breakthroughs

THE YEAR IN REVIEW

YALE CANCER CENTER
SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

40 & five

Yale Cancer Center celebrates forty years • Smilow Cancer Hospital turns five

yale cancer center

Thomas J. Lynch, Jr., MD
Director

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

Renee Gaudette
Director, Public Affairs and Marketing

art + design

Peter Baker Studios LLC
pbakerstudios.com

contributors

Writers
Emily Fenton
Steve Kemper
Jill Max

Photographer
Peter Baker
pbakerphoto.com

Breakthroughs is published annually to highlight research and clinical advances from Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven.

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

Editorial Office
Yale Cancer Center
100 Church Street South, Suite 160
New Haven, CT 06519
renee.gaudette@yale.edu

40 & five

November 2014 marked five years since the opening of Smilow Cancer Hospital at Yale-New Haven! While our initial objectives of building a cancer hospital that redefines excellence in patient-focused care and research have been met we continue to find new opportunities for translational research and ways to make Smilow even better. At the same time, we are also celebrating a significant milestone at Yale Cancer Center - 40 years of our comprehensive cancer center designation from the National Cancer Institute. The combination of Smilow and YCC has allowed us to bring advances from our labs to expand the number of cutting edge treatment and prevention strategies available to our patients.

This past year, we were welcomed into the National Comprehensive Cancer Network (NCCN) as a main member institution. As many of you know, NCCN is a prestigious group of Cancer Centers who come together to set national guidelines for cancer care and I am pleased that our faculty can now share their expertise on the NCCN guideline setting committees.

Our research efforts in 2014 were headlined by continued progress in immunotherapy research. Mario Sznol, MD presented at ASCO on the long term efficacy of combination immunotherapy for patients with advanced melanoma, while Roy Herbst, MD, PhD and Daniel Petrylak, MD published in Nature on positive outcomes using immunotherapy treatment for both advanced lung cancer and bladder cancer.


Roy S. Herbst, MD, PhD


Melinda Irwin, PhD

Cancer prevention research is a priority, with our partnership with Yale School of Public Health as our foundation. Melinda Irwin, PhD has built a national reputation for her expertise on exercise and diet and its impact on cancer and recurrence. Her most recent publications, linking moderate exercise to reduce recurrence rates in breast cancer survivors; quality of diet and mortality in ovarian cancer survivors; and research that shows that exercise improves joint pain caused by aromatase inhibitors prescribed to breast cancer patients, will change the way we counsel our patients and cancer survivors.

I was very excited to welcome Patricia M. LoRusso, DO to our team in August as Associate Director of Innovative Medicine at Yale Cancer Center. Dr. LoRusso is widely regarded as a leading expert on developing new cancer drugs through clinical trials and has already been a wonderful addition to our leadership team. She brings more than 25 years of expertise in medical oncology, drug development, and early phase clinical trials to Yale.


Patricia M. LoRusso, DO


Valentina Greco, PhD

With Dr. LoRusso's focus on Phase I clinical trials, and our redoubled effort on clinical research over the last several years with leadership from Dr. Howard Hochster, Dr. Roy Herbst, and Dr. Paul Eder, we have increased the number of patients participating in clinical trials at Smilow Cancer Hospital three-fold in three years. We plan to build on this momentum into 2015 and beyond.

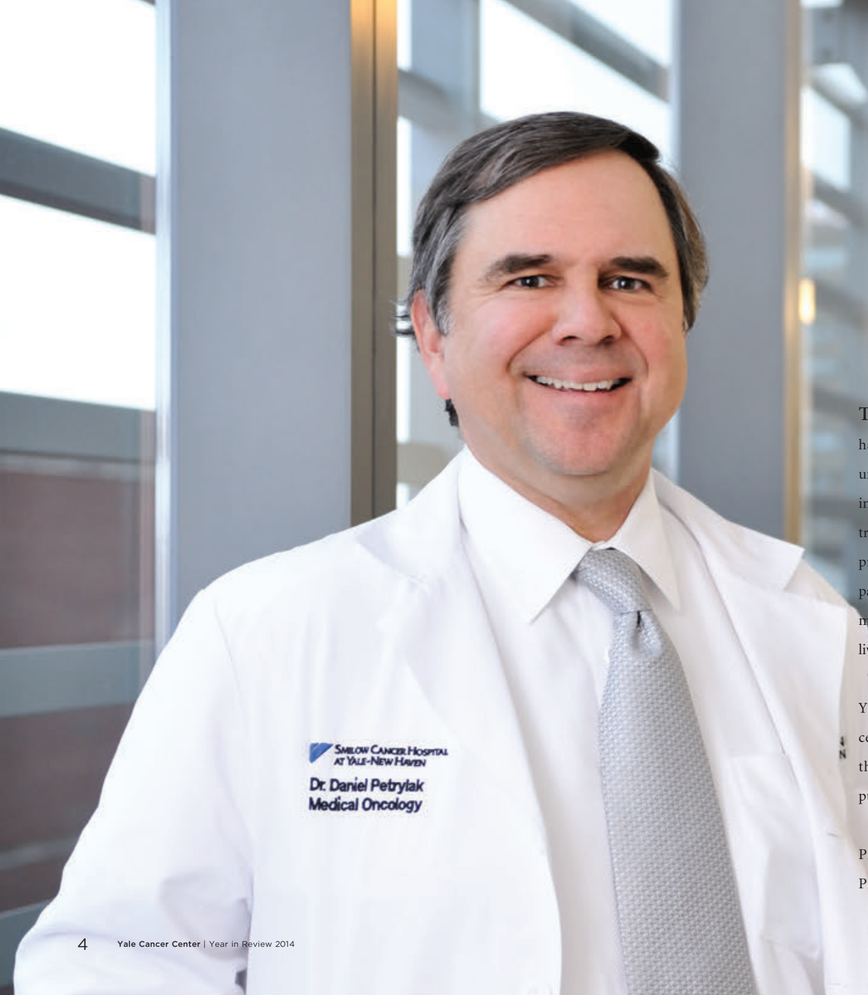
Finally translational research is based on advances in fundamental tumor biology. In 2014, I can think of no greater example than the work of Valentina Greco, PhD, whose laboratory is actively studying the stem cell dynamics in hair follicles. Dr. Greco is anticipating their study can shed light on which cells and signaling pathways go awry in the development of cancerous cells.

As we move into the New Year and our celebrations of five years of Smilow Cancer Hospital and 40 years of Yale Cancer Center, we will continue to expand our presence in Connecticut through our 11 Smilow Cancer Hospital 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 2015.

Sincerely,

Tom Lynch

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



Groundbreaking IMMUNOTHERAPY against bladder cancer

The therapeutic weapons against various cancers have been multiplying rapidly, but for patients with urothelial bladder cancer (UBC), the options have barely improved in 30 years. Worse, the standard chemotherapy treatment for UBC is too toxic for many patients, whose prognosis is already poor, and although the majority of patients initially respond, most relapse. These limitations may soon change if research on a new immunotherapy lives up to its exciting early promise.

The findings, which emerged from a Phase I trial at Yale Cancer Center and other international cancer centers, caused a stir in June at the annual meeting of the American Society of Clinical Oncology and were published in November in *Nature*.

In Yale's part of the trial, Dr. Daniel Petrylak, MD, Professor of Medicine and Urology, Clinical Research Program Leader for the Prostate and Urologic Cancers Program, and Co-Director of the Signal Transduction Program and his colleagues tested a new antibody on 15 patients whose metastatic urothelial bladder cancer had not been reduced by chemotherapy, typically the final option for such patients.

"We found a very high response rate," said Dr. Petrylak. "After twelve weeks of treatment, more than half of the patients had at least a 50 percent decline in their tumor measurements. Two patients had complete disappearance of the tumor. One patient had a cancerous lymph node in his neck, which has completely disappeared; this patient had been on three previous chemotherapies. This was the first time we've seen this dramatic a response in patients at this stage of the disease."

The patients were treated with a new synthetic 'checkpoint blocking' antibody called MPDL3280. It targets a protein named PD-L1 (programmed death-ligand 1) that is expressed by some patients' bladder cancers. About half of the people in Yale's study were positive for PD-L1 expression, and they responded most strongly to MPDL3280. PD-L1 binds to the surface of bladder cancer cells and sends out disinformation that lulls the immune system into shutting down, which allows the cancer cells to proliferate without interference. MPDL3280 prevents PD-L1 from binding to its receptors and thus short-circuits its deceitful signals. The immune system wakes up, detects the cancer cells, and sends T-cells to destroy them.

The responses among the patients at Yale were not only dramatic, but also prolonged. The trial was designed to treat the patients every three weeks for up to a year, but that has been extended, explained Dr. Petrylak, "because the patients' tumors are still responding, and because we really don't know the optimal duration at this point."

