations than targeted drugs to treat them. Still, discovering and identifying the mutations is the necessary first step. The knowledge accumulating in Yale's database of molecular profiles will eventually be translated into therapies that will help patients.

"Our advantage is that the exome sequencing technology was developed here," Dr. Günel explained, "so we have the most experience and sophistication with it, and we now have a very large catalogue of mutations in different genes that can cause cancers so that we can decide which gene is causing a particular cancer. The ongoing cataloguing feeds itself and will help us begin to cure some cancers." He adds that by learning from each cancer patient, Yale is now building its own 'extended cancer exome chip,' which allows for capturing of not only all 22,000 protein coding genes in the genome, but also genomic rearrangements, as well as common mutations in non-coding regions of the genome that affect the expression levels of cancer genes.

> "The drugs are very effective because they **exactly hit the drivers of the cancer**, but they have relatively few side effects. "

Dr. Sklar said this catalogue includes many unexpected discoveries, such as mutations that have never been described in cancers, or mutations familiar in one type of cancer that have never been seen in another type. "So the big question," he said, "is does a drug that works on a mutation in leukemia work on that mutation in pancreatic cancer or breast cancer? I suspect there's a fairly good chance it will. But we need trials to show that."

In fact Yale's expertise in sequencing and profiling has made it more attractive to drug companies looking to initiate Phase I trials of their newly developed targeted drugs. "Molecular profiling is at the very heart of so many trials now," Dr. Lynch said, "because cancer drugs are increasingly designed to target specific molecular populations. Because we are so good at profiling, we're able to get patients on to these Phase I trials quicker, and that's attractive to Pharma."

It's also attractive to the National Institutes of Health, which recently selected Yale from among 150 applicants to be one of three cancer centers that will analyze tumors for mutations and then funnel patients into appropriate Phase I trials.

"We're not just looking at lung cancer, breast cancer, or colon cancer," added Dr. Herbst. "We're thinking about the engine driving each tumor, no matter where it's coming from. If we can figure that out we should be able to target that tumor more effectively and safely. If we can use the cancer tissue for prognosis and to develop predictive drugs to treat patients in more effective ways, I think we're going to make huge advances against cancer."

Smilow Achieves High Scores for

Patient Satisfaction

Physicians, nurses, and staff members at Smilow Cancer Hospital at Yale-New Haven go out of their way to ensure that patients have the best possible experience during their hospital stay. Their efforts are recognized and appreciated by patients, according to a recent survey on patient satisfaction of hospital care.

Smilow scored exceptionally well on nursing care provided on the women's oncology and surgical oncology units in the 2013 Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, the first national standardized survey to measure patients' perspectives of their hospital experience. Nurses scored highly in such areas as treating patients with courtesy and respect, listening carefully, and explaining in ways that patients can understand. "The HCAHPS survey affirms what we want to do every day; take wonderful care of our patients and their families," Catherine Lyons, RN, MS, NEA-BC, Executive Director, Smilow Patient Care Services, said. "When you come into our hospital we want you to leave thinking that you received the best care, the most attention, and the best support."

Achieving a high level of patient satisfaction requires continuous management and maintenance. Ms. Lyons and other leaders read the hundreds of patient comments sent to them weekly by Press Ganey (the company that administers the surveys), the majority of which are positive. "When you come to a place repeatedly for treatment, it sets a higher bar," said Ms. Lyons, who enjoys reading the comments because it gives her a flavor of the patient experience.

Since Smilow opened in 2009, there has been a steady increase in the degree of patient satisfaction, thanks to concerted efforts to improve patient care. "The key to the staff on both units is that they have phenomenal teamwork and their main priority and focus is always the patient and the patient experience," Tracy Carafeno, RN, MS, Patient Service Manager for both units, explained. "They go above and beyond every day."

Initiatives to improve patient satisfaction have included taking steps to ensure that the hospital environment promotes healing and rest by such practices as dimming the lights and closing the doors at night and coordinating care to avoid constantly interrupting those who are trying to sleep. Ms. Lyons and her colleagues also work with nurses and physicians on communication strategies such as encouraging physicians to sit down when talking to patients during rounds. There is an effort to put nurses back at the bedside through such practices as placing computers in patient rooms and bedside change of shift report, in which nurses changing shifts communicate with one another about their patients' status at the bedside, in front of the patient. There is also a shared sense of responsibility. "All the nurses take care of all the patients, not just the ones they're assigned to, and that makes a big difference in the patient experience," Maggie Zampano, RN, OCN, who works on the women's oncology unit, said.

"The leadership team is incredibly proud of the staff at Smilow Cancer Hospital and the HCAHPS results affirm that we are succeeding in providing outstanding patient-centered care," said Thomas J. Lynch, Jr., MD, Physician-in-Chief of Smilow Cancer Hospital at Yale-New Haven.

The survey results will be tied to Medicare reimbursement in 2014, but to Smilow physicians and nurses, they represent something far more important. "People who choose to work in oncology – doctors, nurses, environmental service workers, social workers, pharmacists – get up every day and commit themselves to one of the hardest specialties there is," Ms. Lyons said. "The most important thing to them is knowing they made a difference and that they contributed to their patients having a good experience."

> "The HCAHPS survey affirms what we want to do every day; take wonderful care of our patients and their families."

A Novel Technique for Honing in on Prostate Cancer

Prostate cancer is the most common cancer in men, yet the prostate is the only solid organ in the body that doesn't undergo targeted biopsies. At Smilow Cancer Hospital, that practice is changing. New technology and expertise now make it possible to visualize a prostate tumor within the gland, improving its detection, location, and staging.

Until now, the standard of care for prostate cancer has been to do a random biopsy of the prostate following an elevated prostate-specific antigen (PSA) test or abnormal digital rectal exam. Using ultrasound to locate the prostate, 12 random cores are taken from various areas within the gland. Sampling is random because until now it has not been possible to visualize cancer within the prostate. Aside from the lack of visual data, another problem with this method is that the cores may not be evenly distributed, making it easy to miss small lesions. In about a third of negative biopsies, prostate cancer is found on subsequent biopsies. Even if low-grade cancer is found, doctors can't be sure it's limited to the affected cores.

