YALE CANCER CENTER
SMILOW CANCER HOSPITAL

breakthroughs

THE YEAR IN REVIEW

Empowering Our Patients

yale cancer center

Director
Charles S. Fuchs, MD, MPH

Deputy Director, Administration and Clinical Affairs
Kevin Vest, MBA, FACHE

Director, Public Affairs and Marketing
Renee Gaudette

art + production

Designer
Frankie Winter
Peter Baker Studios

contributors

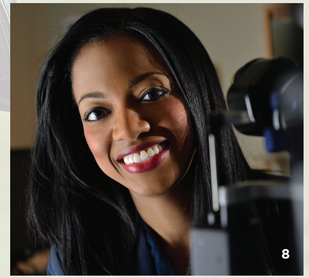
Writers
Steve Kemper
Emily Montemerlo
Kristin Rattini

Photographer
Peter Baker

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

Yale Cancer Center
333 Cedar Street, PO Box 208028
New Haven, CT 06520-8028
yalecancercenter.org

Editorial Office
Yale Cancer Center
2 Church Street South, Suite 312
New Haven, CT 06519
renee.gaudette@yale.edu



As I reflect on my first year as Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital, I am proud of all we have accomplished together and am motivated for the challenges that lie ahead in 2018. The Yale Cancer Center and Smilow Cancer Hospital community is comprised of highly dedicated and talented faculty and staff who are making vital contributions to our cancer research, clinical care, and education mission each day. Their accomplishments are leading to innovative breakthroughs and new options for cancer treatments available to patients globally.

In 2017, we submitted our renewal to the National Cancer Institute (NCI) for our comprehensive cancer center core grant and look forward to their review and site visit later this month. 2017 also saw the three-year review of our Hospital by the Joint Commission, and reviewers found Smilow Cancer Hospital and our Care Centers as models of clinical care, delivery, and innovation. This is a fitting and impressive recognition of the wonderful care and dedication of each and every one of our physicians, nurses, caregivers, staff members, and administrators throughout the Hospital and our 12 site Care Center Network in Connecticut.

Smilow Cancer Hospital is the leading provider of exceptional, compassionate, innovative patient-focused care in our state. Over the past year, we cared for a growing patient population across Smilow Cancer Hospital and our Smilow Care Centers. In addition, we are leading efforts to define new models of value-based care and quality metrics across our entire clinical enterprise through the Oncology Care Model implementation and will evaluate our outcomes and adjust these models in the coming year.

In 2018, we will continue to expand the depth and breadth of our science, including strategic recruitment of new investigators to broaden our translational research infrastructure. Yale Cancer Center will launch a Center for Immuno-Oncology, which will build on our international leadership in immunobiology, cancer immunology, and development of novel cancer immunotherapies. Recognized by many as having set the research foundation for the success of immunotherapy, Dr. Lieping Chen's accomplishments and future research directions in immunotherapy are chronicled in this issue of *Breakthroughs*. I will announce more information on our new Center for Immuno-Oncology in the coming months.

"As I reflect on my first year as Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital, I am proud of all we have accomplished together and am motivated for the challenges that lie ahead in 2018."

This issue of *Breakthroughs* highlights a selection of the strengths of our clinical and research programs. Our team at Yale Cancer Center and Smilow Cancer Hospital is working hard to bring many new breakthroughs to cancer medicine and I look forward to sharing their continued successes with you from New Haven.

Sincerely,

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

Kirsty and her daughters, Ruby and Georgia

Empowering Patients & Families with Knowledge

Even though Kirsty Harris was young and had no personal history of cancer, she decided to pursue genetic counseling due to a strong family history. Her mother was diagnosed with breast cancer before the age of 50, and Kirsty herself had been found to have atypical breast cells. In 2015, when Kirsty and her husband moved from Australia to the United States, she knew the importance of finding care and continuing to be followed. After speaking with her doctor, she was referred to the Smilow Cancer Genetics & Prevention Program at Smilow Cancer Hospital, where she met with genetic counselor Jessica DiGiovanna to discuss her risks and what genetic testing would mean for her. The Smilow Cancer Genetics & Prevention Program is an interdisciplinary team that includes geneticists, genetic counselors, physicians and nurses who work together with the goal of providing cancer risk assessment and taking steps to prevent the development of cancer.

After watching her own mother endure extensive treatment for stage three breast cancer, Kirsty jumped at the opportunity to have a say in her own health and future at the age of 30. In addition to testing for the more commonly known BRCA gene, it was decided that Kirsty be tested for an extended panel of genes, including a lesser known gene, CDH1, which is associated with a higher risk of both breast and gastric cancers. To everyone's surprise, Kirsty tested positive for CDH1 and negative for BRCA. The discovery of this rare gene indicated that Kirsty had a significantly increased risk of developing stomach cancer, even though no one in her family had any form of gastric cancer.

"I had prepared myself for the possibility that I would test positive for BRCA and need a double mastectomy, but nothing could have prepared me for the news that I was also at risk for stomach cancer," said Kirsty. "Thankfully the team at Smilow was prepared for action, and I met with Dr. Xavier Llor within a week of receiving the results."

Xavier Llor, MD, PhD, Associate Professor of Medicine (Digestive Diseases) and Co-Director of the Smilow Cancer Genetics & Prevention Program, commented that it was an unusual finding due to the lack of family history. After going over the results and explaining the high risk for stomach and breast cancer with Kirsty, it was decided that an upper endoscopy would be performed with multiple biopsies taken before a removal of the stomach was considered. Out of the 100 biopsies taken from the stomach, Kirsty was found to have a small foci of cancer cells in one of the samples, or stage I stomach cancer. The cells found were consistent with the theory that the CDH1 mutation was the cause.

"The difficult decision of whether or not to have my stomach removed was therefore made for me," commented Kirsty. "I would have probably delayed the surgery until my children were older, which would have made for a very different story. This was like finding a needle in a haystack. Finding these tiny spots of cancer in my stomach has led to

life-saving results for me and my entire family."

Dr. Llor commented that most often stomach cancer is diagnosed in more advanced stages and that it takes a combination of a high level of knowledge of this rare condition and the proper expertise in genetic testing to create these success stories. "A team approach has been critical to Kirsty's care," said Dr. Llor. "With the recent generalization in the use of genetic panels, more and more cases are being diagnosed that would not have been suspected using the standard clinical criteria, and therefore, would not have been tested for."

Charles Cha, MD, FACS, Associate Professor of Surgery (Oncology and Gastrointestinal), performed the total gastrectomy with little complication. He was able to perform the procedure laparoscopically, which decreased Kirsty's recovery time. Dr. Cha is one of only a few surgeons in the region that has considerable experience in laparoscopic and robotic surgery for gastric cancer. Kirsty commented, "I was extremely lucky to end up in this part of the world with such a highly skilled team right at my doorstep. It made it so that I could get back to caring for my family; I was sitting and playing with my baby girls the very next day and I only have a small scar below my sternum."

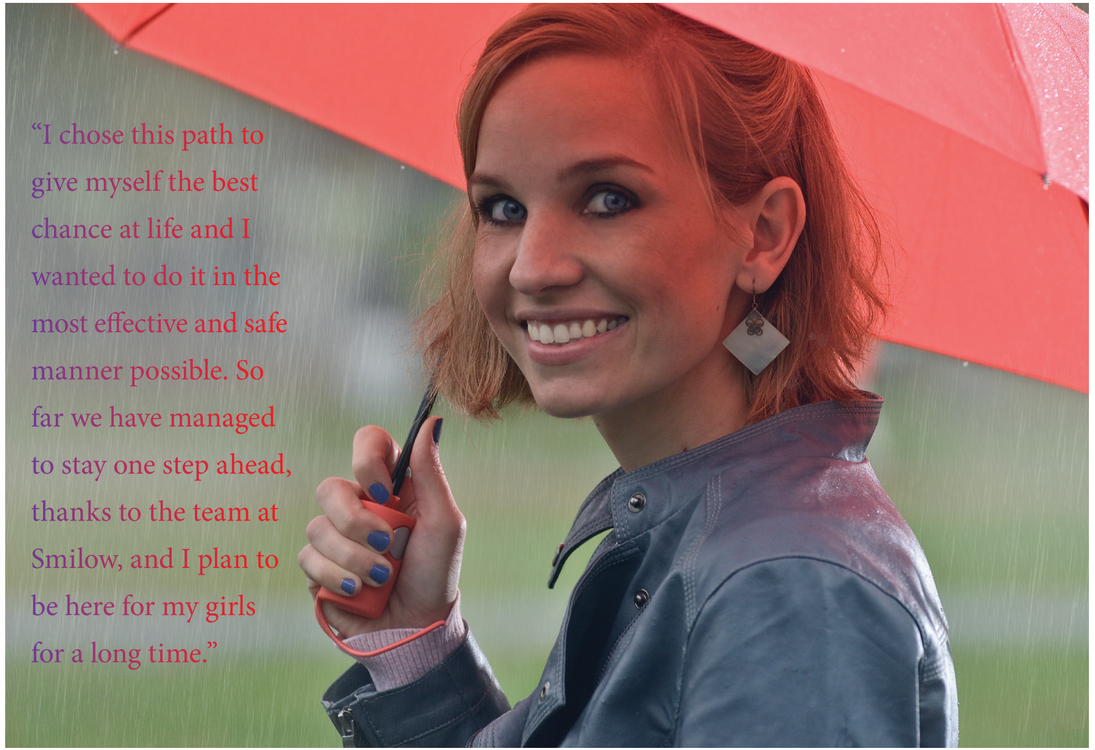
With her recovery well underway, Kirsty met with Erin Hofstatter, MD, Associate Professor (Medical Oncology) and Co-Director of the Cancer Genetics and Prevention Program to focus on her increased risk of breast cancer. Almost a year after the surgery to remove her stomach, she underwent a double mastectomy and was thankfully found to have no sign of cancer.

