

breakthroughs

THE YEAR IN REVIEW YALE CANCER CENTER
SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN



Bringing Clinical Trials into our Communities

yale cancer center

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Over the last year, Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven have focused greater emphasis on the need to provide education and community-based outreach initiatives that are important to our patients. Yale Cancer Center and Smilow Cancer Hospital recognize the importance of impacting the community we serve – the communities in which our patients as well as our physicians, faculty, scientists, and employees share. New Haven and its surrounding towns provide us with an opportunity to care for and educate a diverse population on cancer prevention, screening, and treatment.

In the months ahead, we will implement a highly organized effort to expand cancer screening in diverse populations, particularly in men and women at the highest risk of developing certain cancers. We will establish important initiatives aimed at increasing the opportunity for all patients in our community to access the most recent advances in treatment through our clinical trials. With support from many of their colleagues, Beth Jones, PhD, MPH and Andrea Silber, MD are partnering to lead these efforts.

Our refocused efforts in clinical trial outreach and patient navigation continues Dr. Silber's long tradition of patient education in the community of New Haven. In 2015, Dr. Silber launched OWN IT (Oncologists Welcome New Haven Into Trials) to support more minorities as they consider participation in clinical trials. New Haven's population is approximately two-thirds African American and Latino and we recognize the need for additional support for this diverse population during cancer treatment. What makes these efforts so crucial, is the need to ensure the research that cancer centers do across the country reflects the diverse population of the United States. Although the national cancer research community often falls short of this aspiration, Yale Cancer Center is committed to doing our part to help achieve this important goal.

Yale Cancer Center also continues to expand new scientific programs and recently launched the Yale Cancer Therapeutic Accelerator Program (Yale CTAP) to improve our ability to discover compounds that may be able to be rapidly converted to new treatments for patients. This new program, led by Craig Crews, PhD

and Mark Lemmon, PhD, will facilitate the advancement of these compounds or drugs from Yale Cancer Center laboratories. The program helps to provide Yale Cancer Center drug discovery teams with the support needed to increase the likelihood of commercialization of those compounds. I look forward to sharing some of the success stories from Yale CTAP over the coming year as Dr. Crews and Dr. Lemmon begin to build the team and infrastructure needed to optimize drug discovery at Yale Cancer Center.