One of his patients, Peter Ehmer, now 44, was diagnosed in May 2013 with stage III bladder cancer. He had three months of chemotherapy and surgery to remove his bladder and prostate. He then participated in a different clinical trial at Yale. Nevertheless, two lymph nodes continued to grow. After three treatments with MPDL3280, he had a CT scan.

"Dr. Petrylak called within an hour," said Mr. Ehmer, "to say that the lymph nodes had not just shrunk but disappeared. I was very emotional. I called my wife right away and shared the news with my two kids when I got home. I've been through a lot in the last year and a half, and it's just such a weight off my shoulders."

Mr. Ehmer also confirms another pleasing finding: the side effects of the new immunotherapy, mainly fatigue, are far less severe than those common in chemotherapy.

These strong Phase I findings led the U. S. Food and

Drug Administration (FDA) to designate MPDL3280A a 'breakthrough therapy.' According to the FDA's website, this rare status "is intended to expedite the development and review of drugs for serious or life-threatening conditions." It is given only when early clinical evidence demonstrates that a therapy "may have substantial improvement on at least one clinically significant endpoint over available therapy." Since decades have passed without much progress in the treatment of urothelial bladder cancer, and since another 74,000 Americans will be diagnosed with bladder cancer in 2014, breakthrough therapies are desperately needed for this disease.

MPDL3280A is the newest of several anti-PD1 therapies designed to silence the false signals that turn off the immune system's radar and allow some cancers to grow. Other trials at Yale have found that anti-PD-1 therapies are effective against melanoma, kidney cancer, and non-small cell lung cancer. One of these drugs, nivolumab, was recently approved in Japan for treatment of melanoma. Like MPDL3280A, nivolumab works by thwarting PD-L1, which allows the immune system to switch back on and dramatically shrink tumors. The effects of the antibodies can be long-lasting; the therapies may cause the immune system to produce 'memory lymphocytes' that aren't tricked by the cancer cells' false signals.

Dr. Petrylak recently completed a Phase II trial on MPDL3280A at Yale, but can't yet discuss the findings. He foresees most bladder cancer patients using MPDL3280A in conjunction with chemotherapy. For patients who can't tolerate chemotherapy, however, the new antibody could become a first-line treatment. "We need to sort out the factors that will lead to a response and give patients a durable response," said Dr. Petrylak.

Dr. Petrylak's next step is to look for the optimal sequences and combination of therapies, including surgery, MPDL3280A, and chemotherapy. "We're going to do a variety of sequencing trials to see how we can best utilize this antibody," said Dr. Petrylak, "such as bringing in the drug prior to surgery." He expects these trials to be underway within a year.

"Immunotherapy," he added, "is the most exciting area of genitourinary cancer research. I can see this becoming the standard of care at some point. It's changing the whole field."

"Immunotherapy is the most exciting area of genitourinary cancer research. I can see this becoming the standard of care at some point. It's changing the whole field."

Peter and Alaina Ehmer

PAVING THE WAY FOR THE FUTURE:
HENRY BAKER'S *Tale of Triumph*

Henry Baker

Jenna and Brendan Baker were faced with the most difficult challenge of their life when their seemingly healthy two year old son was diagnosed with cancer. He went to the pediatrician with a fever that was not responding to the normal remedies. Results of a blood test raised suspicion for cancer and immediately Henry was sent to the Emergency Department at Yale-New Haven Children's Hospital where doctors confirmed his diagnosis. Acute lymphoblastic leukemia (ALL) they were told, which at the time meant nothing more to them than the fact that their son was sick, and they were in for the fight of their lives.

Thankfully, Dr. Gary Kupfer, Professor of Pediatrics (Hematology/Oncology) and of Pathology, and Section Chief of Pediatric Hematology/Oncology, was on call that night, and met with Henry and his parents. Henry spent 10 days in the hospital, most of which was focused on getting him strong enough for treatment.

"During Henry's time in the hospital it was about his care and getting him ready for treatment, but also about educating us on what this all meant. We didn't feel lost once we were sent home, which was so important," said Jenna. "They made sure to fully educate us on what symptoms to watch out for, and how to care for him. Henry was too young to tell us exactly what he was feeling, so we had to be vigilant, and they gave us the tools to do that."

ALL is a fast-growing cancer of lymphocyte-forming cells called lymphoblasts. Around 80 percent of children are diagnosed with pre B-cell ALL as opposed to T-cell ALL, and the "pre-B" form of ALL is the type Henry was diagnosed with. Henry's presenting age, white blood cell count, and leukemia subtype, qualified him for a clinical trial through the Children's Oncology Group (COG).

The COG enables members of the Yale Pediatric Hematology and Oncology Program to work cooperatively with other academic health centers to conduct large-scale studies. Because childhood cancer is relatively rare, medical centers must work together to compile enough data. Yale's participation also ensures access to the newest and best treatments available.

"There is a long history of clinical trials in pediatric oncology," remarked Dr. Kupfer. "It is very different when compared to adult cancer care. Clinical trials first began with pediatric patients and in 1948 agents given to pediatric patients became the first drugs to induce remission in children with ALL. We recognize the population is small, and the importance of collaborating with other institutions."

Henry had a central line and port put in for easier blood draw and to avoid any damage to his surrounding tissue during chemotherapy. Henry's parents were taught how to handle the port to avoid infection, and Henry received oral chemotherapy at home every day, and intravenously through his central line at the hospital periodically for 40 months.

"It was very stressful to have to make the decision to put Henry on a clinical trial," said Brendan. "When you hear the term childhood cancer you think you have an idea of what you are in for, but we really had no idea. Living close to New York City and Boston, we met with other doctors, but realized that Smilow was a special place. We were confident that our son was not only getting the best possible medical care, but also the best comprehensive care that included us as a family."

Henry responded very well to the treatment protocol, which was developed to minimize long-term side effects without sacrificing cure. Henry's parents felt comfortable that a clinical trial was the right thing for their son, not only because of his type of cancer, but also because by participating in a trial some good would come from Henry's journey and he would have an impact on the future.

Jenna and Brendan commented that when your child has cancer it is an incredible stress on every aspect of life. Henry was going through the treatments, but they took on the mental burden as if they themselves had cancer. Henry has a twin sister and two older sisters that were in 2nd and 5th grade when he was diagnosed. The Pediatric Hematology and Oncology team partners with psychologists, psychiatrists, social workers, and child life specialists who offer an array of psychosocial services to children receiving cancer care, along with their families. They talked with Henry's older sisters and explained things in a way they could understand, and answered their questions.

Dr. Kupfer explained that a large part of his role is to guide the family through all of the difficult decisions and treatments. The bond formed goes beyond the typical doctor-patient relationship that he learned about in medical school. "You are caring for, and hopefully curing their child of a life-threating illness, and you cannot help but become connected, and this is a very special family. They rose to the challenge that was put in front of them, despite the normal fears and anxieties that any parent would have."

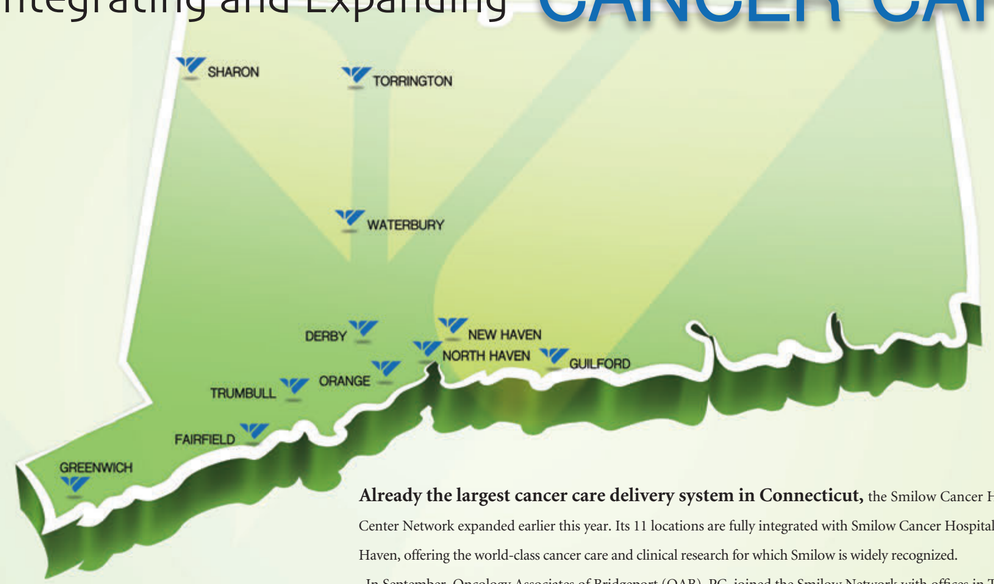
Now six years old, Henry likes to share his story with others and has even spent time in the classroom with Yale medical students. For him, this has been life up until now. Henry went to school as much as possible, which is always a high priority of Dr. Kupfer's for his patients. His parents commented that although he does not fully comprehend what he went through right now, some day he will and the courage and strength he showed at such a young age will be fuel for him.