"My only question for Dr. Hofstatter was how soon we could start the surgery. I chose this path to give myself the best chance at life and I wanted to do it in the most effective and safe manner possible. My daughters, Georgia and Ruby, are three and two years old. So far we have managed to stay one step ahead, thanks to the team at Smilow, and I plan to be here for my girls for a long time." Dr. Nina Horowitz performed the mastectomy and Dr. Henry Hsia immediately scheduled her for reconstruction in an effort to provide seamless care.

Kirsty's mother, who is still living in Australia, decided to undergo genetic testing as well, and was found to carry the CDH1 gene. Looking back at the family tree on her maternal grandfather's side, now knowing what to look for, there were several unusual deaths that could have been related to the gene, although nothing can be confirmed. Her mother had her stomach removed, which ended up revealing a small amount of gastric cancer. She also chose to have her other breast removed, which revealed early stage lobular cancer. Her uncle, who also tested positive for the gene, is scheduled to have his stomach removed later this year.

"The next challenge, far greater than what I have faced so far, is that genetic testing now awaits my daughters when they are older," said Kirsty. "There is a 50% chance that they each will carry the gene, but at least they have their mother and grandmother to guide them and be an example of how strong a person can be and that with medical intervention, we can choose our own future. I truly hope they have a team like I did on their side, fighting for them every step of the way."

Living without a stomach has been difficult for Kirsty, but far easier than the alternative. She commented that she never felt pressured to make a decision, but rather empowered at every stage, starting with the initial decision to undergo testing. And while Kirsty does worry about her future and the obstacles to come, having a future to worry about is worth the struggle.



Renelle Lim, MD

A CLEAR VISION

Renelle Lim, MD, faced a dilemma. During residency training at State University of New York-Downstate Medical Center, Dr. Lim found herself drawn equally to two areas of ophthalmology: cancers of the eye and oculoplastic & reconstructive surgery. Instead of choosing one specialty over the other, Dr. Lim embarked on fellowship trainings in both ocular oncology and oculoplastic surgery.

Dr. Lim underwent intense training at the premier Wills Eye Hospital in Philadelphia. She completed two fellowships, one in oculoplastic surgery and another in ocular oncology where she studied under Carol Shields, MD, and Jerry Shields, MD, "the leading ocular tumor specialists in the world," she said. "Their mega practice allowed me to see rare ocular tumors routinely. While most ophthalmologists see one or two ocular tumors during their entire career, we treated several hundred patients with ocular tumors each year." In addition to her surgical skills, Dr. Lim honed a vision of her practice through both the instruction and examples set by her mentors. "One of the most valuable lessons learned from my fellowship training is to always strive for the highest quality of care," Dr. Lim said.

As the new director of Smilow Cancer Hospital's Ocular Oncology Program, Dr. Lim draws on her dual specialties to treat patients with both common and rare malignancies of the eye, eyelid, and orbit. Her multidisciplinary approach mirrors that of the program. As one of the few programs in the nation with a dedicated full time ocular oncologist in a cancer hospital, the Smilow Ocular Oncology Program draws on the wealth of experience and expertise across all specialties at Smilow Cancer Hospital. "The Smilow Ocular Oncology program does not stand alone," Dr. Lim explained. "A tremendous advantage of our location within Smilow Cancer Hospital is that we can collaborate with many specialists—neurosurgeons, ENTs, dermatologists, plastic surgeons, radiation oncologists, and others—to provide comprehensive treatment for ocular and periocular cancers."

Indeed, Smilow's Ocular Oncology Program uses state-of-the art technology and the newest techniques to provide cutting-edge treatments to patients with all disorders involving cancer in the eye and periocular region. A prime example is plaque brachytherapy, in which a small disc-shaped plaque containing radioactive material is sutured to the surface of the eye over a tumor. Used for uveal melanoma—the most common primary intraocular cancer—and other types of tumors, plaque brachytherapy can deliver radiation directly to the affected area with minimal side effects. Dr. Lim collaborates with radiation oncologists and physicists, who custom design the plaque using advanced computer models and CT simulation so that it provides the optimal dosage of radiation while limiting potential damage to nearby healthy tissues.

Dr. Lim's training in oculoplastics enables her to not only excise ocular tumors but also to reconstruct the eyelid afterward. "I am humbled to be able to provide these services to my patients," Dr. Lim said. "Having such extensive training uniquely benefits my patients."

Patients also benefit from genetic sequencing of tumors, which in some cases can open the door to targeted therapies for their cancer. "The future of cancer treatment is targeted therapy," Dr. Lim explained. "We have the ability to test tumors for gene mutations and to alter treatment options based on the results."

Genetic counselors help patients—and their families—understand the results, and the Smilow nursing staff and social workers support them throughout treatment. "At Smilow, we understand that we are not just treating the patients but their families as well," Dr. Lim said.

As other cutting-edge cancer treatments progress through Yale's research pipeline, Dr. Lim looks forward to adopting them for her own patients as she leads the Ocular Oncology Program in its critical mission: to conserve the life, eye, and sight of each of her patients.

THE SMILOW OCULAR ONCOLOGY PROGRAM DOES NOT STAND ALONE. A TREMENDOUS ADVANTAGE OF OUR LOCATION WITHIN SMILOW CANCER HOSPITAL IS THAT WE CAN COLLABORATE WITH MANY SPECIALISTS. I AM HUMBLED TO BE able TO PROVIDE THESE SERVICES TO MY PATIENTS.

STREAMLINING **SKULL BASE** SURGERIES

Smilow Cancer Hospital's new Skull Base Surgery Program is designed to make these complicated treatments more smooth and effective. "These patients need a lot of care from a lot of different teams," said R. Peter Manes, MD, FACS, Associate Professor of Surgery, whose specialty is nasal and sinus tumors. "They need lots of different appointments and lots of different imaging studies. The idea is to give patients consolidated care. They can call one number and we'll coordinate everything and help them navigate through the system."

"If patients can arrange to see the neurosurgeon, the ENT (Ear, Nose, and Throat) surgeon, the ophthalmologist, and the endocrinologist in a single visit, that is the ideal way to deliver our expertise," said Sacit Bulent Omay, MD, Assistant Professor of Neurosurgery, who teams up with Dr. Manes on skull base surgeries. "And post-operatively as well, because all these specialties follow up with these patients. If it's not well organized, they will have a new appointment every week, which is very inconvenient."

R. Peter Manes, MD, FACS
Sacit Bulent Omay, MD

"Skull base" is a broad category that includes various tumors located behind the eyes and nose, and above the base of the skull in the back of the head. The tumors can arise from the sinuses, the dura (the membrane that surrounds the brain and spinal cord), or inside the brain itself. Most skull base tumors are benign, though carcinomas and sarcomas also occur. Even benign tumors, however, can become problematic by impinging on the brain, vital nerves, and blood vessels. The tumors are tricky to reach through surgery because of their location near the brain, spinal cord, nerve centers, and major blood vessels. Removing them requires the skills of an ENT surgeon and a neurosurgeon working together.

Smilow's program divides skull base surgeries into two categories defined by location: anterior and lateral. Drs. Manes and Omay do anterior surgeries endoscopically, another team handles lateral surgeries. The program includes about 15 physicians, including specialists from ophthalmology, endocrinology, medical oncology, and radiation oncology.

Surgical techniques for treating skull neck tumors have changed drastically in the past decade. "Traditionally, surgery involved a cut along the side of the nose down to the lip," explained Dr. Manes, "and the surgeon would basically lift the face off. For an open craniotomy, they would make a large incision on the top of the head, and then peel back the brain."

Now, for many patients, surgeons can run an endoscope through a nostril to the site of the tumor and resect it, with no disfiguring incisions or risky retraction of the brain. These minimally invasive surgeries also reduce post-operative complications and hospital stays.

Smilow is among several top cancer hospitals that have established special programs for skull base surgeries. "The tumors are really complicated and not easy to reach," said Dr. Omay, "so they are best treated in large academic hospitals where surgical, medical, technological, and nursing support all are available."

For example, consider the process for a patient with a pituitary adenoma, one of the most common skull base tumors. The pituitary gland sits under the brain and behind the nose in a small space that's hard to access. It also sits near the carotid artery, which feeds the brain, and the optic nerve. A pituitary tumor may push on these, causing headaches, vision problems, or other neurological issues. The patient usually seeks help first from a primary care physician, who refers the patient along to specialists.

That's how Rennie Negron ended up in surgery with Drs. Manes and Omay. Ms. Negron, who works as a research program manager at the Yale Institute for Network Science, woke up in the middle of the night with a terrible headache. She also had palsy in one eye. "I thought it was a sinus infection," she said. She went to an urgent care center, which sent her by ambulance to the emergency room at Yale New Haven Hospital. A CT scan revealed a pituitary adenoma.