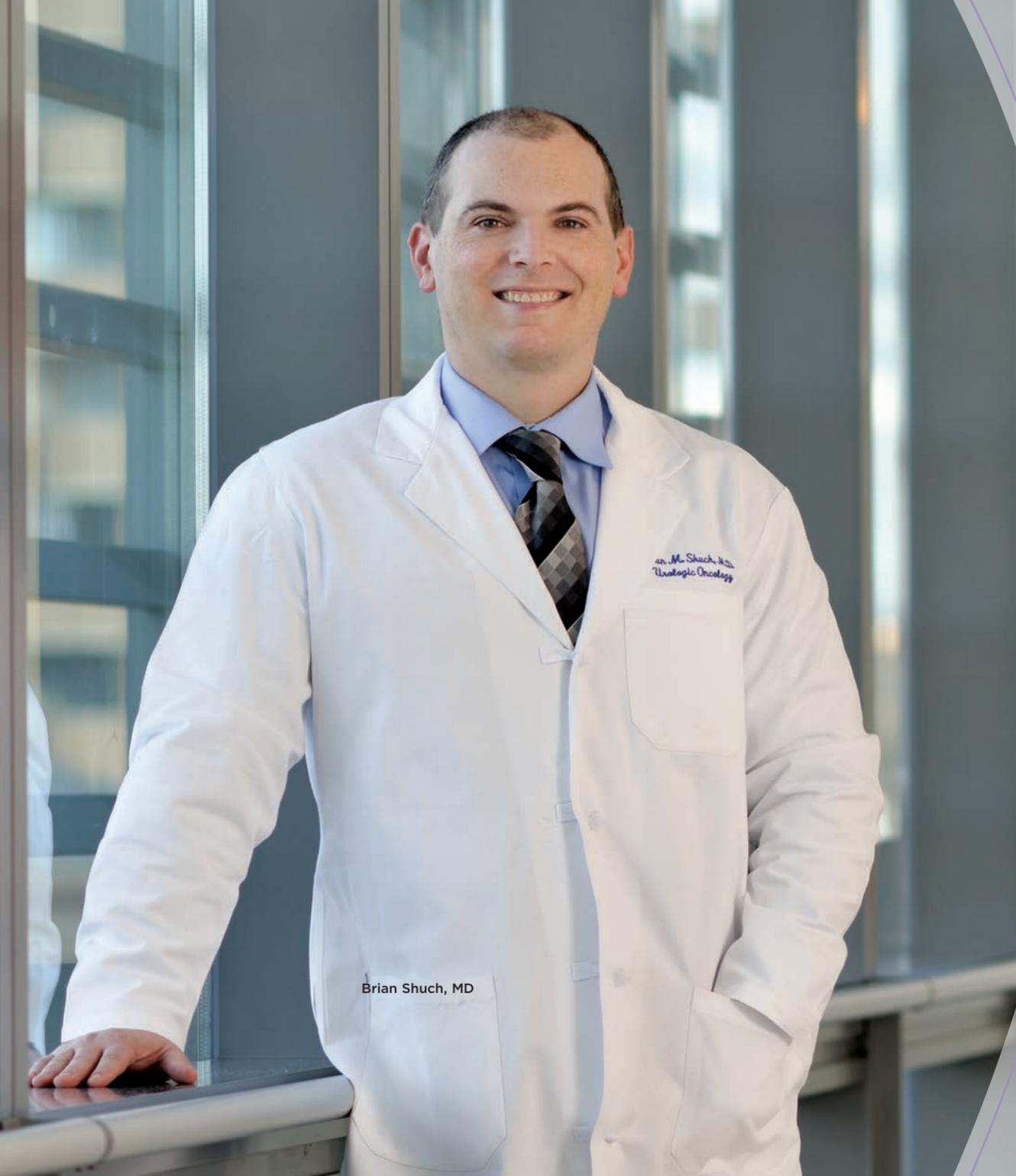
The momentum developed over the first 5 years at Smilow Cancer Hospital continued to expand in 2015. In June, we welcomed Saint Francis Hospital in Hartford to our Smilow Cancer Care Network and have expanded access to Yale Cancer Center physicians along the eastern shoreline from Guilford to Old Saybrook, and most recently to Waterford. Exceptional care and access to clinical trials is now available at 12 locations around the state of Connecticut. Yale's clinical trial accrual also reached an all-time high in 2015 and we continue to strive to make the newest treatment options available to our patients through clinical trial participation.

In addition, Yale Cancer Center's 7 Research Programs and nearly 350 members are continuing their pursuit to understand cancer and find ways to reduce its impact on patients in our community. New discoveries happen daily as scientists from our laboratories and physicians from our Disease Aligned Research Teams (DARTs) at Smilow Cancer Hospital combine their efforts in unique and impactful ways. Many highlights from 2015 are featured in this edition of *Breakthroughs* and I look forward to sharing new research advances and outcomes from our laboratories and clinics with you in the year to come.