"We are still healing as a family a year after his last treatment. It is a process and will always be a part of our lives. The effect is widespread and every hug means something different, every puzzle on the floor, every moment spent with my children is precious," said Brendan.

Jenna commented, "It is a part of who Henry is and who he will become. We talk about it as much as he wants, without dwelling on it. We can't help but think how none of this would have been possible without Dr. Kupfer and his team. You don't get the level of care we received just anywhere. It was truly amazing and everyone knew Henry as a little boy, not as a cancer patient. They carried us through the darkest time, and for that we are forever grateful."

"You don't get the level of care we received just anywhere. It was truly amazing and everyone knew Henry as a little boy, not as a cancer patient."

Integrating and Expanding CANCER CARE ACROSS CONNECTICUT



Already the largest cancer care delivery system in Connecticut, the Smilow Cancer Hospital Care Center Network expanded earlier this year. Its 11 locations are fully integrated with Smilow Cancer Hospital at Yale-New Haven, offering the world-class cancer care and clinical research for which Smilow is widely recognized.

In September, Oncology Associates of Bridgeport (OAB), PC, joined the Smilow Network with offices in Trumbull and Fairfield. The five OAB physicians continue to see patients in these locations, which have been undergoing renovations and expansion to provide improvements that would have otherwise been impossible, such as on-site pharmacy services, upgraded facilities for chemotherapy infusion, and improved safety standards.

Integrating with Smilow has brought increased clinical research activity to all of the Care Centers, with clinical trial accrual more than doubling in 2014. "The Care Center faculty are incredibly motivated and real champions for research," said Anne Chiang, MD, PhD, Chief Medical Officer for the Network and Assistant Professor of Medicine (Medical Oncology). "There's a degree of confidence from both the main campus and faculty physicians on site to feel comfortable opening trials." She noted that earlier this year, a Care Center recruited the first patient to the national Lung-MAP trial, a groundbreaking study for patients with advanced squamous cell lung cancer that is expected to involve more than 200 medical centers during the next five years.

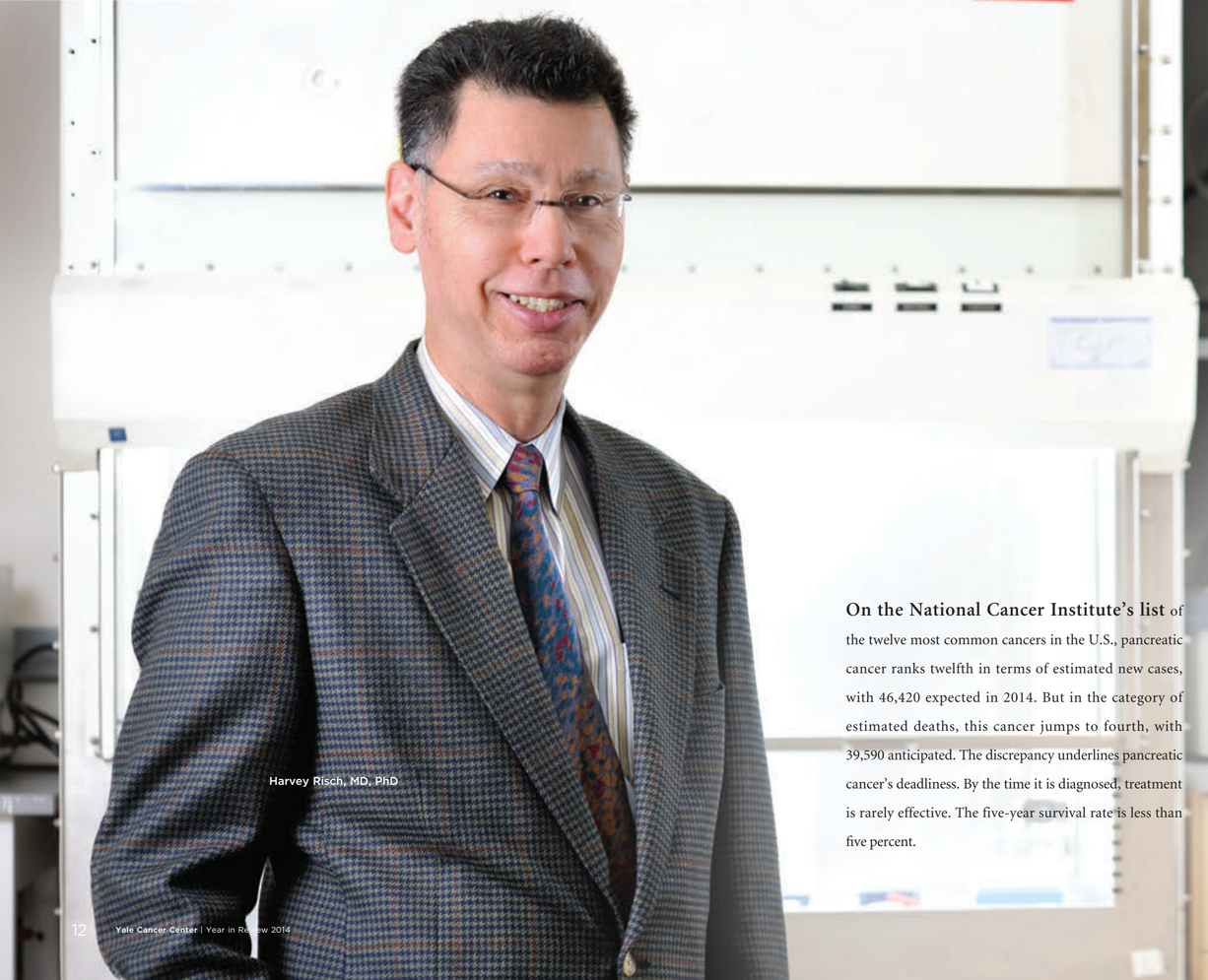
Participating in a clinical trial used to mean that patients would have to leave the care of community physicians, a barrier to accrual that is particularly challenging in minority populations, where participation in adult cancer trials is just three percent. "I have patients who never would have thought about participating in clinical research who have been able to get a cutting edge molecular test that they never would have been able to afford," said Andrea Silber, MD, an oncologist at the Smilow Cancer Hospital Care Center on Yale-New Haven Hospital's Saint Raphael Campus in New Haven. "It's different when they're participating in a trial with doctors and nurses that they know." Almost half of the patients in her practice are from diverse populations and are helping to answer many clinical questions that require this kind of participation.

Besides clinical research, integration across the Smilow Network has brought a host of initiatives aimed at improving the quality of patient care and safety. One example is the innovative telepharmacy model developed to provide sites with the same high pharmaceutical standards available at Smilow Cancer Hospital. In this program, a central team of pharmacists oversees the preparation of chemotherapeutic agents by technicians at the Care Centers, freeing the on-site pharmacists to provide personalized care. This initiative earned Yale-New Haven Hospital the 2014 Award for Excellence in Medication-Use Safety by the American Society of Health-Systems Pharmacists.

The Network also provides patients with access to subspecialty expertise that would not otherwise be available locally. "One of the biggest advantages of this affiliation is it allows us to care for patients in the community while feeling fully supported in terms of rare cancers or common cancers when there are areas of uncertainty as to the optimal treatment," said Neal Fischbach, MD, a medical oncologist who practices in the Trumbull and Fairfield locations. The number of cases presented at tumor boards from the community has increased from about 30 to about 180 since launching the Network in 2012.

The push to standardize care across the Network has involved implementing a single electronic medical record across the sites, as well as an effort to improve quality. Smilow participated in the American Society of Clinical Oncology's Quality Oncology Practice Initiative (QOPI), a quality assessment and improvement program aimed at promoting excellence in cancer care. The Smilow Cancer Care Center in Waterbury has received QOPI certification and Smilow recently applied for certification across the entire Network. Identifying, developing, and implementing such improvements across the Smilow Network widely benefits patients and has already increased patient satisfaction.

Efforts over the last two years to integrate the Care Centers, refine the transition from community practices, and build the infrastructure for operations, quality, and clinical research have resulted in an integrated N etwork with 28 oncologists, 250 staff members and over 7,000 visits to Care Center medical oncologists per month. "Now we're moving into the exciting second phase," said Dr. Chiang, "where we're starting to see the benefits and growth of what has been planted."



Harvey Risch, MD, PhD

A Surprising Defense Against PANCREATIC CANCER

On the National Cancer Institute's list of the twelve most common cancers in the U.S., pancreatic cancer ranks twelfth in terms of estimated new cases, with 46,420 expected in 2014. But in the category of estimated deaths, this cancer jumps to fourth, with 39,590 anticipated. The discrepancy underlines pancreatic cancer's deadliness. By the time it is diagnosed, treatment is rarely effective. The five-year survival rate is less than five percent.