Smilow Cancer Hospital offers the only program in Connecticut that uses a novel technique to perform targeted biopsies of the prostate. The high-tech approach uses MRI combined with the Artemis device, a 3D robotic imaging system, to locate and biopsy areas in the prostate. This technique has been shown to have a much higher cancer detection rate than standard biopsy; preliminary data at Yale show that it reduces the chances of missing cancer from 30 percent to just three percent. "The device allows doctors to more effectively stratify men as to whether or not they need treatment and whether or not they have cancer," said Preston Sprenkle, MD, Assistant Professor of Urology, who has used it to perform 90 targeted biopsies so far.

The technique brings together expertise in urology, pathology, radiology, and engineering. The first step in the process is a multiparametric MRI that uses three different measurements to locate potentially cancerous areas in the prostate gland. A radiologist outlines problematic areas or tumors and ranks them by suspicion level: low, moderate, or high. Back in the clinic, Dr. Sprenkle performs the biopsy with the Artemis device, which combines real-time ultrasound with the MRI image to create a 3D model of the prostate gland. The 12 cores plus any additional areas of suspected cancer are sampled using a mechanical arm to guide the biopsy. "With Artemis, the 3D model of the prostate, and the computer-generated biopsy pattern, it allows us to look at the entire prostate and make sure we are evenly distributing biopsies so it's much less likely that we will miss a tumor, even if it's not visible on the MRI," Dr. Sprenkle explained.

For men on active surveillance – those with low risk disease who do not currently need treatment – the Artemis system provides some assurance that the low-grade disease that has been detected is all that's there. For those who have had negative biopsies but PSA levels that continue to rise, targeted biopsies can help find hard to spot lesions, especially those at the front of the gland that are more difficult to reach. "We can identify cancer that has been missed on the conventional biopsy," said Peter Schulam, MD, PhD, Chairman of Urology and Clinical Program Leader of the Prostate and Urologic Cancers Program. Artemis also lends precision to repeat biopsies because it allows the physician to locate the exact spot sampled in earlier procedures.

Preston Sprenkle, MD and
Peter Schulam, MD, PhD

Dr. Schulam arrived at Yale in 2012 from UCLA and built on his experience there with targeted biopsies to create Yale's program a year ago. Biomedical engineer Richard Fan, PhD, who also arrived from UCLA, lends technological and rapid response support in calibrating the delicate equipment. "Embedding an engineer as part of the team is novel," he said. "It allows for cutting-edge clinical practices that drive engineering research and development and vice versa." Dr. Fan is part of a group of radiologists, pathologists, and urologists that meets monthly to review findings and plan multidisciplinary research.

The team is initiating research studies of long-term active surveillance that will be aided by the Artemis system's ability to precisely biopsy the same tumor repeatedly. They are also beginning to look at high-risk patients, such as those with BRCA2 mutations, which are associated with a higher risk of aggressive prostate cancer, to determine if MRI can help identify disease even in the absence of an elevated PSA or abnormal exam. In these cases, earlier detection might be able to save lives. In biopsied tissue, they are looking at genetic factors in prostate cancer that may predict progression for men on active surveillance. "Ideally if we can identify men who have a low rate of progression, we can safely treat as few men as possible," Dr. Sprenkle said.

Targeted biopsies are the first step toward reaching the ultimate goal of being able to rely on MRI to detect prostate cancer, in much the same way that mammograms are used to detect breast cancer. In the meantime, they are a vast improvement over conventional biopsies. "I think it's really the future of where medicine is going," Dr. Schulam said.

Giving a Voice

to Patients with Head and Neck Cancers

Eric Bowles was 16 when he noticed what he thought was a canker sore on the side of his tongue. Over the next month the sore gradually grew, but only bothered him if directly touched. During routine x-rays at the dentist's office, Eric asked them to be careful since he had a spot on his tongue that was sensitive. The dentist took one look and called an oral surgeon who met with Eric the next day and performed a biopsy of the lesion. Everyone was shocked when the diagnosis came back as squamous cell carcinoma of the tongue.

Classified as a cancer of the head and neck, squamous cell carcinoma of the tongue is not an uncommon diagnosis, but is usually found in older adults with a long history of tobacco and alcohol use. Eric, a junior in high school at the time, did not fit the criteria. He had just started singing lessons to train to become a classical singer, and did not foresee cancer as a part of that future. "I don't remember being particularly afraid when I heard the diagnosis," Eric said, now 21. "At that age I don't think I could have fathomed it being something life-threatening. I just wanted to get done what needed to be done and move on with my life and my singing lessons."

After seeing an ENT doctor, Eric was referred to Clarence Sasaki, MD, The Charles W. Ohse Professor of Surgery (Otolaryngology) at Yale School of Medicine. Along with his parents, Eric attended a Tumor Board where his case was presented and a treatment plan was outlined. Everyone involved knew that Eric was planning on becoming a singer and they assured him that they would do everything they could to spare his voice, while still removing all of the cancer. Because the tumor was more than 5 mm thick, a neck dissection was performed to capture possible spread to lymph nodes. Thankfully no nodes were found to be positive, but it left Eric with a small scar. They then removed thin slices of his tongue until no cancer cells were seen, and after a week in the hospital, Eric was released and began radiation treatments.

"Eric's case is remarkable not only because of his young age and lack of risk factors, in 30 years of practice Eric is one of only two cases that I can recall, but also because of his bravery through a physically and emotionally challenging treatment process," Dr. Sasaki said. "It comes as no surprise that many of my patients are the bravest people I have come to know."

Eric was diagnosed in March of 2009, and received his last radiation treatment on August 20th of the same year. He remarked that the entire process went by quickly, which he said helped both emotionally and mentally. During the week he spent in the hospital before and after his surgery, Eric had his music with him on his iPod, but couldn't bring himself to listen to it and risk associating music with what he was going through.

Eric first knew he wanted to pursue a career in music during an 8th grade field trip to see Phantom of the Opera. He has since been part of the Eastern Connecticut Symphony Choir and the Opera Theater of Connecticut. He will also be joining the chorus of The Yale Graduate Voice Program for their performance of La Boheme.

Immediately following his last radiation treatment, Eric was back with his singing instructor. "My tongue was stiff, which made it hard to sing, so I had to learn exercises to help compensate for that. I was not only starting all over again, but had to learn new techniques," Eric explained. Searching for a reason as to why this cancer, so rare in young adults, decided to strike him, Eric underwent blood tests and genetic testing, but they revealed no explanation. For Eric this was the most frustrating part of the experience, not knowing what caused it.