Dr. Omay explains what happens next in such cases: "The first evaluation is usually an MRI of the brain to understand the nature of the tumor—where it is, the size of it, and its relationship to the neighboring structures. During the second phase, an endocrinologist evaluates the patient because pituitary tumors often disrupt hormones. Then an ophthalmologist evaluates the patient, to assess if there's a vision issue. Next the patient is seen by an ENT surgeon, who evaluates whether the nose is feasible for the operation and if there is enough tissue to make a reconstruction afterwards. When all these consultations and evaluations are done, the patient is finally ready for surgery."

"The tumors are really complicated and not easy to reach so they are best treated in large academic hospitals where surgical, medical, technological, and nursing support are all available."

If the tumor is especially large or difficult, the surgery takes place in a special surgical suite with an intraoperative MRI. Smilow is one of the few hospitals in the country equipped with this expensive high-tech apparatus, which allows surgeons to image the patient's tumor throughout the operation. "If we determine that there is either additional tumor or something else that needs to be done," said Dr. Manes, "we can do it right then without moving or waking up the patient."

During the surgery itself, Drs. Manes and Omay work together closely. First, Dr. Manes guides an endoscope through the nose to the floor of the skull. "He takes me directly to the tumor," explained Dr. Omay. "The endoscope brings a lens and a light source to exactly where the pathology is. You can park it a couple of centimeters from the tumor, so there is a beautiful visualization of what we are doing while we are operating. I do the resection of the tumor and then Dr. Manes helps with the repair. This operation requires a team approach throughout."

During recovery and aftercare, the patient gets follow-up evaluations by the neurosurgeon, the ENT surgeon, the endocrinologist, and the ophthalmologist. "The process involves many teams," said Dr. Omay, "which is why it's important to perform these operations in dedicated centers."

Ms. Negron's surgery went perfectly. Dr. Omay removed the entire tumor, and radiotherapy was unnecessary. Negron has no visual impairment, and her pituitary is functioning fine without supplemental hormonal medication.

"Essentially I have had a full recovery," said the 32-year-old. "I have a 5-year-old daughter and a husband, so being able to get back to normal soon after surgery has been really important for me and my family. Dr. Manes and Dr. Omay were amazing. The way we were able to talk to them, and how they explained the whole process and potential outcomes and challenges, was incredibly helpful through surgery and the recovery process. I couldn't be any happier with the care and the relationships I had with them."

Breakthroughs in HPV+ Head & Neck Cancers

Wendell Yarbrough, MD
Natalia Issaeva, PhD

The number of head and neck cancers (HNC) associated with the human papillomavirus (HPV) is rising to "almost epidemic proportions," said Wendell Yarbrough, MD, MMHC, FACS, Professor of Surgery and of Pathology, Co-Director of the Virus and Other Infection-associated Cancers Research Program, and Director of Smilow Cancer Hospital's Head & Neck Cancers Program. HPV was first discovered as a factor causing HNC in the 1990s, and is now more frequently diagnosed than uterine cervical cancer making it the most common cancer caused by HPV in the United States. "It's a big public health issue, and it affects males three times more frequently than females." This upswing is happening despite the availability of an effective vaccine against HPV, which 40 percent of U.S. adolescents have not received.

There are two types of head and neck cancer – the first is associated with HPV, the other is associated with smoking tobacco. To track how these HNCs develop and progress, Dr. Yarbrough and his lab turned to The Cancer Genome Atlas (TCGA), a national database that contains maps of genomic changes in 33 types of cancer. The scientists were looking for genetic mutations in HPV-associated HNCs.

They found two defective genes that appeared only in HPV+ HNCs among all solid cancers. Both genes—TRAF3 and CYLD—help cells activate immunity against viral or bacterial infection. When the genes mutate, this protection disappears. Equally important, the TCGA data revealed that patients who carried either mutation responded better to therapy and had a significantly better rate of survival. Also good news: about 30 percent of patients with HPV+ HNCs had one of the mutations.

"Patients who are diagnosed with HPV+ head and neck cancer could be easily tested for these two biomarkers with relatively inexpensive, commercially available kits," said Natalia Issaeva, PhD, Assistant Professor of Surgery and a member of Dr. Yarbrough's lab. "If they have one of the mutations, they have a good prognosis and may not require the very aggressive therapy currently used, which involves high doses of radiation and chemotherapy."

The standard aggressive therapies were developed for head and neck cancers caused by tobacco, and as HPV+ HNC was recognized this therapy was also used for these tumors. "At first we didn't know we were treating HPV+ cancers," said Dr. Yarbrough. "We thought they were all the same, but they're very different, and they should be treated differently."

Drs. Yarbrough and Issaeva are now validating the two biomarkers on biopsies from another cohort of patients. If their previous findings are confirmed, a clinical trial will soon follow to test less aggressive treatment for this subset of HNC patients.

The TCGA data also showed that HPV+ HNCs have a distinct methylation profile. Methylation is a DNA modification that regulates gene expression, and so, flaws within this modification can lead to cancer. The scientists noticed that the genomes of HPV+ HNCs were hypermethylated, a condition known to silence some tumor suppressors. What would happen to the tumors if the HPV+ genome was demethylated, which reactivates the silenced genes? The scientists treated both HPV+ and HPV- cancer cells with an FDA-approved demethylating agent called 5-azacytidine (5-aza).

"The HPV+ cancer cells died massively," said Dr. Issaeva. The drug reduced the expression of HPV genes and boosted a tumor suppressor called p53, which began killing cancer cells. There was more good news—5-aza also repressed proteins called matrix metalloproteinases (MMPs), which tumor cells secrete before invading the blood or lymphatic systems.

"That means that demethylation drugs can prevent tumor cells from spreading and can prevent metastasis," said Dr. Issaeva.

The researchers tested their findings in a window clinical trial led by Dr. Hari Deshpande, Associate Professor of Medicine (Medical Oncology), on a small group of patients with HPV+ HNCs. They were biopsied, given 5-aza for five days, then had surgery to remove their tumors. Tumor samples before and after 5-aza treatment were used to compare molecular changes.

"The results corroborated what we saw before," said Dr. Yarbrough. "The tumors were responding dramatically to demethylation even after just five days, with few side effects." Dr. Yarbrough hopes to expand the clinical trial to give more patients longer treatment and has included the trial in a planned Specialized Program of Research Excellence (SPORE) in Head & Neck Cancers application, along with co-Principal Investigator Dr. Barbara Burtness.

Lieping Chen, MD, PhD

Past and Future Transformations in Immunology

Few discoveries in recent cancer research can match the importance of anti-PD1/PD-L1 immunotherapies, perhaps the closest that medicine has come to a cure for cancer. When used against certain cancers, anti-PD-1/PD-L1 antibody drugs switch the immune system back on, which then attacks and drastically shrinks tumors. Currently immunotherapy drugs are FDA-approved against more than 10 cancers, and it's likely that within a few years anti-PD-1/PD-L1 drugs will be approved for 15 other types of cancers that have shown significant response in clinical trials.

The scientist behind these therapies is Lieping Chen, MD, PhD, United Technologies Corporation Professor in Cancer Research and Professor of Immunobiology, Medical Oncology, and Dermatology, and Co-Director of the Cancer Immunology Program at Yale Cancer Center. His discoveries have brought him many honors, most recently the 2017 Warren Alpert Foundation Prize "for transformative discoveries in the field of cancer immunology."

With PD-1/PD-L1, the journey from discovery to FDA-approval was long. Dr. Chen conceived his theory about the tumor molecules that disable lymphocyte function in 1992. In 1999, he discovered the B7-H1 molecule (now also called PD-L1) and showed how the PD-L1 bound to PD-1 in a tumor's microenvironment to shut down the immune response. When Dr. Chen blocked this pathway with monoclonal antibodies to stop the binding, the lymphocytes in the tumor woke up and attacked the cancer cells.

"Most people did not take this concept very well," said Dr. Chen. "It was too new. The majority of immunologists were trying to boost the immune system, in hopes that would get rid of the cancer. The others didn't believe that this molecule would work selectively in the tumor's microenvironment."

Doubts that a mechanism could have this effect delayed the first clinical trial almost 10 years, until 2006. "That was a turning point," said Dr. Chen. "Many patients in the trial still had huge tumor burdens even after chemotherapy, radiotherapy, and targeted therapy, but with anti-PD-1/PD-L1 treatment, their tumors really regressed."

Skeptics called the trial too small. Dr. Chen had to wait another six years before anti-PD-1/PD-L1 was tested in a large trial with a few hundred patients. Once again, all the patients had failed on every other treatment. Once again, the data about tumor regression was astonishing. In some patients the cancer disappeared and didn't return. "People started to believe it was real," explained Dr. Chen.

But this trial and others also showed that 40 to 60 percent of the patients didn't respond to anti-PD-1/PD-L1 therapy. Those tumors are Dr. Chen's new targets.