A study published last summer by Harvey Risch, MD, PhD, Professor of Epidemiology, and several colleagues signals a promising, inexpensive possibility for changing those numbers: aspirin.

The population-based study used data collected from 362 pancreatic cancer patients diagnosed between January 2005 and August 2009 in 30 Connecticut hospitals. It found that patients who habitually took low-dose (75 to 325 milligrams) or regular-dose aspirin significantly reduced their risk of pancreatic cancer. The study also uncovered a correlation between the length of time that people took aspirin and the amount of protection they built against the cancer. Those who began taking it three years before entering the study reduced their risk by 48 percent. After 10 years of regular use, the risk declined by 60 percent.

Dr. Risch also found the reverse correlation: patients who stopped taking aspirin within two years of entering the study were three times more likely to be diagnosed with pancreatic cancer than those who continued the regimen.

It has long been known that daily low-dose aspirin can cut the risk of cardiovascular disease. More recent research has associated the regular use of aspirin with lowered risk of certain cancers, including colorectal, esophageal, ovarian, and breast. Dr. Risch's investigation is the first to demonstrate a link between the duration of aspirin use and risk of pancreatic cancer.

Previous epidemiological studies of aspirin's effects on pancreatic cancer have been inconsistent, said Dr. Risch, most likely for two intersecting reasons, one related to history and the habits of the general public, the other to the nature of the cancer. Thirty years ago, most people took aspirin for temporary relief of pain, fever, or inflammation. That intermittent use made it difficult to study aspirin's long-term effects on disease. But in the mid-1980s, large numbers of people began taking daily low-dose aspirin to prevent cardiovascular disease. This consistent regimen created a population that researchers could investigate over time.

That's exactly what Dr. Risch and other scientists who study pancreatic cancer needed. "From initial cell damage, it takes 10 or 11 years for the formation of pancreatic cancer cells," explained Dr. Risch, "and it's usually another five years before the disease is diagnosed. So from the initiation of disease to diagnosis can be 15 years. Since the general population didn't begin using low-dosage aspirin until the mid-1980s, you wouldn't expect to see any effect on pancreatic cancer until 2000 or 2005 at the earliest, which is why we collected data between 2005 and 2009. We're now in a much better position to start evaluating aspirin usage and risk."

"Anything that cuts the risk of cancer in half is a substantial benefit to the population."

Dr. Risch expected to find an association in the recent study, but the results startled him. "Anything that cuts the risk of cancer in half is a substantial benefit to the population," he said.

Researchers don't yet understand how aspirin inhibits cancer development. The current theory credits the compound's anti-inflammatory properties. We know that inflammation stimulates cells to reproduce more frequently, which can cause genetic alterations that lead to cancer. Aspirin might hinder the inflammation and cell-stimulation that can set off a chain reaction ending in disease.

Dr. Risch thinks that other explanations are also worth exploring. Aspirin works against cardiovascular disease because of its effects on platelets and blood clotting. "That might be relevant for cancer occurrence," he said, "if it works by some mechanism or some other pathway that we haven't established yet."

Despite Dr. Risch's findings and similar studies, both Dr. Risch and the American Cancer Society don't recommend taking a daily aspirin solely as a preventative against pancreatic cancer, because of the risks associated with long-term use of aspirin, such as gastrointestinal bleeding and stroke. About four or five percent of the general population would suffer serious consequences from long-term use of aspirin, whereas only 1.5 percent of the population will get pancreatic cancer. So for the general population, the risks outweigh the benefits.

Yet Dr. Risch is convinced that daily low-dose aspirin should be considered by people with family histories of pancreatic cancer or other cancers and diseases. For instance, about 10 percent of the general population will get colorectal cancer, and 25 to 30 percent will develop cardiovascular disease.

"Aspirin is cheap and well tolerated and seems to reduce the risk of a number of cancers," he said, "so maybe half the population would benefit from a daily low-dosage regimen. Each person has to evaluate the risks and benefits, and discuss them with their healthcare provider. Like everything else today, it has to be tailored a little carefully."

Meanwhile Dr. Risch is looking for ways to detect pancreatic cancer earlier, before little can be done for the patient. He is developing a screening process to predict a patient's risk two or three years before diagnosis.

"For instance, the test could determine that you might have a thirteen percent chance of diagnosis within the next five years," said Dr. Risch, "and on that basis you could choose to have a more aggressive workup to see if there's anything present. It's not clear whether this would make a big difference in terms of outcomes, but advancing surgery by two or three years may help. It's a way to see if we can move the clock back a little."

Dr. Risch's collaborators in the study included Samantha Streicher, a doctoral student in his lab, and Dr. Lingeng Lu and Dr. Mark Kidd at Yale Cancer Center, and Dr. Herbert Yu at the University of Hawaii Cancer Center.

Donald M. Engleman, PhD

Turning Cancer's Metabolism Against Itself

Tumors, by their very nature, are acidic, and the most acidic cancers are also the most aggressive. A team of scientists at Yale Cancer Center, has developed a way to use a tumor's acidity to guide drug therapy directly into its cells.

Because acidity is common across all tumors, this new delivery system also outflanks the problem of tumor heterogeneity, which often allows cancer cells to escape therapies aimed at a specific biomarker. But cancer can't escape its basic acidic metabolism. "The only way the tumor could become resistant," said Donald M. Engelman, PhD, Eugene Higgins Professor of Molecular Biophysics and Biochemistry, "is to stop growing, which is fine with everybody."

The breakthrough demonstrates the multiplier effect of combining insights from several disciplines to create something revolutionary. Nearly 20 years ago Dr. Engelman's lab discovered that a small piece of soluble protein called a pHLIP peptide would spontaneously insert itself across a membrane in an acidic environment. "But what I didn't know until mid-2005 or 2006," said Dr. Engelman, "was that tumors are acidic." This information came from colleagues Dr. Oleg Andreev and Dr. Yana Reshetnyak, now at the University of Rhode Island, who wondered if pHLIP would enter tumors. Dr. Engelman began exploring the idea.

Meanwhile two other Cancer Center researchers—W. Mark Saltzman, PhD, Goizueta Foundation Professor and Chair of Biomedical Engineering, and Frank J. Slack, PhD, formerly of the Yale Cancer Genetics and Genomics Program and now at Harvard—were collaborating on a project. Dr. Slack's lab had developed a genetically engineered mouse model for lymphoma, and Dr. Saltzman's lab had designed technology capable of delivering drugs via nanotechnology.

Which leads to another key collaborator: Peter M. Glazer, MD, PhD, Robert E. Hunter Professor and Chair of Therapeutic Radiology. Dr. Glazer's lab is expert at designing and synthesizing analog treatment compounds. Dr. Glazer provided peptide nucleic acids (PNAs) that Dr. Saltzman loaded onto nanoparticles that targeted lymphoma in Dr. Slack's mice. Early experiments indicated that the PNAs slowed down the growth of lymphomas by interfering with the tumor's microRNAs (miRs). These are small but influential signaling RNAs that shut down tumor suppressors and thus are critical to the spread of cancer. The principal miR implicated in lymphoma is miR-155.

This is when Dr. Engelman joined the collaboration. He offered a new method of delivery—pHLIP, the peptide whose attraction to acidity allows it to penetrate cancer cells. "The beauty of pHLIP," said Dr. Engelman, "is that it essentially uses the acidity of the tumor as a biomarker." The team loaded pHLIP with anti-miR PNAs aimed at switching off signals from miR-155. "It's like a guided missile delivering a warhead," explained Dr. Engelman. "The missile is guided by acidity, the propulsion system is the pHLIP, which penetrates the defensive system of the cancer cell, and the PNA is the warhead."

When they tested this weapon on Dr. Slack's mice, the tumors died and metastasis was suppressed. Because the weapon attacked only cancer cells, side effects on surrounding cells were minimal. The team took a video of a cancerous mouse, unable to move and clearly almost dead. Three days after being treated, this same mouse looked transformed, ambling around its cage.

"So it was a constellation of research by four labs," said Dr. Engelman. "Each of us contributed expert knowledge that made the whole enterprise work, and it was all made possible by the Cancer Center, which funded it and brought us together."

Dr. Engelman is excited by the delivery system's possibilities. Many hundreds of microRNAs have been identified in human cells, and if science can identify their functions, he says, "then we could throw switches for all kinds of purposes, not just for treating cancer."

Suchitra Krishnan-Sarin, PhD

The Growing Use Of E-Cigarettes Among Youth

Electronic cigarettes, which deliver a dose of nicotine via vapor instead of smoke, were not introduced to the marketplace until 2007 but have spread like wildfire. Estimated sales of e-cigarettes are on pace to grow from $1.7 billion in 2013 to $2.5 billion in 2014.