According to Dr. Sasaki, cancers of the mouth are typically associated with tobacco abuse in 75% of afflicted patients in their 50s and 60s; alcoholism increases this risk by 15 times. Whereas the human papillomavirus, type 16, 18, 31 or 45, is often found in patients age 40-50 with cancers involving deeper structures of the tonsils or base of tongue. Eric did not fit either of these profiles.

"Without the comfort and care Yale gave to my family and me, this would have been a completely different experience," Eric said. "They made sure to explain everything to us before anything was done, and walked us through every procedure. It was important for me to be involved in the process, but I think even more so for my parents."

Except for a scar that runs from Eric's ear to the middle of his neck, he feels as though he is back to where he would be had he not been diagnosed and is currently researching music schools to attend. Because radiation therapy may affect thyroid function later in life, Eric may require thyroid replacement therapy, but his future is bright. Eric learned a lesson early on in life, that cancer can easily break down barriers such as age, but that we too can break the barriers of cancer through new treatments, a positive attitude, and high-quality care.

The Immense Benefits of Phase I Trials

When Joseph Paul Eder, MD, Director of Experimental Therapeutics and the Phase I Research Group, came to Yale in the summer of 2012, only a few Phase I clinical trials were underway. A more robust Phase I program was important to achieve Yale's mission. Eighteen months later, 10 Phase I trials are open, and by the end of 2014 Dr. Eder expects that number to be somewhere between 15 and 18.

Among the most exciting trials now underway, he says, are five using "checkpoint inhibitor" immunotherapies that activate the immune system and shrink tumors. The targets are melanoma, kidney cancer, lung cancer, and others. These trials have built Yale Cancer Center's reputation as an innovator in immune-based therapies. Three additional trials will soon open. "These are complicated new treatments," Dr. Eder said. "The pharmaceutical companies want to bring their trials to the people with experience and expertise with these novel agents and their unique effects, good and bad."

He gives several reasons why it's important that these early clinical trials of new cancer therapies have started coming to Yale: "We urgently need new and better treatments for our patients who have run out of other treatment options. Many of the therapies we use in cancer medicine are not good therapies – they are just the best we have. These agents and trials allow us to look for new causes for drug effectiveness or drug resistance. The trials bring in additional resources for the work that needs to be done by our scientists. They establish us as a place that can get additional funding to help basic scientists explore new areas – the NIH is more likely to send funds your way if you are doing work that intersects with clinical medicine. Patients are certainly interested in research that translates into some sort of clinical impact. So are pharmaceutical companies."

Previously, these companies did not often think of Yale as a place to conduct trials of their experimental drugs. Since her arrival at Yale in May, Juliane Juergensmeier, PhD, Research Scientist, Developmental and Experimental Therapeutics, has been in discussion with large and small pharmaceutical companies to explain that Yale Cancer Center can handle their trials, no matter how difficult or complicated.

"They can see that we are building an outstanding center of clinical and scientific excellence here, and are interested not just in accruing patients to their trials but in also progressing scientific understanding of the disease and treatment." All companies have been receptive to Dr. Juergensmeier's approach. Over the last six months, a number of them visited Yale for portfolio presentations and smaller detailed discussions with scientists.

Like Dr. Eder, Dr. Juergensmeier has many years of experience in both academia and industry, and understands the needs of both. "We know what Pharma needs," Dr. Eder said. "We know how to put together a message that will resonate with all the different levels – not just the scientists but the people who control resources, who see that we can help them get to their next milestone of drug development."

Phase I trials also may come to Yale Cancer Center from other avenues, such as the industry contacts of veteran Yale investigators. Dr. Eder spent much of his time in 2013 working to get Yale into the clinical trials network of the National Cancer Institute.

The fourth potential source of trials is scientific hypotheses developed at Yale and then brought into the clinic. That takes longer, explained Dr. Eder, "because you don't have Pharma handing you a protocol and a budget." But he expects such trials soon, possibly in the area of therapy utilizing nanoparticles. Drs. Eder and Juergensmeier work closely with Dr. Roy Herbst and Dr. Karen Anderson, the co-leaders of the Developmental Therapeutics Research Program and at Yale Cancer Center to bring new agents from the labs at Yale into the clinics.

Perhaps the group most pleased about the influx of Phase I trials are patients. Many of them come to Smilow Cancer Hospital at Yale-New Haven with advanced tumors. Existing therapies have failed them and they are looking for options. "That's where clinical trials come into cancer medicine," Dr. Eder said. "They offer the hope that patients and providers want."

Lessons from a Virus

The Epstein-Barr virus, (EBV) is one of the most common viruses in humans but also one of the most mysterious. In many people it remains latent for many years, but in others it causes several forms of cancer – Hodgkin lymphoma, Burkitt lymphoma, nasopharyngeal carcinoma, and B-cell lymphoma, which occurs in immunodeficient people such as those with AIDS. For cancer scientists, the question is 'What causes the virus to wake up and trigger disease?'

I. George Miller, Jr., MD, John F. Enders Professor of Pediatrics and Professor of Epidemiology and of Molecular Biophysics and Biochemistry, has been working on EBV since 1967. It has given up its secrets slowly.

In 1985, he and his colleague, Jill Countryman, discovered a viral protein that acts as a master switch between the latent and replicating stages of EBV. They named this gene ZEBRA (Z EB Replication Activator). Dr. Miller has been studying it ever since. His most recent finding is one of his most exciting.

ZEBRA belongs to a family of related cellular proteins called AP-1 (activator protein). Both ZEBRA and AP-1 are transcription factors – they recognize specific sequences in DNA and bind to them. "We noticed that there are five amino acids in AP-1 that contact DNA specifically," Dr. Miller said. "Four of them were in exactly the same position as on ZEBRA. But the fifth one in ZEBRA was a serine and in AP-1 it was an alanine."

Dr. Miller's lab made a mutant ZEBRA that replaced that serine amino acid with the alanine from AP-1. Dr. Miller and his colleague, Amy Francis, described the surprising consequence of that tiny change in a paper published in 1997: "It basically inactivated the ability of the ZEBRA protein to drive the lytic cycle of EBV," he said. That is, it blocked the protein's ability to push the virus into the replication that leads to cancer.