"From this therapy we learned that a tumor creates an immune inhibitory mechanism in its microenvironment," he said. "So it doesn't matter how much you boost the immune system in other parts of body, because these local tumor sites are so strong and can completely shut down immunity inside the tumor. My current research is driven by this idea—to go into the tumor microenvironment, tease out the molecular pathways, and study them to identify the fundamental mechanisms that allow cancer to shut down the immune response in tumors, especially that do not respond to anti-PD-1/PDL-1 therapy. Then, we will devise a therapeutic approach to fix those problems. It's almost like starting from scratch again, and it's really exciting."

He and his 25-person lab are focusing on solid tumors with few effective treatments and poor survival rates—lung, breast, colorectal, and pancreatic cancers. But this time he wants to shorten the lag time between discovery and clinical application. He is doing that through strong alliances with pharmaceutical and biotech companies.

"We are changing the model a little bit," explained Dr. Chen. "We will cut the time from discovery to clinical trial from 20 years down to five years or maybe even three. It's going to be faster and better."

Among the pharmaceutical companies working with Dr. Chen are Pfizer and Boehringer Ingelheim. His newest alliance set a record for a biotech start-up: investors raised $67 million in 2016 for a new company called NextCure, based on Dr. Chen's future breakthroughs.

Dr. Chen can't talk yet specifically about the fruits of these partnerships except to say that a few drugs are getting close to clinical trials. The first new drug will likely go to trial in mid-2018, just two-and-a-half years from the lab.

"This is the model we're looking for," said Dr. Chen. "Acceleration. It's now obvious that there are pathways in some tumors that are immune suppressive, and I expect in the next few years many will be discovered so we can use immunotherapy against them."

The Evolutionary Histories of Cancers

Jeffrey Townsend, PhD

A group of Yale scientists are using the tools of evolutionary biology to study cancer, with surprising results. A paper published last year [ed.--2017] in the *Proceedings of the National Academy of Sciences* demonstrated that these tools can transform our basic understanding of how cancer begins and spreads, and also can help researchers prioritize targets for attack.

The study's main author is Jeffrey Townsend, PhD, Elihu Associate Professor of Biostatistics and of Ecology and Evolutionary Biology, and Director of Bioinformatics at the Yale Center for Analytical Sciences. An evolutionary biologist, Dr. Townsend turned his attention to cancer a few years ago because he saw an opportunity to harness well-established principles from his field to enable new technologies and expand the impact of cancer databases.

"With high throughput sequencing," said Dr. Townsend, "we now can sequence the whole exomes of different cancers, both primary tumors and metastases. Until recently we couldn't get enough data to do that. Now we can begin to infer how the expressed genomes of the cancers at different tissue sites are related to each other."

To do this, he uses a tool that evolutionary biologists call molecular evolutionary models. These models compare sequences of DNA from different organisms to discover how and when the organisms diverged, which also reveals how closely or distantly they are related. A second tool, "reconstructed ancestral states," uses DNA sequencing to trace how a gene evolved, which enables evolutionary biologists to extrapolate the gene's ancestral states along an evolutionary timeline.

He and his team performed whole exome sequencing of autopsy samples archived at Yale from 40 people with 13 types of cancer. They sequenced samples from normal tissue, 32 primary tumors, and 139 sites of metastases. Many of the samples were taken at multiple points during a patient's treatment, which allowed the scientists to construct a timeline of the cancers' emergence and evolution, and to detect the cancers' genetic origins and relationships to each other. The findings have upended some assumptions.

First, Dr. Townsend produced family trees for each tumor and its metastases. "If all the metastases had a common genetic origin within the primary tumor," he said, "they would have only brother-sister relationships with other metastases. That wasn't true." Instead, he found that the metastases often diverged genetically from the primary tumor very early in the tumor's history, in some cases even before the primary tumor had been diagnosed. This early divergence contradicts what Dr. Townsend calls "the longstanding linear model of cancer progression," which holds that mutations lead to cell proliferation that causes a primary tumor, followed by mutations that explode into metastases.

"That model assumes all metastases would be related," said Dr. Townsend. "But when you see metastases being quite divergent from each other and from the primary tumor, very early in the primary tumor, I would say that our results put the final 'nail in the coffin' of linear thinking about cancer."

This has important implications for treating cancer. A patient often follows a familiar sequence: diagnosis of a primary tumor, remission, recurrence with metastases, and treatment of the metastases. Using targeted therapy against the primary tumor may not touch less genetically-related metastases within the tumor, so they pop up later.

This insight led to another third important finding: after reconstructing the tumors' ancestral states, Dr. Townsend and his colleagues noted two well-known genes that repeatedly mutated early in the evolution of all the primary tumors and metastases—the oncogene KRAS and the tumor suppressor TP53. Both are known cancer drivers, but the hard evidence provided by his analyses makes their early evolutionary role news. The frequent presence of these well-known culprits in the genetics of cancer at the root of diverse cancer lineages, the authors wrote, "implies that they play key formative roles in the origin of cancer and that they deserve redoubled attention for their roles in tumorigenesis."

Dr. Townsend notes that no good drugs currently exist against KRAS and TP53, though some for KRAS are in the pipeline. "The mutations that happen very early are where we should put our effort in the design and development of new drugs," he said, "because anything that addresses the genesis of cancer will address later cancers as well. We have to figure out how we can corner the cancer—and destroy all of it—instead of destroying just one part and allowing the other parts to develop resistance."

Dr. Townsend hopes to perform further studies on samples of many cancers taken from living patients to learn how and when each type develops and evolves. "Evolutionary biology can help us understand each cancer's life history," he said, "and from that can come a strategy for treating them."

Patricia LoRusso, DO
Joann Balazs Sweasy, PhD

Boosting Mutations to Kill Cancer

Three years ago Patricia LoRusso, DO, Professor of Medicine and Associate Director of Experimental Therapeutics at Yale Cancer Center, was drawn to Yale in part because of the strong basic science work done here. The group investigating DNA damage repair (DDR) especially impressed her, but she noticed that little of their work had made the jump from the lab to the clinic. Once she arrived, she began looking for ways to change that.

Around the same time, the FDA approved a new drug called olaparib, a PARP inhibitor. PARPs are a group of proteins crucial to the repair of damaged DNA. If defective DNA isn't fixed or removed, the cell weakens and often dies. PARP inhibitors hasten cell death by blocking DNA repair. BRCA mutations are associated with several cancers, including ovarian, breast, pancreatic, and prostate cancers, as well as others. Olaparib stops BRCA deficient tumor cells from repairing their DNA, causing further deterioration and cell death.

Dr. LoRusso had done clinical trials on PARP inhibitors before coming to Yale. Yale's DDR group was deeply involved in research about the mechanisms of DNA repair. "Pat and I started talking," said Joann Balazs Sweasy, PhD, Ensign Professor of Therapeutic Radiology and Professor of Genetics, and Associate Director of Basic Science at Yale Cancer Center, "and we found lots of ways to collaborate. There's a natural synergy between the clinic, through Pat, and the basic scientists in the DNA repair group here."

One current project originated when Dr. LoRusso put two observations together. Clinical research had shown that only about 15 percent of women with triple negative breast cancer respond to immune checkpoint inhibitors—immunotherapy drugs. Other clinical research, done after genetic profiling of tumors became common, showed that about 15 percent of women with breast cancer have BRCA mutations.

"So my thought was," explained Dr. LoRusso, "could these 15 percent responders to immune checkpoint inhibitors actually be patients who had BRCA mutations? And if we treated BRCA-mutant patients with a PARP inhibitor, could we increase the responsiveness of the tumor to immune checkpoint inhibitors?"

To investigate this idea she formed a team of basic scientists, translational scientists, and clinicians. They wrote a clinical trial based on the concept, which was approved by the NCI's Experimental Therapeutics Clinical Trials Network (ETCTN). Dr. LoRusso is now enrolling patients. "We're using PARP inhibitors, including olaparib, to create more mutations in BRCA-mutant breast cancer patients," said Dr. Sweasy, "because we know that tumors with high levels of mutations have high levels of neoantigens, and we are trying to figure out if tumor cells with high levels of neoantigens will respond more strongly to immunotherapy."

Neoantigens are proteins produced in response to genetic changes caused by tumor cells. The more mutations, the more neoantigens, which sit on the mutated cells' surfaces and, as foreign bodies, should draw attention from the immune system. Cancer cells are adept at eluding detection, but the greater the number of neoantigens, the less likely that cancer cells can go unnoticed.

"Immunotherapy reactivates the immune system and increases the number of tumor infiltrating lymphocytes (TILs)," explained Dr. Sweasy. "We think the TILs will recognize these neoantigens as targets and kill the tumor cells." Her lab is testing this hypothesis on mouse models and human cancer cell-lines. She calls the results encouraging but preliminary.

Provoking mutations to improve outcomes sounds counterintuitive. "Twenty years ago, the more mutations you had, the worse it was," said Joseph Paul Eder, MD, Professor of Medicine, who is overseeing several clinical trials on olaparib. "Now, patients with the highest burden of mutations are most likely to respond to these new immune checkpoint therapies. But these drugs haven't worked nearly as well in breast cancer as in some other cancers, so the thought is that by inducing even more DNA damage and more mutations with olaparib, we might push breast cancer into the group that's sensitive to immunotherapies."