More and more young people are among those buying, according to Suchitra Krishnan-Sarin, PhD, Associate Professor of Psychiatry and Co-leader of the Yale Tobacco Center of Regulatory Science (TCORS). The Yale TCORS, created by a $20 million federal grant in 2013, is one of 14 such research centers being funded by the Food and Drug Administration (FDA) and the National Institutes of Health to study the risks of e-cigarettes.

At the moment, no one knows what is in the vapors that millions of people are pulling into their lungs, what is in their exhalations, or what the effects are on health. None of this is regulated because there is not enough research available to base regulations on. "To get to that point we need sufficient scientific evidence," said Dr. Krishnan-Sarin, "and we don't have it yet."

Yale's TCORS is focused on the role played by flavors such as menthol, cherry, and chocolate that are added to the tobacco in e-cigarettes. The Center's scientists are studying whether flavors make e-cigarettes more enticing, especially to youth. They are investigating whether these flavors change behaviors and perceptions about the risks of tobacco, and also whether they increase the likelihood of nicotine addiction.

In 2012, Dr. Krishnan-Sarin and her colleagues began collecting information about e-cigarettes in 10 Connecticut middle schools and high schools. Through focus groups and anonymous surveys, the researchers are compiling data about use-rates and why kids are attracted to these products.

"We are seeing significant rates of increase in the use of these products by youth," said Dr. Krishnan-Sarin. In the most recent data, 25 percent of the high school students had tried e-cigarettes, and 12 percent had used them in the past month. "That's substantial," she said. Among middle school students, 3.5 percent had tried e-cigarettes, 1.5 percent in the past month. Perhaps equally alarming, among those who had not yet tried e-cigarettes, 32 percent of high schoolers and 26 percent of middle schoolers said they might try them in the future.

This echoes the findings of the latest National Youth Tobacco Survey by the Centers for Disease Control and Prevention, which found that the number of youths who had never smoked but had used e-cigarettes nearly tripled between 2011 and 2013. Worse, half of the kids using e-cigarettes expected to start smoking regular cigarettes within a year.

The Yale researchers have found that e-cigarettes are not used just by cigarette smokers, but by kids who have never smoked a regular cigarette. "Many state that if the products didn't have flavors, they would never have tried them," explained Dr. Krishnan-Sarin. E-cigarettes are also being advertised on television, which cannot be used to advertise cigarettes.

The manufacturers of e-cigarettes tout them as an alternative for smokers who want to quit, and as a cleaner form of nicotine delivery, far less toxic than the carcinogenic chemicals in tobacco smoke. Researchers are looking into those claims.

Meanwhile, notes Dr. Krishnan-Sarin, "vaping shops" are offering unregulated electronic products some of which are being shown to deliver much higher nicotine levels than a regular cigarette. "We know so little about e-cigarettes," she said, "and there's this increase in use-rates among youth, which is very concerning because you may be creating a generation that is addicted to nicotine. Will they then move on to regular cigarettes?"

It will be another few years, she added, before the FDA has enough scientific evidence from Yale and the other Tobacco Centers to consider writing regulations.

How Immune Cells Go Rogue

Oscar R. Colegio, MD, PhD

As a waste by-product of tumor metabolism, lactic acid has largely been overlooked by cancer scientists. New research at Yale Cancer Center, however, demonstrates that this common chemical compound, produced by the rapid division of neoplastic cells, transforms immune cells called macrophages into abettors of tumor growth. The researchers also identified an enzyme within tumor-associated macrophages (TAMs) that plays a critical role in promoting tumor development. Further, they discovered that removing this single enzyme, called arginase 1 (ARG1), from a macrophage decreased the size of tumors by half.

"That speaks to the important role of macrophages in tumor progression," said Oscar R. Colegio, MD, PhD, Assistant Professor of Dermatology. "They make up only one to five percent of the cells in our tumor models, yet eliminating one enzyme from that cell type reduces tumor size significantly."

The research took seven years. Dr. Colegio's postdoctoral research mentor and now main partner throughout the investigation is Ruslan M. Medzhitov, PhD, David W. Wallace Professor of Immunobiology and Investigator of the Howard Hughes Medical Institute. At the beginning, they knew that macrophages are found in all tumors, and that the more of them a tumor contains, the worse the prognosis, which suggests that tumors somehow recruit macrophages and corrupt their normal function as tumor suppressors, turning them into promoters of cancer. Dr. Colegio and his colleagues set out to find the signals that instructed macrophages to become cancer's allies.

"The recruited macrophages act as if there's a wound that won't heal or a tissue that's stressed," explained Dr. Colegio, "so they produce growth factors and vascularize the tumor to restore homeostasis. But that can't happen in neoplasia, so the macrophage ends up feeding the tumor's growth."

The research team learned that macrophages are recruited early in the tumor's development. Through a series of in vitro experiments on macrophages, the scientists detected two proteins critical for tumor growth: a signaling protein called vascular endothelial growth factor (VEGF), and the enzyme arginase 1 (ARG1). Further research revealed that these two proteins used a signaling pathway mediated by a transcription factor called HIF1A (hypoxia-inducible factor 1-alpha). The signals and proteins functioned to convince the macrophages that they were in a state of hypoxia, stimulating the macrophages into furious activity that helped the tumor grow.

At that point, they still didn't know the primary activator. More investigation took them beyond proteins into molecules, and finally to the surprising source within the tumor: lactic acid. Experiments in mouse models led to the insight that knocking out Arg1 diminished tumor size.

For Dr. Colegio, all of this links to his clinical work caring for recipients of solid organ transplants. To prevent rejection of the transplanted organ, these patients must take strong immuno-suppressant drugs, but the drugs cause a one hundred-fold increased risk of numerous, aggressive skin cancers, mostly squamous cell carcinoma. That's what led Dr. Colegio to study tumor-activated macrophages.

He's now analyzing fresh skin cancers taken from patients, and has found that even in very early stages of skin cancer, the number and density of macrophages is the same as in the later invasive phases. "So we suspect that macrophages help to coordinate the invasion process," said Dr. Colegio, "and if they play a role in that, this may be a target that has not yet been exploited in anti-cancer therapies, or in early cancers to try to prevent progression. We could target either the macrophages or use an arginase inhibitor to knock out the enzymatic function that's vital to tumor progression."

Dr. Colegio is excited by the wider implications of his team's findings. The principles, he said, "will likely hold true not just specifically for one cancer type but more broadly across any proliferating tissue."

The Links Between HIV And Cancer

Walther Mothes, PhD

Most people think of cancer and HIV as diseases with little in common. But the two are strongly connected, said Daniel DiMaio, MD, PhD, Waldemar Von Zedtwitz Professor of Genetics and Deputy Director of Yale Cancer Center. "That's why HIV studies have always been an important part of our portfolio at the Cancer Center."

So it can be frustrating when asked why a cancer center is studying HIV. "It's mostly a matter of educating people," explained Dr. DiMaio.

That begins by understanding that HIV is a virus, and that some viruses cause cancer. Viruses cause about 15 percent of all cancers. Hepatitis B and C viruses account for most of the world's liver cancer. The human papillomavirus accounts for all of the world's cervical cancer and approximately 30% of head and neck cancers in the United States. Though a direct link between HIV and cancer hasn't yet been found, researchers have started to suspect that one exists.

The indirect links between HIV and cancer are well established. "There are at least three connections," said Walther Mothes, PhD, Associate Professor of Microbial Pathogenesis and newly appointed Co-Director of the Cancer Center's Molecular Virology program, who studies HIV.

First, notes Dr. Mothes, if HIV is left untreated, AIDS quickly weakens the immune system, opening the door to cancer viruses such as Kaposi sarcoma-associated human herpes virus-8 (HHV8), Epstein-Barr virus, and human papillomavirus. Second, even people whose HIV infection is controlled with antiretroviral therapy are more susceptible to cancer than the general population because their immune system remains compromised by the infection. Unsurprisingly, they have a higher incidence of cancers typical of AIDS, such as Kaposi sarcoma, but HIV also seems to amplify the activity of other virus-induced cancers, including anal, liver, and cervical cancers. "Cancer remains a leading cause of death among AIDS patients," said Dr. Mothes.

A possible third connection between HIV and cancer is also emerging. In HIV-infected patients who have been on antiretroviral therapy for many years, researchers are finding indications that the virus integrates into chromosomal DNA and causes clonal expansion of T-cells. "That's a precursor to the development of cancer," explained Dr. Mothes. There's a possibility that over time, in addition to HIV's indirect role as an immunosuppressant, the virus may become recognized as a direct carcinogen.

All of this is why new research has excited HIV scientists. To elude attack by the immune system, the virus mutates constantly and changes its shape. This protean quality has defeated all attempts to formulate a vaccine. Now Dr. Mothes and others have used electron microscopy to look deep into HIV and watch in real time as the virus changes shape and attacks cells.