> "The thing I like is that it's a long story. The virus keeps teaching us about what's going on in the cell."

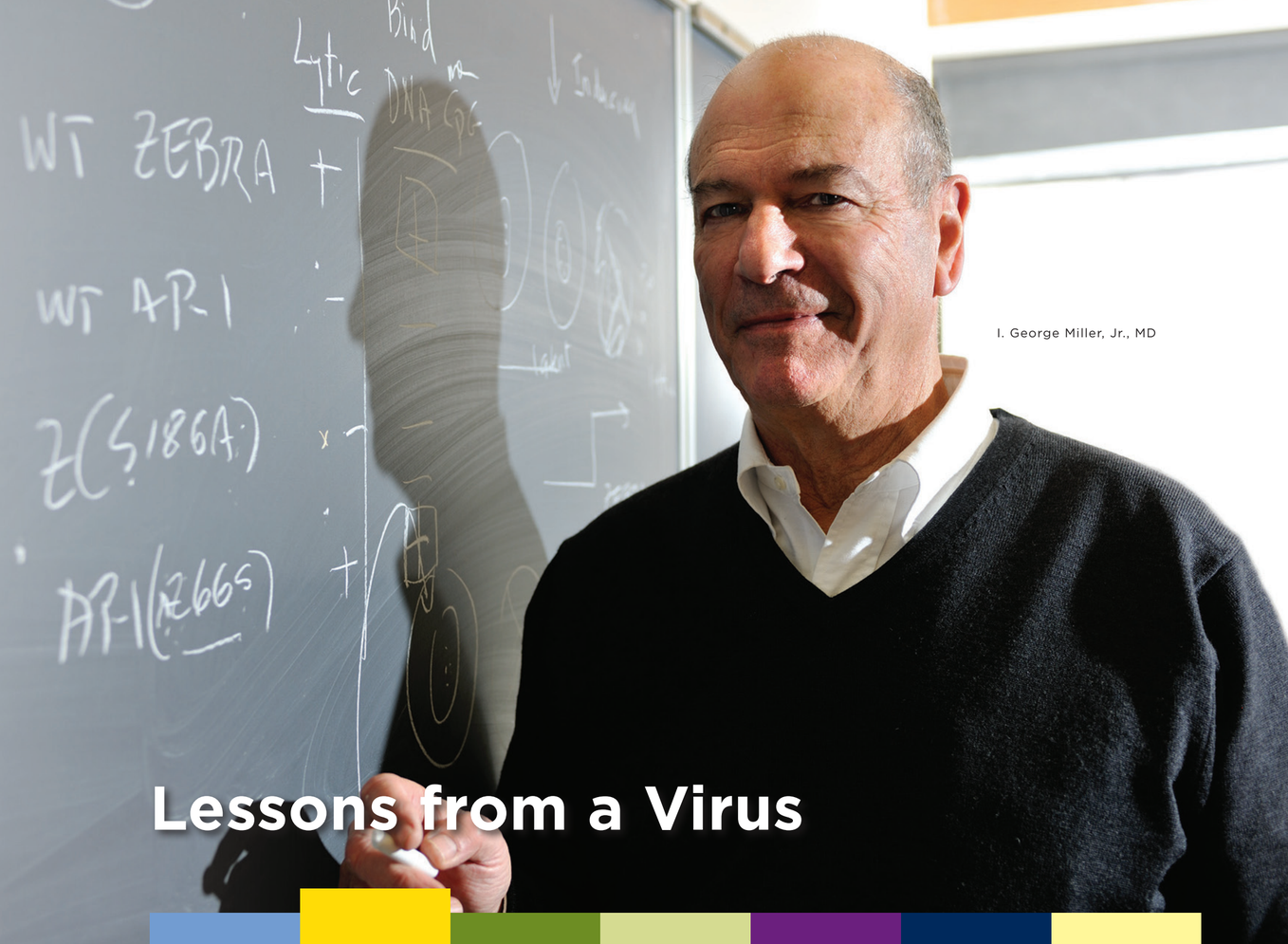
Next, in a paper published last May in *Proceedings of the National Academy of Sciences*, Miller and his colleague, Kuan-Ping Yu, did the opposite experiment; they created a mutated AP-1 by substituting the variant amino acid from ZEBRA – the serine – for the alanine on AP-1. With that change, AP-1 suddenly was able to drive EBV into replication. And like ZEBRA proteins, these mutated AP-1 proteins preferentially bound to methylated DNA, a feature associated with cancer.

"That's important," Dr. Miller said. "It overturns the dogma, which you'll find in all the textbooks, that DNA methylation is inhibitory to gene expression. As a general tool to explore the role of promoter methylation in cancer biology, I think this is going to be very powerful."

This finding also makes Dr. Miller wonder whether mutations in other cellular proteins, similar to the ones he made, could cause a virus to move from latency to replication. If so, molecular profiling could reveal those mutations in a patient and provide advance warning about the risk factors before the virus activated into replication and cancer.

Dr. Miller and his collaborators are now trying to understand which genes are regulated by methylation. That knowledge could provide clues for designing drugs to inhibit the binding of transcription factors to methylated DNA. "We're looking for ways to wake up silenced genes with these cellular proteins that now bind to methylated DNA," he said. "We might be able to program cells to go back into normal cells, to activate or repress gene expression. Ultimately we'll be able to alter the way methylation regulates the gene expression of the cell." But first, he added, there's a lot of basic science to do.

Dr. Miller expects EBV and ZEBRA to keep surprising him, like the way they overturned the received wisdom that DNA methylation represses gene expression. "The thing I like is that it's a long story," he said. "I think there's going to turn out to be cellular genes where methylation helps gene expression. The virus keeps teaching us about what's going on in the cell."



I. George Miller, Jr., MD

The Metabolism of Cancer

In the 1920s, Nobel Prize Winner Dr. Otto Warburg proposed that cancer was a metabolic disease. He was unable to discover a mechanism to prove his theory, so it fell to the sidelines of cancer research.

In recent years, however, there has been a resurgence of interest in the metabolism of cancer, evidenced by the growing number of publications on the subject. Among the active researchers in this emerging area is Xiaoyong Yang, PhD, Associate Professor of Comparative Medicine and of Cellular and Molecular Physiology.