Dr. Sweasy's BRCA study is one of four that make up projects that the DNA Repair team is moving forward into a team science grant. This team, led by Drs. LoRusso and Sweasy, collaboratively hopes to submit a new SPORE application (Specialized Programs of Research Excellence), a prestigious grant awarded by the NCI, focusing on DNA Repair. Yale already has two SPOREs, in lung cancer and skin cancer, but this one would be unique – focusing on a mechanism that is important in multiple types of tumors, instead of one tumor type or similar groups of tumors.

"Each has basic scientists, translational scientists, and clinical scientists," said Dr. LoRusso, "to take discoveries from the labs into the clinic and then back into the labs for refinements, with the ultimate intent to improve outcomes for patients."

Secrets of the BRCA1 Gene Finally Revealed

Ryan B. Jensen, PhD
Patrick Sung, DPhil

The BRCA1 gene and its association with breast cancer were discovered in 1990. We have learned much about it since. We know that mutations in the gene can be inherited. We know that BRCA1 has been linked to additional cancers, including ovarian, prostate, and pancreatic. We also know that the BRCA1 gene produces a tumor suppressor protein that plays an important role in DNA repair. But the dark mystery at the gene's core—the molecular mechanism that triggers mutations and leads to cancer—has stumped researchers for a quarter of a century, until now.

In 2017, Yale scientists revealed the elusive mechanism after purifying the BRCA1 protein in conjunction with an associated factor called BARD1. This breakthrough opens new possibilities for attacking cancers linked to mutations of BRCA1. The findings appeared in the October 2017 issue of the journal *Nature*.

"A lot of very good people have tried to purify the protein," said the paper's senior author, Patrick Sung, DPhil, Professor of Molecular Biophysics and Biochemistry. "I am proud to say that we are the first to succeed."

They had to overcome considerable obstacles. The protein is fragile and prone to quick degradation, so the researchers had to work for many hours in a room being kept at four degrees Celsius. The protein is hard to express and tends to fold incorrectly, and it is unusually large, which makes it extremely challenging to purify, said Dr. Sung. A misstep at any point in this painstaking process renders the protein inactive and useless for research.

"You need a lot of training and experience to know what measures to take to preserve activity," said Dr. Sung.

"You have to be incredibly tenacious," added Ryan B. Jensen, PhD, Associate Professor of Therapeutic Radiology, a supporting author on the paper. Dr. Jensen would know—in 2010 he was the first to purify the BRCA2 protein. Only a few laboratories in the world can successfully purify BRCA proteins, and two of them are at Yale—Drs. Sung and Jensen's.

Dr. Sung has been tracking proteins related to DNA repair for more than 20 years, which is what led him to BRCA1. The gene's precise role in the repair process was unknown. Purified BRCA1 protein allowed Dr. Sung and his colleagues to study its properties and run experiments that pinpointed its function in DNA repair.

They have found that the complex of BRCA1 and BARD1 binds and stimulates an enzyme called RAD51, known to be important in repairing double-strand breaks in DNA. (Dr. Sung first described the function of RAD51 in 1994.) Dr. Sung's team found that when mutations occur in the BRCA1-BARD1 complex, RAD51 is not activated and DNA repair falters, which can lead to mutations and cancer.

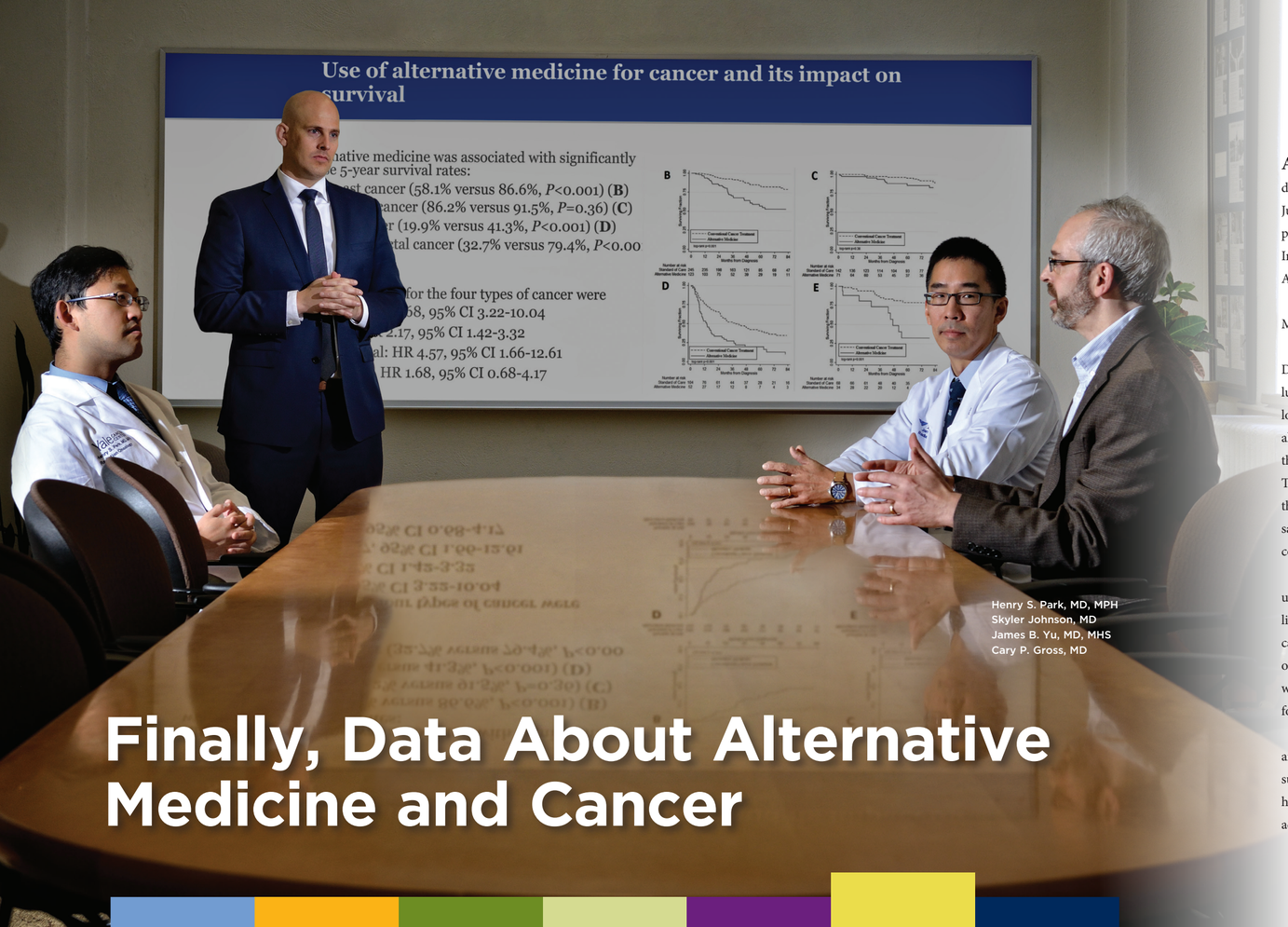
"Now that we know that BRCA1 and BARD1 interact with RAD51, we can target that interface," said Dr. Sung. "Before, we didn't know what to target. That's why basic science is so important. The next step would be to develop compounds that regulate the activity of the target, to enhance it or inactivate it."

Many drugs are designed to kill cancer cells by damaging their DNA. Yet some cancer cells manage to repair their DNA and become resistant to chemotherapy and radiotherapy. Deciphering the mechanisms of DNA repair pathways is critical, explained Dr. Jensen, because such knowledge points the way to therapies that block those pathways and kill resistant cells.

Understanding the mechanisms within BRCA1 and BRCA2 also has predictive value. Right now, if a young woman is worried about her family's history of breast or ovarian cancer, she can get a diagnostic test to see if she carries a BRCA mutation. Sometimes the result clearly indicates either low risk or high risk, but often the test reports "variants of uncertain significance," which leaves the woman in fear and limbo. Should she prophylactically remove her ovaries and breasts? Does she have time to have children first? These are anguishing decisions. These new discoveries about BRCA1 and BRCA2 will make it possible to tell whether her mutation affects DNA repair severely or only slightly, and hence what her risk is for cancer with regards to age.

"And it all comes from understanding how the proteins work," said Dr. Jensen. "That's why what Patrick and I do, biochemistry, is really important—this tedious work of purifying proteins one at a time and figuring out mechanistically what they do."

Dr. Sung agrees. "I understand why the general public wants to see cures, but unless you understand the basic biology, you will never have a cure."



Finally, Data About Alternative Medicine and Cancer

According to Altmetric, which tracks the distribution and discussion of research papers online, a July article by several Yale physicians is the most-discussed paper ever published in the Journal of the National Cancer Institute (JNCI). The title of this blockbuster: "Use of Alternative Medicine for Cancer and Its Impact on Survival."

"It struck a chord," said senior author James Yu, MD, MHS, Associate Professor of Therapeutic Radiology.

The Yale researchers used the U.S. National Cancer Database to collect information on patients with breast, lung, colon, and prostate cancer from 2004 to 2013. They looked for people who reported using only unproven alternative treatments instead of conventional medical therapies such as surgery, radiation, and chemotherapy. The researchers found 280 such people and then compared their outcomes after 5½ years to 560 people with the same cancer, diagnosis, age, and race who had received conventional treatment.