Sincerely,

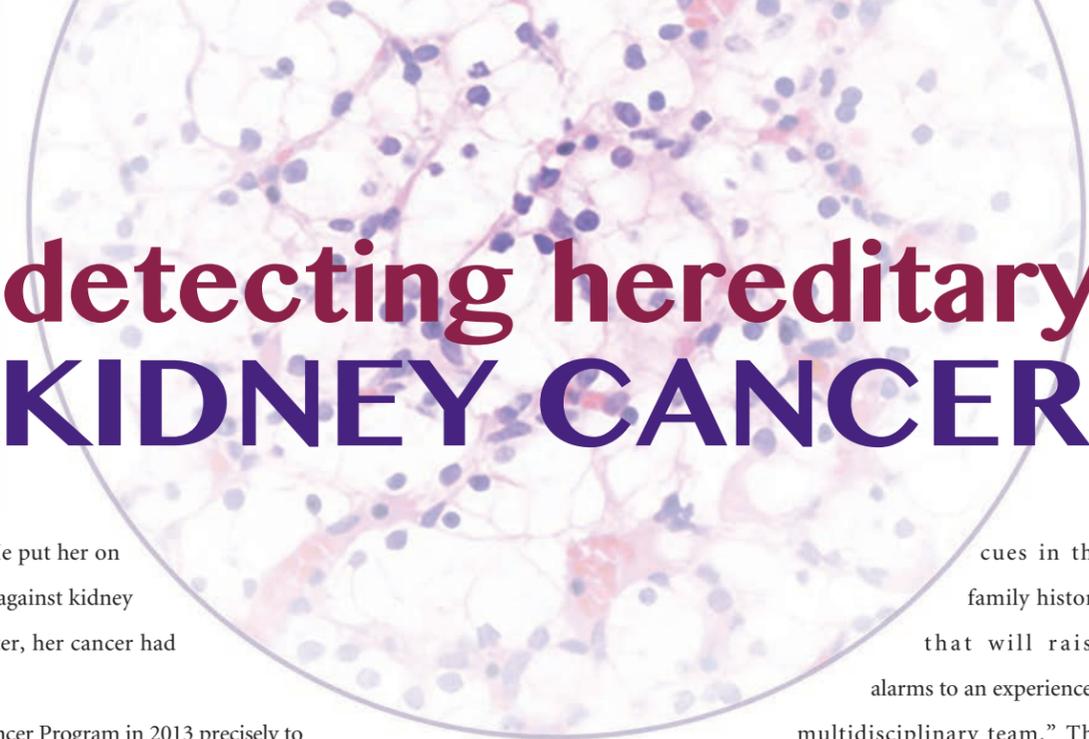
Peter G. Schulam, MD, PhD

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Brian Shuch, MD

detecting hereditary KIDNEY CANCER



Brian Shuch, MD, Assistant Professor of Urology and of Radiology and Biomedical Imaging, has a patient in her 70s who probably wouldn't be alive if not for the Hereditary Kidney Cancer Program, which Dr. Shuch directs. Before Dr. Shuch saw her, she had lost a kidney to cancer and wasn't responding to standard chemotherapy. Her doctor referred her to Dr. Shuch's program, which specializes in kidney cancers caused by heredity or acquired genetic mutations.

As always, Dr. Shuch delved into her family history. Her mother had died of kidney cancer. So had both of her own children, who hadn't responded to standard treatment of the disease. Dr. Shuch suspected an inherited syndrome. A genetic test confirmed it: she had a variant of an uncommon kidney cancer called

hereditary leiomyomatosis and renal cell cancer (HLRCC). He put her on an experimental regimen of chemotherapy not typically used against kidney cancer, but known to be effective against HLRCC. A year later, her cancer had essentially disappeared.

Smilow Cancer Hospital launched the Hereditary Kidney Cancer Program in 2013 precisely to help such patients and to educate the physicians who diagnose them. Kidney cancer is one of the most common forms of the disease, with an estimated 61,500 new cases each year. Scientists once assumed that kidney cancers occur sporadically, but newer research suggests that five to eight percent stem from genetic predisposition. Dr. Shuch believes this number will continue to rise.

"We haven't even begun to scratch the surface of inherited predisposition," he said. "Lineage studies show that about 80 percent of kidney cancers cluster in about a quarter of the population, strong evidence that kidney cancer has a strong hereditary basis."

Currently, however, genetic syndromes associated with kidney cancer often go unrecognized by physicians, to the detriment of patients. The standard of care used against sporadic forms of the disease may be ineffective against hereditary syndromes. Certain syndromes are associated with asymptomatic signs of kidney cancer. Four syndromes, for example, can manifest themselves as skin problems. Few physicians have the training to recognize these signs. Similarly, a syndrome called Von Hippel-Lindau syndrome may be accompanied by retinal tumors.

"I've had patients lose their vision by a delay in the diagnosis of manifestations outside the kidney," said Dr. Shuch. "A urologist and oncologist who are focused on their areas of expertise often miss subtle signs in the physical exam or

cues in the family history that will raise alarms to an experienced multidisciplinary team." The team at Yale includes urologists, pathologists, dermatologists, geneticists, and genetic counselors.

Just a day earlier, Dr. Shuch had seen a patient referred to him by the team's dermatologist because of a skin lesion called a leiomyoma, sometimes a sign of HLRCC. When Dr. Shuch teased out the patient's family history, he learned that all three of his sisters had had their uteruses removed in their 30s because of fibroids, another sign of HLRCC, and his 23-year-old nephew had advanced kidney cancer.

"That patient doesn't have any symptoms of kidney cancer," said Dr. Shuch, "but he absolutely needs testing and genetic screening for a presumed diagnosis of HLRCC. We've had patients whose lives were potentially

saved by identifying an asymptomatic kidney cancer through screening and treating it before dissemination.”