The researchers saw how the virus infects: a surface spike protein penetrates a healthy cell and fuses with it. To escape detection, this protein stays closed as much as possible, opening only briefly to change shape and infiltrate another cell. "To infect a cell," described Dr. Mothes, "the virus needs to open up."

If researchers can devise a drug that keeps the spike protein closed, the virus can't infect. Scientists have discovered that some AIDS patients have developed "broadly neutralizing antibodies" that offer protection against the disease, but no one knew how the antibodies work. It now appears as if these antibodies block infection by locking the spike protein in the closed position.

This gives researchers a target for a vaccine. "It's a major advance," said Dr. Mothes. "If we can generate a vaccine to protect the population against HIV, and if patients no longer have to take antiretroviral medications, we would also relieve many people from the burden of cancer. That is one reason that it is important for a cancer center to include the study of HIV."

Blocking Metastasis In Breast Cancer

From a cancer cell's point of view, metastasis is a risky, complicated migration. First the cell must escape the primary tumor and launch itself into the bloodstream. Then it must find a way to exit this flow and establish itself on the shores of a distant organ. Finally it must develop the means to multiply and colonize a hostile foreign environment. Every stage is fraught with physiological hazards and requires a knack for adapting to new conditions.

Scientists have long been curious about how cancer cells survive their metastatic journey. The cells don't change their essential genetic nature, which is why breast cancer cells, for example, are recognizable wherever they land after metastasis. Rather, the cells rely on reversible modifications in gene expression through epigenetic changes, using enzymes that help them stay alive while moving from one environment to the next. But which enzymes? And how do those enzymes function in metastasis? Identifying these regulators of gene expression is the necessary first step to stop the migration of cancer cells.

A team at Yale Cancer Center led by Qin Yan, PhD, Associate Professor of Pathology, has discovered a regulating enzyme called RBP2 that breast cancer cells need in order to metastasize to the lung. "We found that not only is this enzyme implicated in metastasis," explained Dr. Yan, "but also that if you suppress it, metastasis is suppressed. That suggests that RBP2 is a good candidate for a targeted cancer therapy against metastasis." This is an exciting breakthrough, since breast cancer strikes more women than any other cancer and is particularly adept at aggressive metastasis, usually to the lungs, bones, or brain. Once this cancer metastasizes, the options for treatment dwindle, along with survival rates.

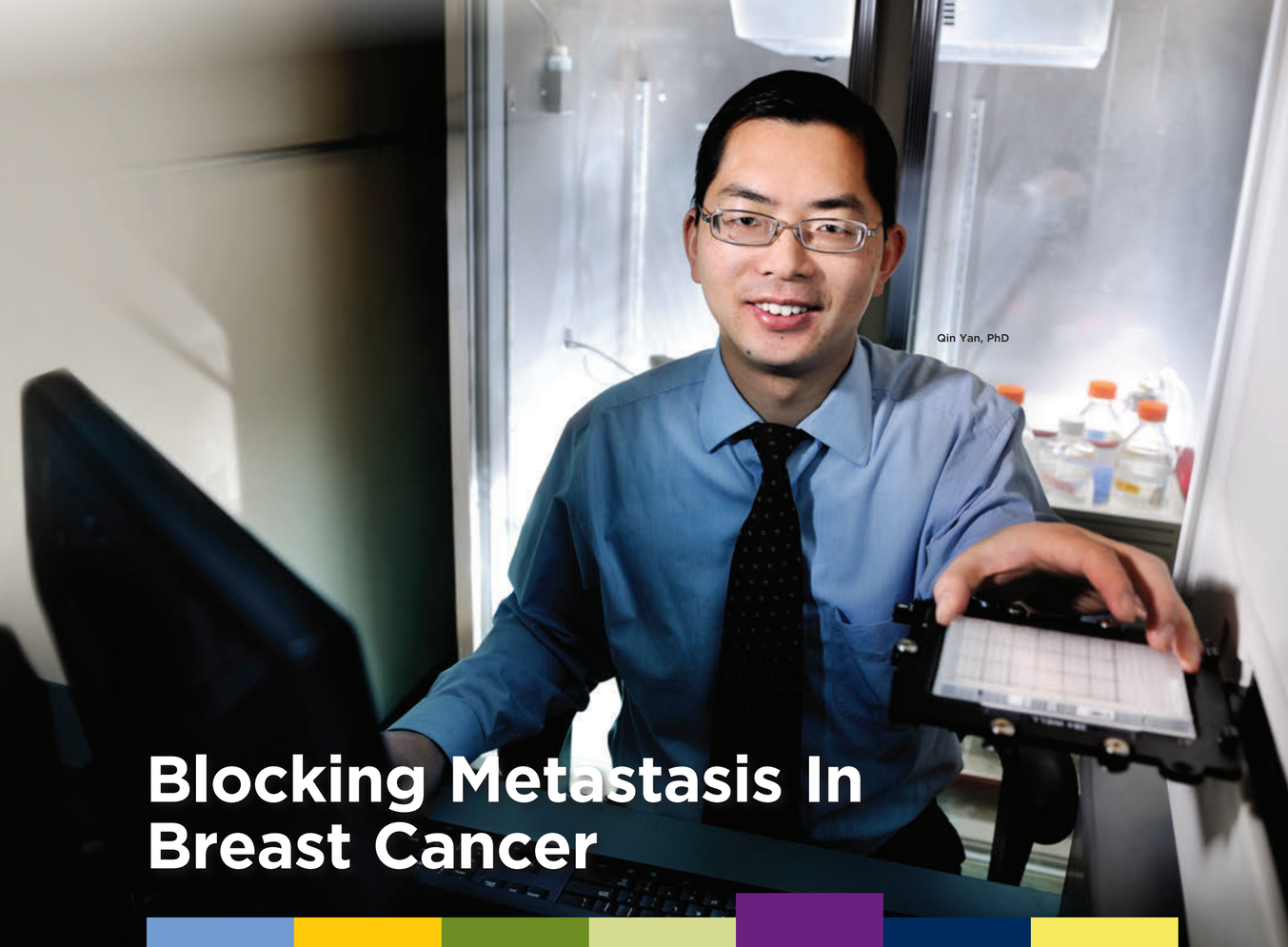
Tracking down RBP2 (also known as JARID1A or KDM5A) and deciphering its function took Dr. Yan and his colleagues three years. First they used gene expression datasets of breast cancer patients to identify RBP2 as a recognized regulator of metastasis. Then they did global genome-wide profiling to determine which genes were regulated by RBP2 and to confirm its importance. Next they completed cell-based assays, which confirmed that RBP2 expression is critical in breast cancer tumorigenesis and metastasis. Lastly they tested these findings in two mouse models, one of which required them to use a genetically engineered mouse model that Dr. Yan created. Experiments in the mouse models validated their findings derived from the clinical datasets.

Dr. Yan and his colleagues also began screening small molecules to look for inhibitors of RBP2. They identified some first-in-class compounds that modulate or suppress the enzyme's activity. "We are further developing those compounds so that we can use them in the clinic," said Dr. Yan.

Some of that work is being done through the National Cancer Institute's Experimental Therapeutics Program, called NExT, which aims to advance breakthrough discoveries in the laboratory into new therapies for cancer patients. Dr. Yan's team is taking a three-pronged approach. The first prong is using traditional medicinal chemistry, to search for derivatives of the inhibitory compounds that are more potent and specific. The second is an expansion of the initial molecular screening from 10,000 molecules to 100,000, again with the goal of finding stronger, more specific compounds. The third approach involves computational-based drug design for inhibitors of RBP2.

"We have already identified some better compounds," said Dr. Yan, "but in a year or so we hope to have much more potent ones." He and his colleagues will test the new compounds first in biochemistry assays, then in cells, then in mice. If all goes well, the next stage would be a clinical trial. Dr. Yan expects to see that in about three years.

Our hope is to take what we know from the clinic and run it through the experimental system, and after we know the mechanism and the inhibitors, we bring it back into the clinic, so we are learning in both directions."



Qin Yan, PhD

Ryan B. Jensen, PhD

The Interconnected Mysteries Of DNA Repair And Breast Cancer

The DNA in the nuclei of our cells gets tattered every day from forces within, such as free radical damage, and also from without, such as the sun's UV rays. The result is an estimated 20,000 DNA lesions per cell each day. The body's DNA repair system is superb at fixing these, but no system is perfect. If defective DNA is left unmended, it can cause cellular mutations that lead to cancer.

Ryan B. Jensen, PhD, Assistant Professor of Therapeutic Radiology and Pathology, is unraveling the connections between DNA repair, breast cancer, and ovarian cancer. His lab is looking for the instigating molecular events that trigger mutations by tracing their origins to the BRCA2 (Breast Cancer Susceptibility) gene. It is well established that women who inherit a mutation in BRCA2 are at high risk of developing breast and ovarian cancer. Without the BRCA2 mutation, for instance, women have a 12 percent chance of getting breast cancer; with the mutation, the risk jumps to 90 percent over a patient's lifetime. What's unclear is why BRCA2 mutations strike the breast and ovaries.