The results were clear. Patients who initially relied on unproven alternatives were, on average, 2.5 times more likely to die within the 5½ year window. Within particular cancers, the risk associated with alternative medicine was often much worse—almost six times higher for patients with breast cancer, four times for colon cancer, two times for lung cancer.

Skyler Johnson, MD, Resident in Therapeutic Radiology and the paper's lead author, thinks the discrepancy in survival rates would be even more alarming if the patients had been followed for longer than five years to take into account slow-growing cancers such as prostate cancer. He also calls the 280 people identified as using only alternative medicine "a huge underestimate" because the researchers excluded a large group of patients who had been coded as having refused treatment, with no reason given. Dr. Johnson suspects that many of them chose an alternative therapy first but did not report it to their physicians.

Another interesting finding from the paper was that people who preferred alternative treatments tended to have had more formal education, and higher incomes.

The researchers have some theories about this seeming conundrum. Dr. Johnson mentions the Dunning-Kruger effect, in which people overestimate their knowledge, in part by relying on the Internet. Dr. Yu speculates that people with higher incomes can afford more types of healthcare and know how to seek them out, such as clinical trials. "But in this case it's wishful thinking," he said. "These alternatives don't necessarily cause harm, but they're placebos, and placebos don't cure cancer, but they can delay real cancer care."

Co-author Cary P. Gross, MD, Professor of Medicine and of Epidemiology, wasn't that surprised by the demographic finding, citing increased skepticism about science and conventional medicine that has driven things such as the anti-vaccination movement. "And just as the Internet and social media have fueled discord in the political process," he added, "they also have enabled conspiracy theories about medicine and health to spread rapidly and wildly."

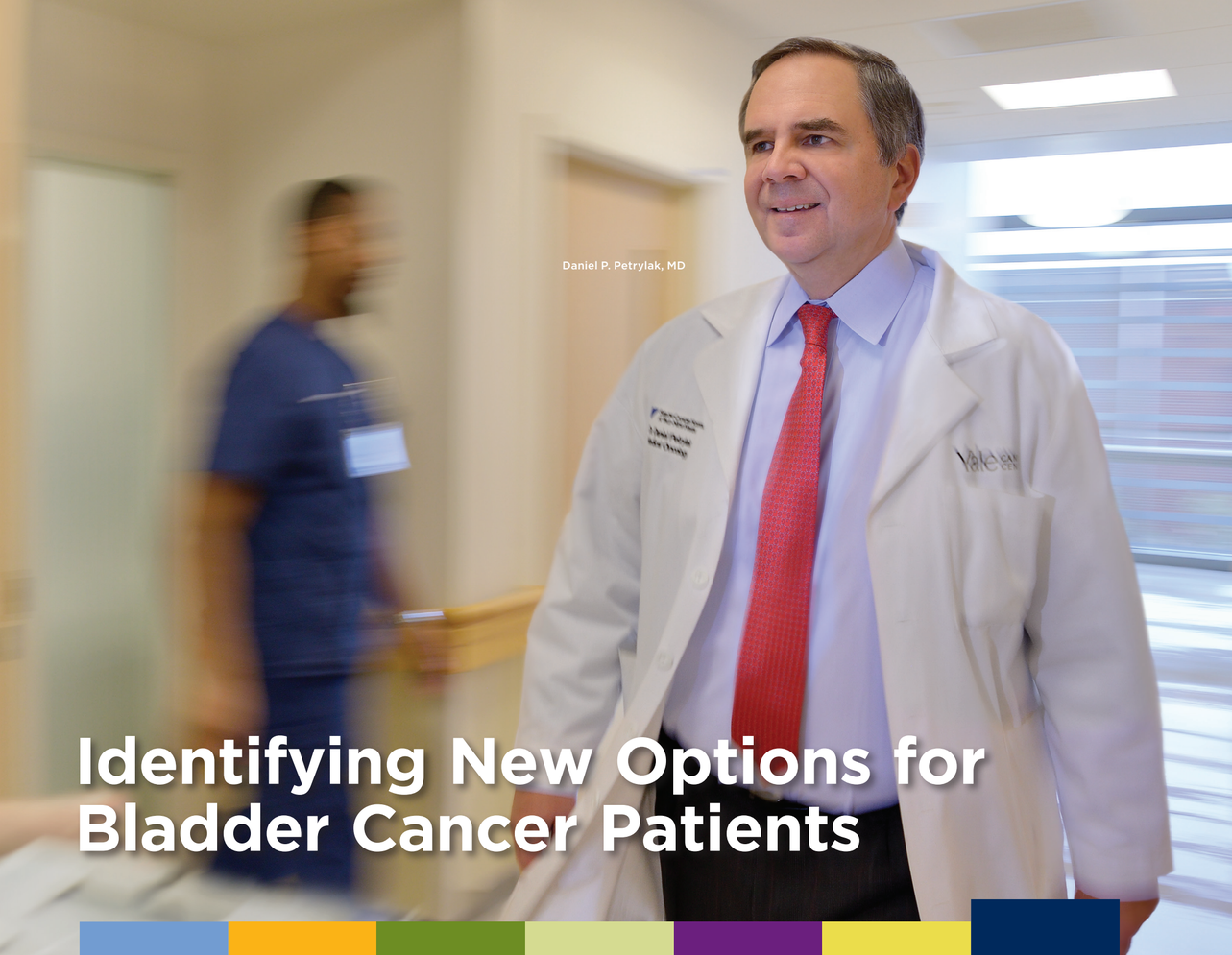
The researchers also believe, based on their own patients, that the number of people choosing alternative treatments over conventional ones is increasing. "I understand the human impulse to think there's got to be something else," said Dr. Yu. "And when the answer is 'no, there isn't', then there's the opportunity for someone to say, 'Just rub these crystals or sit in a salt bath or eat special food.'"

All of the researchers noted that the problem should not be pinned only on patients and providers of alternative medicine. "Physicians need to shoulder some of the blame as well," said Dr. Johnson. "We need to take the time to really listen to patients' concerns and explain things more clearly. That builds a relation of trust, and makes them more willing to believe the data."

Dr. Yu agrees. "We need to bring these conversations about alternative therapies to the forefront," he said, "and because of this study we now have the data to help us." The researchers also noted that their work focused on alternative medicine, when patients choose not to receive conventional medical therapies, rather than "complementary medicine," in which patients undergo conventional cancer treatment as well as additional therapies from disciplines that are not part of traditional Western medicine.

The researchers know that facts and data won't be enough to persuade everyone, a common symptom of our time, but their paper is a start. They hope it convinces a few people to reconsider relying on alternative treatments, or prompts someone to insist that a loved one see an oncologist. "That's why we do research," said Dr. Johnson. "We try to help people one at a time, and hopefully our research can help patients and families to make more informed decisions."

Identifying New Options for Bladder Cancer Patients



Daniel P. Petrylak, MD

The therapeutic options for patients with urothelial carcinoma, the most common form of bladder cancer, are limited. The standard first-line treatment, platinum-based chemotherapy, causes severe side effects, helps only about two thirds of the recipients, and has a median survival of only about 1.5 years. Options for the other 80 percent, in whom the cancer continues to progress or turns metastatic, are poor to nonexistent.

That bleak state of affairs could be altered by the results of a recent worldwide Phase III RANGE clinical trial. Its principal investigator was Daniel P. Petrylak, MD, Professor of Medicine and Urology, and Co-Director of the Signal Transduction Research Program. He and his co-investigators tested a new combination therapy on bladder cancer patients who had previously been unsuccessfully treated with platinum-based chemotherapy. About 10 percent of these patients also had failed to respond to checkpoint inhibitors. "This was a group that you would expect to do poorly," said Dr. Petrylak.

The trial included 530 patients with advanced or metastatic bladder cancer from 124 sites in 23 countries. The patients were randomly split into two groups. About half of them received docetaxel, a non-platinum-based chemotherapy drug, plus a placebo. The other half received docetaxel in combination with ramucirumab, an anti-angiogenic drug. The results confirmed what Dr. Petrylak and his co-investigators had found in their Phase II study.

"We showed about a doubling of the objective response rate, to 24 percent, and also significantly improved progression-free survival when ramucirumab was combined with docetaxel, compared to docetaxel alone," said Dr. Petrylak. "This is the first Phase III trial in which a combination therapy has shown an advantage over chemotherapy alone," said Dr. Petrylak.

He presented these results at the European Society for Medical Oncology (ESMO) Congress last September in Madrid. The investigators' paper was published in *The Lancet*.

Ramucirumab inhibits VEGFR-2 (human vascular endothelial growth factor receptor 2), a protein whose signals stimulate cells to form new blood vessels. Tumors are highly vascular. By blocking VEGFR-2's signals to nutrient-hungry cancer cells, ramucirumab cuts off the blood supply that cancer depends upon to survive and spread.

"Ramucirumab is already approved for other tumor types such as gastric cancer and lung cancer," said Dr. Petrylak. "Adding anti-angiogenesis agents to chemotherapy has become a standard of care in those cancers, and it's a way to move forward in the treatment of urothelial carcinomas." Dr. Petrylak hopes that the Phase III results will encourage the FDA to consider approving ramucirumab for bladder cancer, especially if the overall survival data for patients who took the combination therapy mirrors the progression-free survival data. "If we see a survival benefit, that trumps everything," he said. He expects to have those numbers sometime this year [ed.--2018].