Part of Dr. Shuch’s mission is to educate physicians to take a comprehensive family history, and to be alert for signs that a patient should be referred to his program for evaluation and genetic testing. One of the clearest signs is early onset of kidney cancer. The average age for a diagnosis is 64, and the cancer rarely hits people younger than 45 – but the inherited forms often strike before that age. Other signs: unusual pathology, bilateral disease, and multifocal disease.

Dr. Shuch and his colleagues have developed a genetic screening panel for the known syndromes, which at this point number about 15. Yale is one of the first centers with such a panel, which allows the team to test multiple genes at once.

Genetic testing is crucial not only for patients with symptoms of hereditary kidney cancer, but for their parents, siblings, and children. Early detection can mean the difference between life and death. HLRCC, for instance, is one of the most aggressive syndromes. Before Dr. Shuch’s program began, Yale had not identified a single patient with HLRCC, but in the past two years, nine families have been diagnosed with it. “Rather than lumping them in with generic kidney cancer and treating them the same,” explained Dr.

Shuch, “we have been able to offer them unique treatment strategies focused on the genetic alterations associated with that syndrome.”

That has prolonged lives. James Uhl, for instance, was 45 when diagnosed with kidney cancer. The disease had spread to his liver, lungs, bones, brain, eyes, and lymph system. He was referred to Dr. Shuch, who found HLRCC. In January 2014, Dr. Shuch removed Mr. Uhl’s left kidney, part of his liver, and multiple lymph nodes, then put him on a unique regimen not designed for kidney cancer but often effective against this particular syndrome. It worked well for six months, an unusual span against a cancer so advanced. After trying several other regimens, in late 2015 Dr. Shuch got Mr. Uhl into a clinical trial at the NCI. Dr. Shuch doubts that Mr. Uhl would have had the last two years with his family without the Smilow program.

“Brian’s knowledge of the disease has offered me tremendous guidance,” said Mr. Uhl, who remains optimistic. “Without the work being done by him and his team, little would be known about this aggressive disease. Because of their research, more and more treatment options are going into trial phases, which gives patients like me a lot of hope.” He’s also grateful that Dr. Shuch identified his syndrome, because his children, 10 and 8, can be tested very early for the gene. “I’ll be able to potentially save my children’s lives,” he said.

As knowledge about the genetics associated with each kidney cancer syndrome grows, targeted therapies become possible. “Rather than treating kidney cancer as one disease,” said Dr. Shuch, “we’ve learned it’s a group of cancers arising from the same organ, but all very different.”

New knowledge is changing treatment in other ways as well. For instance, three of the syndromes produce kidney cancers that pose no risk of metastasis until the tumor reaches a certain threshold. Until then, the cancer can be managed, and patients can be spared unnecessary surgery—that is, if the syndromes are identified early, which is why testing can be so important.

In 2016 the program will expand to other urologic cancers with heritable syndromes such as prostate, bladder, and testicular cancers. Dr. Shuch and his colleague are also planning a tele-genetic counseling service so that other cancer centers can benefit from Yale’s expertise.

“So much of this is not just cancer treatment,” explained Dr. Shuch, “it’s preventing the delayed management of new tumors by aggressive screening. A delay in diagnosis could be the difference between cure and cancer dissemination.”



Bringing CLINICAL TRIALS into our **Communities**

Andrea Silber, MD, Associate Clinical Professor of Medicine, has never forgotten one of her first patients in New Haven nearly thirty years ago, a young black mother of four. She had breast cancer but had never been treated. Within a week, she was dead.

“It was incredibly sad, and it stuck with me,” said Dr. Silber, a medical oncologist who specializes in breast cancer. “I was also struck by the fact that in New Haven, whenever you see people of color with cancer, it’s worse in so many ways. They may come in later, or the onset may come at a much younger age, or they may have other chronic conditions that make it difficult to treat their cancer. I’ve had a long interest in decreasing cancer health

Andrea Silber, MD

disparities in New Haven.”

For decades these disparities didn't get much attention

“I'm so grateful for being in this clinical trial,” Ms. Castellani said. “Dr. Silber was the only doctor who didn't give up on me. She took her time and gave me this option, and she explained everything.”

from the medical establishment. That has recently started to change, spurred partly by the Affordable Care Act. Dr. Silber is determined to add to the momentum.