"The question," Dr. Yang explained, "has always been, how does a normal cell become a cancer cell? It's becoming more and more clear from large-scale genomic studies that the mutations that lead to cancer are often relevant to cellular metabolism. Many groups in the world are starting to look at the difference between cancer cells and normal cells in terms of metabolic features."

In the metabolism of normal cells, chemical processes convert nutrients into energy, allowing the cells to sustain themselves and maintain routine growth. In cancer cells, this orderly process breaks down. Cancer cells are not content to sustain themselves. They want to proliferate and colonize. To do so, Dr. Yang explained, they "reprogram" cell metabolism and send signals that cause the cell to grow wildly. Dr. Yang believes that metabolic changes drive most, perhaps all, of cancer cell growth.

This cellular proliferation requires an abnormal amount of fuel. "A tumor is like a manufacturing plant," Dr. Yang said. "It needs machines to allow mass production of building blocks to constantly produce new cells. For that to happen, the cancer cell absolutely must reprogram the metabolic pathways of normal cells by upregulating a lot of biosynthetic enzymes."

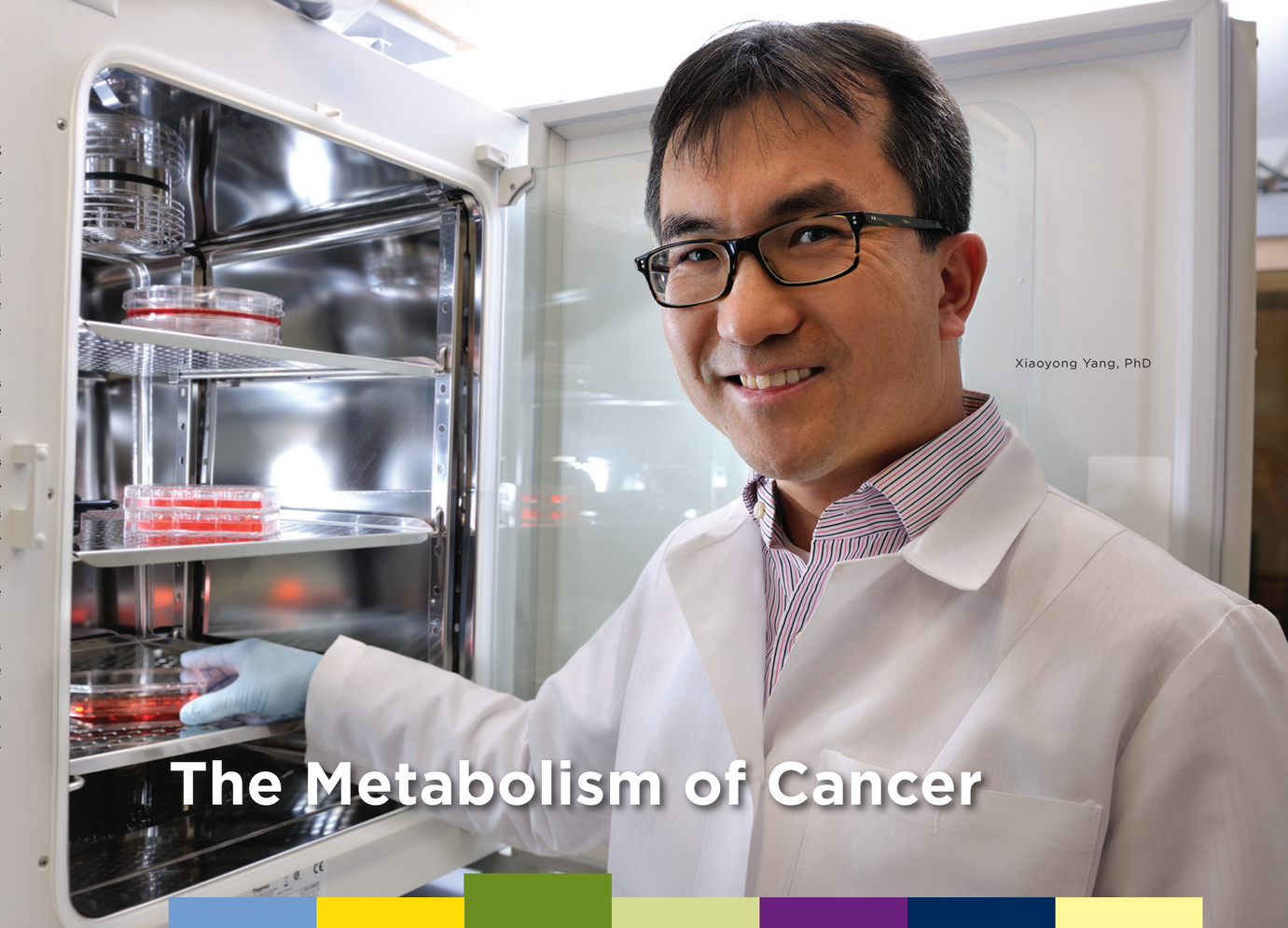
Dr. Yang and his lab are working to understand how this reprogramming occurs – the signals that change a cell's metabolism. They are focused on a unique sugar (and metabolic fuel) called O-GlcNAc modification that attaches to many proteins. "Cancer cells are addicted to glucose," Dr. Yang said. "They eat and eat and grow and grow."

Dr. Yang has found that O-GlcNAc acts as a molecular switch, sending signals that regulate protein function. He and his colleagues have also found that O-GlcNAc can attach to a certain metabolic enzyme, which seems to cause reprogramming of the metabolic pathway. This enzyme is also found in many types of cancer. As 2013 ended, specifics about this research remained confidential, but Dr. Yang and his colleagues expect to publish a paper detailing this breakthrough in 2014.