The trial also confirmed the Phase II finding that patients who took ramucirumab with docetaxel did not experience more side effects than patients who took docetaxel alone. "That's important," explained Dr. Petrylak. He was also pleasantly surprised to find that patients who received the combination therapy had less anemia. "With most chemotherapy agents," he said, "you see a degradation of performance status"—a measure of a patient's general well-being—"but we didn't see that here."

The progression-free survival rate of patients on the combination therapy was 4.07 months versus 2.76 months for those on docetaxel alone, a small improvement that raised questions about its clinical relevance.

"The counterargument is that the objective response rate doubled," said Dr. Petrylak, "and in my mind that's clinically significant." In other words, the improved rate sounds notably relevant to patients who need a further option.

He also points out that that there is no FDA approved agent for patients who have failed at checkpoint inhibition therapy, as most do—75 percent don't respond. Dr. Petrylak and his colleagues are currently running trials that combine immune checkpoint inhibitors with anti-angiogenic agents—for instance, ramucirumab with the inhibitor pembrolizumab. They think such combinations may be synergistic.

"There are a lot of possible combinations, and they are opening a lot of doors," said Dr. Petrylak. "It's a very exciting time in bladder cancer. When I came to Smilow five years ago this was a disease that had no real options for treatment once patients progressed after primary chemotherapy, and now our patients will likely have multiple options in the next couple of years."

Yale Cancer Center Leadership

Yale Cancer Center

Charles S. Fuchs, MD, MPH
Director

Louis R. Chênevert
Chairman, Director's Advisory Board

Daniel C. DiMaio, MD, PhD
Deputy Director

Kevin Vest, MBA, FACHE
Deputy Director, Finance and Administration

Mark A. Lemmon, PhD
Co-Director, Cancer Biology Institute

Robert Garofalo, PhD
Associate Director, Research Affairs

Roy S. Herbst, MD, PhD
Associate Director, Translational Science

Melinda L. Irwin, PhD, MPH
Associate Director, Population Sciences

Harriet Kluger, MD
Associate Director, Education, Training & Faculty Development

Patricia M. LoRusso, DO
Associate Director, Experimental Therapeutics

David F. Stern, PhD
Associate Director, Shared Resources

Joann B. Sweasy, PhD
Associate Director, Basic Science

Anees B. Chagpar, MD
Assistant Director, Global Oncology

Beth Jones, PhD, MPH
Assistant Director, Diversity and Health Equity

Gary Kupfer, MD
Assistant Director, Pediatrics

Ruth McCorkle, RN, PhD
Assistant Director, Psychosocial Oncology

Nita Ahuja, MD, MBA
Assistant Director, Surgery

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

Edward Snyder, MD
Assistant Director, Membership

Yale Cancer Center Research Programs

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

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

Cancer Prevention and Control
Melinda L. Irwin, PhD
Xiaomei Ma, PhD

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

Virus and Other Infection-associated Cancers
Walther H. Mothes, PhD
Wendell G. Yarbrough, MD

Radiobiology and Radiotherapy
Peter M. Glazer, MD, PhD
Joann B. Sweasy, PhD

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

Yale Cancer Center Shared Resources

Biostatistics and Bioinformatics
Shuangge Steven Ma, PhD

Cesium Irradiator
Ravinder Nath, PhD

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

Flow Cytometry
Ann Haberman, PhD

Pathology Tissue Services
David Rimm, MD, PhD

Rapid Case Ascertainment
Rajni Mehta, MPH

Yale Center for Genome Analysis
Shrikant Mane, PhD

Yale Center for Molecular Discovery
Craig Crews, PhD

Smilow Cancer Hospital

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

Abe Lopman
Senior Vice President, Operations and Executive Director

Rogerio C. Lilenbaum, MD
Chief Medical Officer

Catherine Lyons, RN, MS
Vice President, Patient Services

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

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

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

Sonia Grizzle
Director, Financial Operations

Arthur Lemay
Executive Director, Smilow Cancer Network

Smilow Cancer Hospital Clinical Programs

Brain Tumor
Clinical Program Leader:
Joachim M. Baehring, MD
Disease Aligned Research Team Leader:
Kevin P. Becker, MD, PhD

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

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

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

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

Head and Neck Cancers
Clinical Program Leader:
Wendell G. Yarbrough, MD
Disease Aligned Research Team Leader:
Barbara A. Burtness, MD

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

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

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

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

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

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

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

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

Thoracic Oncology
Clinical Program Leader
Frank C. Detterbeck, MD
Disease Aligned Research Team Leader:
Roy S. Herbst, MD, PhD

Yale Cancer Center Membership

Radiobiology and Radiotherapy

Ranjit S. Bindra
Daniel J. Boffa
Douglas E Brash
David Joel Carlson
Richard E. Carson
Sandy Chang
Zhe (Jay) Chen
Veronica Lok Sea Chiang
John W. Colberg
Joseph N. Contessa
Shari Damast
Roy H. Decker
Jun Deng
Francesco D'Errico
Frank C. Detterbeck
James S. Duncan
Suzanne B. Evans
Peter Michael Glazer
Fanqing Guo
James E. Hansen
Hoby Patrick Hetherington
Susan A. Higgins
Zain A. Husain
Fahmeed Hyder
Ryan B. Jensen
Megan C. King
Gary Kupfer
Patty J. Lee
Wu Liu
Meena Savur Moran
Evan Daniel Morris
Ravinder Nath
Henry Park
Abhijit A. Patel
Kenneth B. Roberts
Faye A. Rogers
Peter Schulam
Patrick Sung
Joann Balazs Sweasy
Lynn D. Wilson
James Byunghoon Yu
Zhong Yun

Cancer Genomics, Genetics, and Epigenetics

Allen Everett Bale
Linda M. Bartoshuk
Susan J. Baserga
Jean L. Bolognia
Marcus W. Bosenberg
Demetrios Braddock
Tobias Carling
Nancy Carrasco
Sidi Chen
Keith Adam Choate
Lynn Cooley
Jose Costa
Nadya Dimitrova
Mark B. Gerstein
Antonio J. Giraldez
Murat Gunel
Shangqin Guo
Ruth Halaban
Stephanie Halene
Shilpa Hattangadi
Christos Hatzis
Erin Wysong Hofstatter
Natalia B. Ivanova
Lucia Beatrice Jilaveanu
Samuel G. Katz
Sajid A. Khan
Kenneth Kay Kidd
Yuval Kluger
William H. Konigsberg
Diane S. Krause
David J. Leffell
Peter Lengyel
Bluma Lesch
Peining Li
Haifan Lin
Zongzhi Liu
Xavier Llor
Janina Longtine
Jun Lu
Shrikant M. Mane
Miguel A. Materin
James Michael McGrath
Mandar Muzumdar
Karla Neugebauer
James P. Noonan
Manoj Pillai
Manju Prasad
Lajos Pusztai
Peter E. Schwartz
Emre U. Seli
Gerald S. Shadel
Jeffrey L. Sklar
Hugh S. Taylor
Jeffrey Townsend
Vikram Wali
Scott Donald Weatherbee
Sherman Morton Weissman
Andrew Zhuo Xiao
Mina LuQing Xu
Tian Xu
Qin Yan
Hongyu Zhao

Virus and Other Infection-associated Cancers

Kathleen M. Akgun
Daniel C. DiMaio
Ayman Sayed El-Guindy
Jorge E. Galan
Andrew Goodman
Stavroula Hatzios
Ya-chi Ho
Stanley David Hudnall
Natalia Issaeva
Akiko Iwasaki
Caroline Helen Johnson
Benjamin L. Judson
Amy Caroline Justice
Michael J. Kozal
Priti Kumar
Brett D. Lindenbach
Jun Liu
I George Miller
Kathryn Miller-Jensen
Walther H. Mothes
Elijah Paintsil
Noah Wolcott Palm
Anna Marie Pyle
John K. Rose
Christian Schlieker
Joan A. Steitz
Richard E. Sutton
Tamar Hamosh Taddei
Peter John Tattersall
Anthony N. Van den Pol
Sten H. Vermund
Yong Xiong
Wendell Gray Yarbrough

Cancer Immunology

Stephan Ariyan
Philip William Askenase
Kevin Patrick Becker
Jeffrey R. Bender
Alfred L. M. Bothwell
Richard Bucala
Lieping Chen
Oscar Rene Colegio
Joseph Edgar Craft
Peter Cresswell
Richard L. Edelson
Brinda Emu
Richard A. Flavell
Francine M. Foss
Michael Girardi
Earl John Glusac
Ann M. Haberman
David Hafler
Douglas John Hanlon
Nikhil Joshi
Susan M. Kaech
Paula B. Kavathas
Steven H. Kleinstein
Smita Krishnaswamy
Carrie L. Lucas
Mark Joseph Mamula
Jennifer Madison McNiff
Ruslan M. Medzhitov
Eric R. F. Meffre
Deepak Narayan
Joao P. Pereira
Jordan Stuart Pober
Aaron Ring
Carla Vanina Rothlin
Nancy Hartman Ruddle
Kurt Schalper
David G. Schatz
Stuart Evan Seropian
Brian Richard Smith
Edward Leonard Snyder
Mario Sznol
Robert E. Tigelaar
Mary M. Tomayko
Jun Wang