"No one has a clue why that is," said Dr. Jensen, "why it's not the lungs or the brain. That's a big mystery. My lab is doing basic research to understand the biology of what BRCA2 does, and what happens when it can't do its job. BRCA2 is a DNA repair protein that responds to DNA double-strand breaks. These physical breaks in the DNA helix are healed by BRCA2 through a complex process called homologous recombination. But if the breaks aren't repaired properly, you get mutations in the genes that drive the cancer process."

One reason for the mystery is that scientists didn't understand BRCA2 biochemistry. To study it would require, for starters, purifying the protein coded for by the BRCA2 gene. But the BRCA2 protein is large, unstable, and fragile, all obstacles to purifying it. Dr. Jensen and his colleagues worked on the problem for several years, and in 2010 became the first to succeed at purifying the entire BRCA2 protein. Using the same process, they are now purifying mutant forms of BRCA2 taken from patients.

That allowed the researchers to study the proteins without all the interfering noise within cells. They put the purified proteins—normal and mutant—into test tubes or in vitro assays, mixed them with broken pieces of DNA, and watched how they handled repair or failed to. The goal is to pinpoint how and why something goes wrong when BRCA2 is mutated, and why this defect leads cells down the path towards tumorigenesis in the breast or ovaries.

In addition to the biochemical research, Dr. Jensen's lab is studying BRCA2 genetics. Using breast and ovarian cells isolated from human patients, they can then treat the cells in tissue culture with various chemotherapy drugs, and study the cellular response of the BRCA2 gene. Most of the drugs cause DNA damage. Dr. Jensen wants to know what happens when BRCA2 is depleted from a breast or ovarian cell. "Does it instantly become genomically unstable? Does it die? If it doesn't die, how does it survive? Does it become a tumor cell? Those are the genetic questions we're trying to address."

Once Dr. Jensen and his colleagues have the biochemical and genetic answers, drug-makers will have targets for new therapies against breast and ovarian cancer. And perhaps other cancers as well.

"A failure in DNA repair," explained Dr. Jensen, " is probably the driving force behind all mutations that arise in cancer. DNA damage is an ever-present danger, and if these DNA repair genes are not working properly, you're getting more genomic instability and mutations. DNA repair genes are in charge of this process. If we can understand that process, we can develop new therapeutic avenues for treating cancer."

If we know that, a patient could come in and get the sequencing done, and then get the drugs that are most effective."

Silencing The Signals That Lead To Melanoma


Narendra Wajapeyee, PhD

Melanoma ranks among the most lethal cancers, causing about 80 percent of all skin cancer deaths. Scientists have traced most melanomas—nearly 70 percent of them—to mutations in the BRAF and NRAS genes. But what happens in the interval between the onset of these mutations and the proliferation of melanoma cells? What signals and mechanisms set off the cascade of responses that ends in skin cancer?

The answers to these questions, once unclear, have recently been answered by findings at Yale Cancer Center. Narendra Wajapeyee, PhD, Assistant Professor of Pathology, and his team have traced the connections. BRAF and NRAS cannot form tumors without the crucial contribution of a microRNA called miR-146a. The discovery, noted Dr. Wajapeyee, reveals one of melanoma's vulnerabilities and gives drug developers an obvious target. "They can test approaches against miR-146a," he said, "to see whether we can effectively cure metastatic melanoma."

Previous research has established that microRNAs (miRNAs) regulate gene expression and play a part in tumorigenesis and metastasis, but the miRNA activator in melanoma was unknown. Dr. Wajapeyee and his team worked for almost five years to reach their breakthrough. They began by analyzing melanomas to find the most common miRNAs upregulated by the BRAF and NRAS oncogenes. They identified the miRNA with the most elevated levels: miR-146a. But their work was just beginning.

They began studying miR-146a's downstream effects on signaling pathways that lead to melanoma. They learned that miR-146a targets a protein called NUMB and suppresses it. NUMB ordinarily regulates Notch, a receptor pathway favored by cancer. So when NUMB is suppressed and miR-146a begins overexpressing, the signals from Notch, now unregulated, get amplified. This prompts even heavier production of miR-146a, inducing skin cancer cells to proliferate and grow faster. Result: melanoma.

Next Dr. Wajapeyee and his team theorized that suppressing miR-146a would interfere with Notch signaling and disrupt the progression toward melanoma. Without help from miR-146a, Notch signaling was silenced and the melanoma cells stopped growing. "We found that miR-146a is required for BRAF and NRAS transformation," explained Dr.Wajapeyee, "and that they cannot form tumors without it."

The findings suggest a clear method of fighting melanoma: knock down production of miR-146a to stop it from blocking NUMB and activating Notch signaling, or target the Notch pathway itself. Dr. Wajapeyee noted that pharmacological antibodies that specifically inhibit Notch already exist, and these can be tested against melanoma cells. Unfortunately these older Notch inhibitors have strong gastrointestinal side effects.

"But the new Notch antibodies are highly specific," said Dr. Wajapeyee, "blocking only specific forms of Notch that are pro-oncogenic. They are highly effective and do not produce any GI-tract problems." He and his team, in initial testing on cell lines, found that the most effective treatment against melanoma was a combination of drugs that inhibited both the production of miR-146a and the Notch signaling pathway. He also foresees possibilities in combining these targeted therapies with immunotherapies.

Among all cancer types, he noted, melanoma has the highest number of mutations on its genome. "For that reason, the melanoma cells will find ways to escape most therapies. So it may be best to combine two or three approaches and kill them early on before they evolve.

Dr. Wajapeyee and his team are now using genomics and screening to identify a new target: the genes that allow melanoma cells to survive while circulating in the bloodstream after the primary tumor metastasizes. "If we can intercept these cells," said Dr. Wajapeyee, "we can make them die in the bloodstream and prevent metastasis."

Yale Cancer Center Leadership

Yale Cancer Center

Thomas J. Lynch, Jr., MD
Director

Daniel C. DiMaio, MD, PhD
Deputy Director

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

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

Howard S. Hochster, MD
Associate Director, Clinical Sciences

Melinda L. Irwin, PhD
Associate Director, Population Sciences

Patricia M. LoRusso, DO
Associate Director, Innovative Medicine

David F. Stern, PhD
Associate Director, Shared Resources

Anees B. Chagpar, MD
Assistant Director, Diversity and Health Equity

Peter G. Schulam, MD, PhD
Assistant Director, Surgery

Gary Kupfer, MD
Assistant Director, Pediatrics

Ruth McCorkle, RN, PhD
Assistant Director, Psychosocial Oncology

Jeffrey Sklar, MD, PhD
Assistant Director, Pathology & Tissue Acquisition Services

Edward Snyder, MD
Assistant Director, Membership

Yale Cancer Center Research Programs

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

Cancer Immunology
Lieping Chen, MD, PhD
Madhav V. Dhodapkar, MBBS

Cancer Prevention and Control
Melinda L. Irwin, PhD
Yong Zhu, PhD

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

Molecular Virology
Walther H. Mothes, PhD
Wendell G. Yarbrough, MD

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

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

Yale Cancer Center Shared Resources

Biostatistics
Xiaopan Yao, PhD

Cesium Irradiator
Ravinder Nath, PhD

Clinical Research Services
Howard S. Hochster, MD

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 at Yale-New Haven

Thomas J. Lynch, Jr., MD
Physician-in-Chief

Abe Lopman
Senior Vice President, Operations
Executive Director

Rogerio C. Lilenbaum, MD
Chief Medical Officer

Catherine Lyons, RN, MS
Executive Director, Smilow Patient Care Services

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

Michael D. Loftus
Vice President, Financial Operations

Arthur Lemay
Executive Director, Smilow Cancer Network

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

Smilow Cancer Hospital Clinical Programs

Brain Tumor
Clinical Program Leader:
Joachim M. Baehring, MD
Translational Working Group Leader:
Kevin P. Becker, MD, PhD

Breast Cancer
Clinical Program Leader:
Anees B. Chagpar, MD
Translational Working Group Leader:
Lajos Pusztai, MD, DPhil

Endocrine Cancers
Clinical Program and Translational Working Group Leader:
Tobias Carling, MD, PhD

Gastrointestinal Cancers
Clinical Program and Translational Working Group Leader:
Howard S. Hochster, MD

Gynecologic Cancers
Clinical Program Leader:
Peter Schwartz, MD
Translational Working Group Leader:
Alessandro D. Santin, MD

Head and Neck Cancer
Clinical Program Leader:
Wendell G. Yarbrough, MD
Translational Working Group Leader:
Barbara A. Burtness, MD