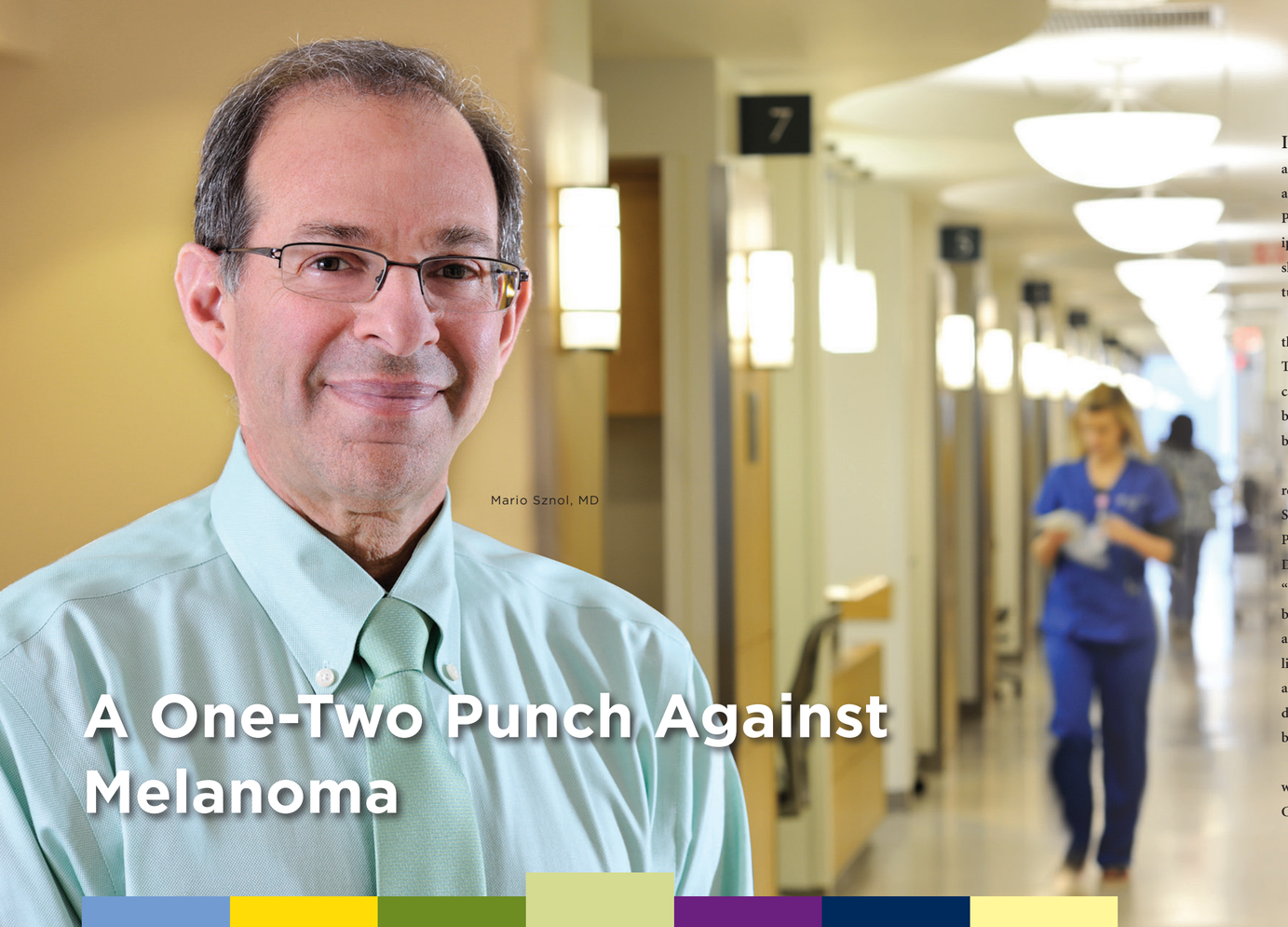
"We think this will be useful for the diagnosis and treatment of cancer," he said. "With a better understanding of how metabolic reprogramming occurs, we have a good chance of finding a molecular target for treatment of many different cancers, without causing harm to normal tissues." Or, he added, it might be possible to develop pharmacological approaches that hinder the reprogramming of normal cells or that starve cancer cells by stopping the abnormal metabolism that is prone to produce the building blocks.

Because the metabolic approach to cancer shows such broad promise, many researchers and institutions are plunging into it. Dr. Yang hopes to keep Yale in the forefront. To that end, he and two colleagues began an initiative last December called the Cancer Metabolism Interest Group. Previously, the scientists at Yale studying metabolism and those studying cancer didn't have much contact. Now they meet monthly to share research, listen to presentations, and review the growing volume of new publications.

"We hope to take advantage of Yale's strengths in both areas," Dr. Yang said, "and to use and share the cutting-edge tools available here that are related to cancer metabolism, such as epigenomics, proteomics, and metabolomics. Hopefully we can develop a new way to approach questions related to cancer metabolism."



Xiaoyong Yang, PhD



Mario Sznol, MD

A One-Two Punch Against Melanoma

In a Phase I trial at Yale Cancer Center, a new combination of drugs proved highly effective against an especially dangerous cancer: melanoma. Patients in the trial were treated with two antibodies, ipilimumab and nivolumab. Separately, each drug had shown promise as a cancer-fighter, but together they turned into a powerhouse of immunotherapy.

When cancer cells invade, they send disinformation that tells the body's immune system to turn off. The new drugs work synergistically to block the cancer's disinformation signals and reactivate the body's immune response, which causes T cells to turn back on and start fighting.

"CTLA-4 and PD-1 are two of the most important regulatory checkpoints for immune activation," Mario Sznol, MD, Professor of Medicine, Clinical Research Program Leader of the Melanoma Program, and Co-Director of the Yale SPORE in Skin Cancer explained, "but they work at different places. CTLA-4 – which is blocked by ipilimumab – works earlier in the process, and PD-1 – which is blocked by nivolumab – works a little later to turn off the lymphocytes when they are already around or inside the tumor. Blocking at two different places seems to cause more T cell activity than blocking at only one."

The results of the trial, which began in 2009 and was done jointly with Memorial Sloan-Kettering Cancer Center, were published last summer in *The New England Journal of Medicine*. They are impressive. About 70 percent of the patients demonstrated some type of response to the treatment, and many of them benefitted dramatically. In about a third of the patients, the tumors were reduced by 80 percent or more. "And we got the impression that not only were more patients responding," Dr. Sznol said, "but that they were responding faster, and that the amount of tumor reduction was greater than we had seen with either component alone."

The drug combination not only worked fast, it also produced prolonged responses. Most of the responding patients have not had regrowth of their tumors, with follow-up of at least a year and in one patient nearly 3 years. This kind of activity is expected to translate into longer survival. Advanced melanoma is typically fast and deadly, but the one-year survival rate of patients in the trial was about 80 percent.