Developmental Therapeutics

Karen S. Anderson
Masoud Azodi
Joachim M. Baehring
Aarti Khushal Bhatia
Debra Schwab Brandt
Ronald R. Breaker
Barbara Ann Burtness
Charles H. Cha
Herta H. Chao
Yung-Chi Cheng
Anne Chiang
Gina G. Chung
Jason Michael Crawford
Craig M. Crews
Henk De Feyter
Hari Anant Deshpande
Vincent T. DeVita
Joseph Paul Eder
Barbara E. Ehrlich
Jonathan A. Ellman
Donald Max Engelman
Tarek Fahmy
James J. Farrell
Gigi Galiana
Scott Nicholas Gettinger
Sarah B. Goldberg
Steven D. Gore
Ya Ha
Dale Han
Roy S. Herbst
Seth B. Herzon
Nina Ruth Horowitz
Iris Isufi
William L. Jorgensen
Patrick A. Kenney
Kevin Kim
Harriet M. Kluger
Jaseok Koo
Jill Lacy
Rogerio C. Lilenbaum
Dieter M. Lindskog
Elias Lolis
Patricia LoRusso
Scott J. Miller
Jennifer Moliterno
Gil G. Mor
Natalia Neparidze
Terri Lynn Parker
Pasquale Patrizio
Peter Natale Peduzzi
Joseph Massa Piepmeier
Nikolai Alexandrovich Podoltsev
Thomas Prebet
Lynne J. Regan
John David Roberts
Michal Gillian Rose
W. Mark Saltzman
Alessandro D. Santin
Clarence Takashi Sasaki
Alanna Schepartz
William C. Sessa
Brian Matthew Shuch
David Adam Spiegel
Preston Sprenkle
Stacey M. Stein
Mario Strazzabosco
Seyedtaghi (Shervin) Takyar
Vasilis Vasiliou
Gottfried Von Keudell
Amer Zeidan
Daniel Zelterman
Jiangbing Zhou

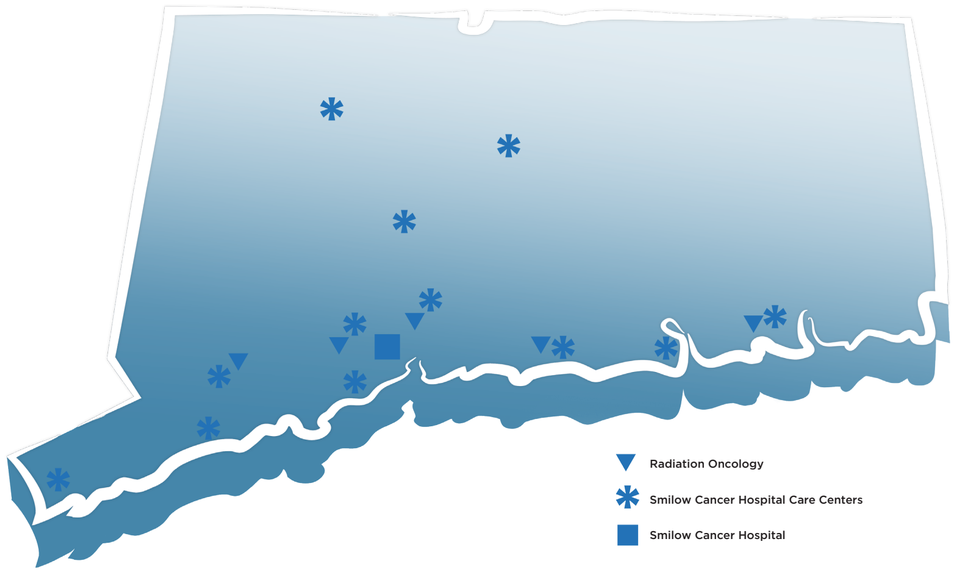
Signal Transduction

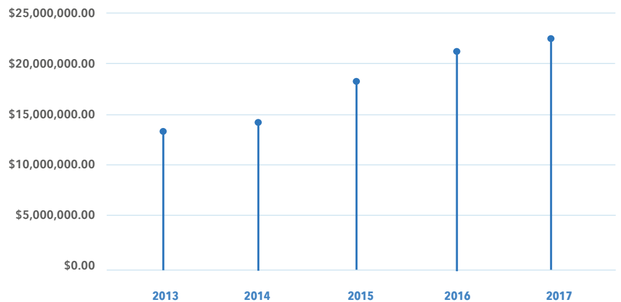
Anton M. Bennett
Titus Boggon
David A. Calderwood
Toby C. Chai
Gary Vincent Desir
Michael P. DiGiovanna
Rong Fan
Kathryn M. Ferguson
Clare Ann Flannery
John P. Geibel
Sourav Ghosh
Valentina Greco
Julie Hens
Mark W. Hochstrasser
Valerie Horsley
Michael E. Hurwitz
Karl L. Insogna
Richard Glenn Kibbey
Joseph W. Kim
Daryl Klein
Anthony J. Koleske
Michael Oliver Krauthammer
TuKiet T. Lam
Francis Lee
Mark A. Lemmon
Andre Levchenko
Michael Mak
Darryl T. Martin
Wang Min
Jon Stanley Morrow
Peggy Myung
Michael H. Nathanson
Don X. Nguyen
Daniel Petrylak
Katerina Politi
David L. Rimm
Joseph Schlessinger
Martin A. Schwartz
David F. Stern
Yajaira Suarez
Derek K. Toomre
Benjamin E. Turk
Narendra Wajapeyee
Robert Martin Weiss
Kenneth R. Williams
Dan Wu
John Joseph Wysolmerski
Xiaoyong Yang

Cancer Prevention and Control

Kerin Bess Adelson
Prasanna Ananth
Steven L. Bernstein
Brenda Cartmel
Anees B. Chagpar
Elizabeth Brooks Claus
Amy Joan Davidoff
Nicole Cardello Deziel
Leah McArthur Ferrucci
Charles S. Fuchs
Lisa Fucito
Bonnie Elyssa Gould Rothberg
Cary P. Gross
Caitlin Elizabeth Hansen
Theodore R. Holford
Scott Frederick Huntington
Melinda Liggett Irwin
Beth A. Jones
Manisha Juthani-Mehta
Nina S. Kadan-Lottick
Jennifer M. Kapo
Brigid Killelea
Tish Knobf
Suchitra Krishnan-Sarin
Donald R. Lannin
James Mark Lazenby
Michael Leapman
Haiqun Lin
Lingeng Lu
Shuangge Steven Ma
Xiaomei Ma
Asher Michael Marks
Ruth McCorkle
Sherry McKee
Rajni Lynn Mehta
Sarah Schellhorn Mougalian
Linda M. Niccolai
Marcella Nunez-Smith
Stephanie Samples O'Malley
Jonathan Thomas Puchalski
Elena Ratner
Harvey A Risch
Peter Salovey
Tara Sanft
Dena J. Schulman-Green
Dave Sells
Fatma M. Shebl
Sangini S. Sheth
Andrea Lynn Maria Silber
Mehmet Sofuoglu
Shiyi Wang
Yawei Zhang
Yong Zhu

Yale Cancer Center and Smilow Cancer Hospital





TOTAL NCI FUNDING (DIRECT COSTS)

FEMALE (N=3,635)

Primary Site	Total	Percent
Breast	1,192	32.8%
Lung & Bronchus	375	10.3%
Melanoma	228	6.3%
Thyroid	226	6.2%
Corpus & Uterus	203	5.6%
Colon & Rectum	152	4.2%
Brain & CNS	158	4.3%
Non-Hodgkin Lymphoma	147	4.0%
Pancreas	102	2.8%
Other	752	20.7%

Total : 3,635

MALE (N=3,094)

Primary Site	Total	Percent
Prostate	423	13.7%
Lung & Bronchus	404	13.1%
Melanoma	298	9.6%
Colon & Rectum	151	4.9%
Non-Hodgkin Lymphoma	177	5.7%
Oral Cavity & Pharynx	184	5.9%
Urinary Bladder	135	4.4%
Kidney & Renal Pelvis	129	4.2%
Brain & CNS	122	3.9%
Other	941	30.4%

Total : 3,094

2016 TOP TEN CANCER SITES AT SMILOW CANCER HOSPITAL
ANALYTIC BY GENDER

Publications from Yale Cancer Center Members

June 2012 – July 2017

3653 publications by members

695 - High Impact Publications IF>10

73 - *Journal of Clinical Oncology*
9 - *New England Journal of Medicine*
35 - *Cell*
22 - *Science*
35 - *Nature*
123 - *Nature* specialty journals
14 - *Journal of Clinical Investigation*
29 - *Journal of the National Cancer Institute*
27 - *Molecular Cell*
19 - *Immunity*
33 - Blood
26 - Lancet

YaleNewHaven**Health**

Smilow Cancer Hospital

333 Cedar Street, P.O. Box 208028, New Haven, CT 06520-8028

Yale CANCER CENTER

A Comprehensive Cancer Center Designated by the National Cancer Institute

YaleNewHaven**Health**

Smilow Cancer Hospital

333 Cedar Street, P.O. Box 208028, New Haven, CT 06520-8028

Yale CANCER CENTER

A Comprehensive Cancer Center Designated by the National Cancer Institute