Hematology
Clinical Program Leader:
Steven D. Gore, MD
Translational Working Group Leader:
Madhav V. Dhodapkar, MD, PhD

Melanoma
Clinical Program Leader:
Stephan Ariyan, MD
Translational Working Group Leader:
Harriet Kluger, MD

Pediatric Oncology and Hematology
Clinical Program and Translational Working Group Leader:
Gary Kupfer, MD

Phase I
Clinical Program Leader and Translational Working Group Leader:
Joseph Paul Eder, MD

Prostate and Urologic Cancers
Clinical Program Leader:
Peter G. Schulam, MD, PhD
Translational Working Group Leader:
Daniel P. Petrylak, MD

Sarcoma
Clinical Program Leader:
Gary E. Friedlaender, MD
Translational Working Group Leader:
Dieter M. Lindskog, MD

Therapeutic Radiology
Clinical Program Leader:
Lynn D. Wilson, MD, MPH
Translational Working Group Leader:
Roy H. Decker, MD, PhD

Thoracic Oncology
Clinical Program Leader:
Frank C. Detterbeck, MD
Translational Working Group Leader:
Roy S. Herbst, MD, PhD

Yale Cancer Center Membership

Cancer Genetics and Genomics

Allen Everett Bale
Linda M. Bartoshuk
Susan J. Baserga
Lauren Paige Blair
Jean L. Bolognia
Marcus W. Bosenberg
Demetrios Braddock
Tobias Carling
Nancy Carrasco
Jaehyuk Choi
Lynn Cooley
Jose Costa
Bernard G. Forget
Alan Garen
Mark B. Gerstein
Antonio J. Giraldez
Murat Gunel
Shangqin Guo
Ruth Halaban
Stephanie Halene
Shilpa Hattangadi
Christos Hatzis
Erin Wysong Hofstatter
Josephine J. Hoh
Natalia B. Ivanova
Samuel G. Katz
Sajid A. Khan
Kenneth Kay Kidd
Yuval Kluger
William H. Konigsberg
Diane S. Krause
Rossitza Lazova
David J. Leffell
Peter Lengyel
Peining Li
Richard P. Lifton
Haifan Lin
Xavier Llor
Jun Lu
Shrikant M. Mane
Miguel A. Materin
James Michael McGrath
Karla Neugebauer
James P. Noonan
Manoj Pillai
Manju Prasad
Lajos Pusztai
Peter E. Schwartz
Emre U. Seli
Gerald S. Shadel
Jeffrey L. Sklar
Matthew Perry Strout
Hugh S. Taylor
Robert Udelsman
Scott Donald Weatherbee
Sherman Morton Weissman
Andrew Zhuo Xiao
Mina LuQing Xu
Tian Xu
Qin Yan
Hongyu Zhao

Cancer Immunology

Stephan Ariyan
Philip William Askenase
Kevin Patrick Becker
Jeffrey R. Bender
Alfred L. M. Bothwell
Richard Bucala
Lieping Chen
Debbie Chirnomas
Oscar Rene Colegio
Dennis L. Cooper
Joseph Edgar Craft
Peter Cresswell
Kavita Dhodapkar
Madhav V. Dhodapkar
Richard L. Edelson
Brinda Emu
Richard A. Flavell
Francine M. Foss
Jorge E. Galan
Michael Girardi
Earl John Glusac
Ann M. Haberman
Douglas John Hanlon
Paula B. Kavathas
Steven H. Kleinstein
Mark Joseph Mamula
Jennifer Madison McNiff
Ruslan M. Medzhitov
Eric R. F. Meffre
Deepak Narayan
Joao P. Pereira
Jordan Stuart Pober
Carla Vanina Rothlin
Nancy Hartman Ruddle
David G. Schatz
Stuart Evan Seropian
Warren D. Shlomchik
Brian Richard Smith
Edward Leonard Snyder
Mario Sznol
Robert E. Tigelaar

Cancer Prevention and Control

Kerin Bess Adelson
Steven L. Bernstein
Elizabeth H. Bradley
Brenda Cartmel
Anees B. Chagpar
Elizabeth Brooks Claus
Amy Joan Davidoff
Nicole Cardello Deziel
Robert Dubrow
Elizabeth A. Ercolano
Leah McArthur Ferrucci
Bonnie Elyssa Gould Rothberg
Cary P. Gross
Theodore R. Holford
Melinda Liggett Irwin
Beth A. Jones
Nina S. Kadan-Lottick
Jennifer M. Kapo
Anthony W. Kim
Tish Knobf
Suchitra Krishnan-Sarin
Stephanie Lynn Kwei
Donald R. Lannin
Steven B. Leder
Haiqun Lin
Shuangge Steven Ma
Xiaomei Ma
Asher Michael Marks
Susan T. Mayne
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
Benjamin A. Toll
Shiyi Wang
Herbert Yu
Yawei Zhang
Tongzhang Zheng
Yong Zhu

Developmental Therapeutics

Maysa Mahmoud Abu-Khalaf
Karen S. Anderson
Masoud Azodi
Joachim M. Baehring
Debra Schwab Brandt
Ronald R. Breaker
Barbara Ann Burtness
Charles H. Cha
Herta H. Chao
Yung-Chi Cheng
Anne Chiang
Jennifer Nam Choi
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
Leonard Raymond Farber
James J. Farrell
Scott Nicholas Gettinger
Sarah B. Goldberg
Steven D. Gore
Ya Ha
Dale Han
Roy S. Herbst
Seth B. Herzon
Howard S. Hochster
Michael Edwin Hodsdon
Nina Ruth Horowitz
Sven-Eric Jordt
William L. Jorgensen
Juliane M. Juergensmeier
Patrick A. Kenney
Harriet M. Kluger
Jaseok Koo
Jill Lacy
Jia Li
Rogerio C. Lilenbaum
Dieter M. Lindskog
Elias Lolis
Patricia LoRusso
Thomas James Lynch
Gaetane Celine Michaud
Scott J. Miller
Jennifer Moliterno
Gil G. Mor
Natalia Nepanidze
Terri Lynn Parker
Pasquale Patrizio
Peter Natale Peduzzi
Andrew J. Phillips
Joseph Massa Piepmeier
Nikolai Alexandrovich Podoltsev
Lynne J. Regan
John David Roberts
Michal Gillian Rose
Thomas J. Rutherford
W. Mark Saltzman
Alan Clayton Sartorelli
Clarence Takashi Sasaki
Alanna Schepartz
William C. Sessa
Brian Matthew Shuch
David Adam Spiegel
Preston Sprenkle
Stacey M. Stein
Seyedtaghi (Shervin) Takyar
Vasilis Vasiliou
Jiangbing Zhou

Molecular Virology

Janet L. Brandsma
Daniel C. DiMaio
Ayman Sayed El-Guindy
Andrew Goodman
Stanley David Hudnall
Natalia Issaeva
Akiko Iwasaki
Benjamin L. Judson
Susan M. Kaech
Martin Alexander Kriegel
Priti Kumar
Brett D. Lindenbach
Robert E. Means
I. George Miller
Kathryn Miller-Jensen
Walther H. Mothes
Anna Marie Pyle
Michael Robek
John K. Rose
Alessandro D. Santin
Christian Schlieker
Joan A. Steitz
Richard E. Sutton
Peter John Tattersall
Anthony N. Van den Pol
Yong Xiong
Wendell Gray Yarbrough

Radiology 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 DErrico
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
Wu Liu
K. Brooks Low
Sheida Mani
Meena Savur Moran
Evan Daniel Morris
Ravinder Nath
Abhijit A. Patel
Richard E. Peschel
Kenneth B. Roberts
Faye A. Rogers
Peter Schulam
Yung H. Son
Patrick Sung
Joann Balazs Sweasy
Lynn D. Wilson
Sandra L. Wolin
James Byunghoon Yu
Zhong Yun

Signal Transduction

Anton M. Bennett
Titus Boggon
David A. Calderwood
Lloyd Garnet Cantley
Toby C. Chai
Pietro De Camilli
Michael P. DiGiovanna
Rong Fan
John P. Geibel
Sourav Ghosh
Valentina Greco
Jaime Grutzendler
Mark W. Hochstrasser
Valerie Horsley
Michael E. Hurwitz
Karl L. Insogna
Richard Glenn Kibbey
Joseph W. Kim
Anthony J. Koleske
Michael Oliver
Krauthammer
TuKiet T. Lam
Joseph Anthony Madri
Wang Min
Jon Stanley Morrow
Michael H. Nathanson
Don X. Nguyen
Daniel Petrylak
Katerina Politi
David L. Rimm
Joseph Schlessinger
Mark J. Solomon
David F. Stern
Derek K. Toomre
Benjamin E. Turk
Narendra Wajapeyee
Robert Martin Weiss
Kenneth R. Williams
Dan Wu
John Joseph Wysolmerski
Xiaoyong Yang

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

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

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