"That's probably the highest number we've ever seen," Dr. Sznol said. "It's 20 percent higher than the one-year survival that we would have expected with anti-PD-1 alone. In fact, among the first cohort of 25 patients treated at Yale," he added, "about half are now without any evidence of active disease." That sounds very much like a cure, though Dr. Sznol is too cautious a scientist to make that claim – yet. A randomized study is now underway to test the trial's main findings.

The combination of drugs did cause moderate to severe adverse effects in more than half of the patients. Nivolumab has been very well-tolerated in solo trials, so much of the toxicity seems to be coming from ipilimumab. The question is always whether the benefits outweigh the adverse effects. Dr. Sznol said that he and most of the patients would answer with an emphatic yes. Doctors eventually get the bad side effects under control, and meanwhile the drugs are shrinking most patients' tumors and very likely extending most patients' lives. "I think most of the patients are very happy," Dr. Sznol said, "because they have done very well. It's kind of amazing."

Also amazing, he noted, is how quickly advances have occurred in the treatment of melanoma. Before the FDA approved ipilimumab two years ago, the best drug available for melanoma was the 20-year-old workhorse interleukin-2. Nivolumab could be approved within a year.

The promising combination of ipilimumab and nivolumab is now being tested, or soon will be, on other cancers at Yale – lung cancer, renal cancer, pancreatic cancer, and glioblastoma, among others. "But this isn't the only combination," Dr. Sznol explained, "and it may not even be the best combination. I think we're just scratching the surface of the potential of these approaches." He believes that immunotherapy will soon become the dominant method of treating cancer. "Over time," he said, abandoning caution for just a moment, "one can almost envision an endgame."

The Genetic Landscape of the Brain

Meningiomas are the most common brain tumor, striking nearly 170,000 Americans. Until recently they have largely been mysteries. Part of that mystery was solved earlier this year by a team of researchers led by Murat Günel, MD, FACS, FAHA, Nixdorff-German Professor of Neurosurgery and Professor of Genetics and of Neurobiology and Director of the Yale Program in Brain Tumor Research. Their discoveries promise to alter clinical treatment of patients afflicted with these tumors.

Unlike malignant brain tumors, meningiomas grow slowly and are histologically benign 80 percent of the time. Nevertheless they can cause neurological damage or stroke, so they are typically treated through the invasive options of surgery or radiation. "There have been no chemotherapy options," Dr. Günel explained, "because the genetic make-up of meningiomas has been poorly understood. Before our work, we did not know how these tumors happened."

Previous research had linked about half of meningiomas to a mutation of the gene NF2, though the mechanism remained unclear, as did the cause of all other meningiomas. Dr. Günel and his team used what he calls "the revolution of genomic technologies" to genotype and sequence 300 meningiomas.

They discovered that the vast majority of benign meningiomas stem from mutations of just five genes. The roles played by four of the genes – AKT1, SMO, KLF4, and TRAF7 (the fifth is NF2) – were previously unknown. Further, the researchers found that the tumors generated by these mutated genes grow in different parts of the brain. Tumors associated with NF2, for instance, tend to form in the cerebral hemispheres, whereas tumors associated with the other four genes group in areas along the skull base.

"The correlation of tumor location with the mutational landscape is fascinating," Dr. Günel said. "For the first time, just by looking at the location of these tumors with an MRI, we can tell, with a certain degree of certainty, the mutation profile of the meningioma."

This genetic mapping and the resultant diagnostic insights will open the way for individualized treatments that target each type of meningioma. For instance, SMO mutations have been found in basal cell carcinoma (BCC) and medulloblastomas. There is already an FDA-approved drug for use in patients with BCC, so Dr. Günel is now testing it on SMO meningiomas in animal models. If the drug affects these tumors, he will begin clinical trials on patients.

The Yale researchers found a TRAF7 mutation in about a quarter of the meningiomas. Almost nothing is known about this gene, but wherever the team found its mutated form, they also found a better-known partner – either KLF4, a transcription factor, or AKT1, which activates the PI3K pathway. KLF4 is one of the four so-called "Yamanaka" factors, which are sufficient to induce formation of stem cells from terminally differentiated somatic cells. This discovery, which won Dr. Yamanaka the Nobel Prize in 2012, combined with the finding of the exact mutation (K409Q) in its DNA binding domain in several meningiomas, raised the interesting possibility that meningiomas arose from dedifferentiation of mature meningeal cells into progenitor cells, allowing for their uncontrolled growth. While KLF4 mutations were novel, the AKT1/PI3K pathway is well-known and has been implicated in various cancers; several medications against it are now in clinical trial. Since TRAF7 is unstudied, Dr. Günel and his team are hoping to track its mutation through its co-existence with AKT1 and the PI3K pathway. They want to see if a PI3K inhibitor can cripple or stop a TRAF7 meningioma.

These findings have the potential to give people with meningiomas the option of personalized chemotherapy – treatment that may be more effective and less invasive than the current options of surgery and radiation.

The genetic mapping of benign meningiomas was relatively easy to solve, noted Dr. Günel, because they have far fewer genetic abnormalities than cancerous tumors. He and his team continue to focus on malignant forms of meningiomas and the most deadly brain cancer, glioblastoma multiforme. Once the new genomic technologies provide further insight into the complex landscape of these malignant tumors, new drugs can be investigated to target them. For our patients, he adds, "a cure cannot wait."

Dr. Murat Günel, MD, FACS

Linda M. Niccolai, PhD

The HPV Vaccine – Good News That Could Be Better

No one gets cervical cancer without first being infected by the human papillomavirus (HPV). That's why cancer prevention scientists, including Linda M. Niccolai, PhD, ScM, Associate Professor of Epidemiology and Director of the HPV-IMPACT Project, are so enthusiastic about the vaccine that prevents several strains of HPV. Since the vaccine became available in 2006, millions of doses have been given. By the end of 2010 about 50 percent of all adolescent girls aged 13 to 17 had received at least one dose of the three-dose regimen.

The fact that the vaccination rate had climbed from zero to 50 in just a few years is very good news, said Dr. Niccolai, because it prevents the four most common strains of HPV, including those that account for 70 percent of cervical cancers as well as some cancers of the anus, penis, vagina, vulva, and oropharynx. But there's a problem: by the end of 2012, the percentage of all vaccinated adolescent girls had barely budged, to 54 percent.

"This is a recommended vaccine for all adolescents," Dr. Niccolai explained, "so to be stuck at about 50 percent is really no good, especially when compared to other vaccines like meningococcal and Tdap, which are up around 80 percent. This stall motivates a lot of my research and is a tremendous concern among providers whose job is to protect health. We really need to understand what the barriers are."

To that end Dr. Niccolai and her colleagues have started a qualitative study at the Yale-New Haven Hospital Primary Care Center, interviewing the parents of young adolescents to see what they know about the vaccine and what could be hindering vaccination of their children.

Her frustration at the stalled vaccination rate has been compounded by findings from her recent research as Director of the HPV-IMPACT Project with the CT Emerging Infections Program, which tracks the impact of the vaccine on females in Connecticut. She has found that high-grade cervical lesions – the precancerous stage of cervical disease – have already declined by about 25 percent among Connecticut women in their early 20s, perhaps because they were vaccinated as girls. "It's evidence that the vaccine can have a tremendous health impact, which speaks to the need to do a better job of getting kids vaccinated," she said.

In a paper published in 2013 in *Cancer*, Dr. Niccolai and colleagues showed that the encouraging decline in high-grade lesions also has a troubling side. They found disparities in the impact of the HPV vaccine – there were lower rates of decline in lesions among black, Hispanic, and low-income women than among white or higher-income women. "We don't yet know what that means," Dr. Niccolai said.

About fifteen types of HPV can cause cervical cancer. The vaccine protects against two, HPV 16 and 18. About half of all high-grade lesions among white women are caused by these two strains of the virus, but among black, Hispanic, and low-income women, the comparable number is about 35 percent, which indicates that they may get less protection from the vaccine and hence less protection against cervical cancer.

"This will require a lot of ongoing monitoring," Dr. Niccolai said. A new vaccine now in Phase III clinical trials could help mitigate the disparity. "It would prevent nine different types of HPV, which are responsible for 90 percent of cervical cancers."

> "It would prevent nine different types of HPV, which are responsible for 90 percent of cervical cancers."

Asked where she will focus her attention in the coming year, Dr. Niccolai immediately said, "Interventions. We need to get more kids vaccinated." That means targeting parents, providers, and adolescents. She has a pilot grant from Yale Cancer Center to look into one possible way to overcome the barriers to vaccination: she will be exploring the feasibility of working with school-based health centers in New Haven and surrounding communities to vaccinate kids at school.

"That would eliminate the need for them to return to a clinic to get the three doses," she explained. "They could give them all right at school."

Ranjit S. Bindra, MD, PhD

Fighting Gliomas by Disabling DNA Repair

Most radiosensitizers – drugs that are supposed to make tumor cells more sensitive to radiation – work poorly on the malignant brain tumors called gliomas. For that reason, the treatment of gliomas has not advanced much in recent decades. Patients typically have surgery, followed by radiotherapy and chemotherapy. But gliomas are notorious for being resistant to radiation and for recurring in the same location. This usually leads to another invasive round of treatment.

The tumors' resistance and recurrence both seem to stem from their ability to repair double-strand breaks of DNA quickly and then start growing again. Ranjit S. Bindra MD, PhD, Assistant Professor of Therapeutic Radiology and Pathology, wanted to find a radiosensitizer that could disable a glioma's DNA repair system. A glioma that can't repair itself likely can't recur. The challenge was to find such a compound among the hundreds of thousands of possibilities.

Before joining Yale, Dr. Bindra had developed a new way to measure double-strand break repair by using fluorescent proteins that glow red or green when a cell repaired a double-strand break. This technique allowed him to devise a powerful screen to test compounds that might inhibit DNA repair.

"Surprisingly, we ended up with 80 to 90 of them, mostly unknown structures," he said. "But one of them was previously an FDA-approved drug. That interested us very much." Its name was mibefradil, popular for hypertension in the 1990s but long off the market.

As Dr. Bindra tested the drug further, it kept surprising him. There are two main DNA repair pathways: homologous recombination (HR) and non-homologous end joining (NHEJ). HR repairs DNA breaks by using a copy from within the cell. NHEJ simply sticks together the two ends of a double-strand break. About 90 percent of our cells, both normal and tumorigenic, repair DNA through NHEJ, because this pathway is easier and a second copy for HR is not always available in the cell.

"We found that mibefradil was specifically blocking non-homologous end joining," Dr. Bindra explained. He tested it with radiation on glioblastoma cell lines and learned that it not only blocked double-strand repair but was relatively nontoxic to normal tissues.

The drug works on gliomas like this: one of the proteins within the NHEJ pathway is called DNA-PK (protein kinase). "It basically orchestrates the process of trimming and preparing the ends of double-strand breaks for religation," Dr. Bindra said. "Our preliminary data suggested that mibefradil blocks the ability of DNA-PK to function."

During his investigation of the drug, he also learned that a start-up biotechnology company in Virginia, Tau Therapeutics (now called Cavion), was also researching the potential of repurposing mibefradil against gliomas. Dr. Bindra connected with the company and the two groups are now closely collaborating. Researchers at Cavion discovered that the drug not only blocks the function of DNA-PK, but it also cleaves the protein in two.

With Cavion's support, Dr. Bindra has been designing a Phase I trial to open at Smilow Cancer Hospital for patients with recurrent glioblastomas. He hopes to enroll 20 to 30 patients for this study, and to begin treatments by late spring, finishing in about a year and a half.

"Since mibefradil is already available as an Investigational New Drug (IND) for cancer applications," he said, "we can give it to patients a week before surgery and get a tissue specimen during surgery. We then will be able to study in vivo tissue and see whether the drug is getting into the tumor and is cleaving DNA-PK. It's a highly translational study. We're quite excited, and because of the collaborative nature of Yale, the neurosurgeons, neuro-oncologists, pathologists, and radiation oncologists are all excited to get involved."

The hope is that using mibefradil with radiation will greatly prolong survival in patients with recurrent gliomas. If the trial is a success, Dr. Bindra hopes that the drug will become a standard treatment for glioblastomas. He also hopes that this trial will add to the growing momentum of bench-to-bedside research at Yale Cancer Center. "We want to test as many new therapies in glioma patients as possible," Dr. Bindra concluded. "If you build it they will come…and we want drug companies and patients to know that this is the place to come for novel, cutting-edge therapies."

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Signal Transduction

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