One of her tools is a new program called OWN IT (Oncologists Welcome NewHaven Into Trials). OWN IT's purpose is to get more minorities from inner city New Haven into clinical trials for new cancer treatments conducted at Smilow Cancer Hospital. Minorities are under-represented in such trials nationwide. The city of New Haven, for instance, is about two-thirds black and Latino, yet those groups account for about 12 percent of the participants in Yale's cancer clinical trials. (The trials that Dr. Silber accrues to are more than 50 percent minority.)

According to Dr. Silber, these low numbers have consequences. First, minorities are missing out on the most

cutting-edge treatments for their cancers, which affects their survival rates. Second, the lack of minorities can skew trial results – Dr. Silber has noticed that new medications given to her patients often don't live up to their hype.

“So I would go back and look at the trial,” she said, “and I realized that my patient never would have been chosen for the study, because it eliminated anyone with complicating factors like diabetes or high blood pressure or obesity, which are common among my cancer patients from the inner city. If you test all your oncologic drugs only on the healthy, the wealthy, and the wise, your test doesn't equate to real life and doesn't address the problems we see in New Haven.”

One of OWN IT's tasks is to remove the barriers keeping minorities out of trials. The first barrier is mistrust. “People in town have been afraid of being someone's research project,” said Dr. Silber. “They say, ‘Why should I do this? Who is this going to help? I don't want to be experimented upon.’” To overcome these suspicions and build trust, says Dr. Silber, physicians must become more patient and communicate more clearly. “Everyone has a right to understand what's happening to their bodies, and it's my obligation to explain it in a way they understand.”

That's how Dr. Silber convinces her patients to enter clinical trials at Smilow. Maria Castellani, a mother of three, had a bout with stage 3 breast cancer in 2011 and survived, but in June 2014 the disease returned, in the aggressive triple negative form. It spread to her lungs, lymph nodes, and bones. She saw four oncologists, one of whom gave her six months to live. Three of them never mentioned clinical trials. The fourth suggested a trial, but instead of explaining it, merely handed Ms. Castellani a thick packet of baffling technical information.

Distraught and despairing, she finally connected with

Dr. Silber, who suggested a clinical trial with Orteronel. Ms. Castellani's mother, brothers, and uncles warned that she would be treated like a lab rat, but she trusted Dr. Silber and joined the trial in July 2015. By the end of the year, her lymph nodes were clear, her lungs were stable, and her bone cancer was fading.

“I'm so grateful for being in this clinical trial,” she said, crying a little. “Dr. Silber was the only doctor who didn't give up on me. She took her time and gave me this option, and she explained everything. I don't have enough to pay her for what she's done for me.”

Similarly, Marta Vega was diagnosed with stage 3 breast cancer. Her oncologist was hurried and distant. Terrified and in denial, she didn't want to consider treatment of any kind. Then she saw Dr. Silber, who carefully explained a breast cancer trial to her and said, “If you were my sister, I would recommend this.” Her warmth and patience persuaded Ms. Vega, who received experimental chemotherapy from March to August 2014. Her tumor shrank 75 percent, and surgery took care of the rest. “If it wasn't for Dr. Silber,” said Ms. Vega, “I wouldn't have survived, because I would not have done

the clinical trial.” During treatment, Dr. Silber asked her to speak to two Latina patients with breast cancer who were afraid of trials. “I was kind of an advocate,” said Ms. Vega, “and I felt good because I was helping someone else and telling them it's OK.”

After Wendy Ormond was diagnosed with breast cancer, she went into a tailspin. She began drinking and contracted pancreatitis before she could have surgery, and her blood pressure also shot up. She was referred to Dr. Silber, who sent her to a heart doctor to get her blood pressure under control. She also convinced Ms. Ormond to overcome her terror of doctors and enter a clinical trial. “I trusted her,” said Ms. Ormond simply. “I knew she wouldn't get me into something that would hurt me. I love that lady.” She began the trial in February 2015, and her blood tests continue to improve.

OWN IT will address the barriers of fear and mistrust, says Dr. Silber, by building a relationship between Yale and the people in the city surrounding it. That will take time. She has always devoted time to community outreach, but now new funding from the National Institutes of Health and other sources will allow her to hire patient

navigators and a community health educator who can hold educational sessions at community centers, schools, and churches, to explain clinical trials and their advantages.

She adds that the city's primary care physicians and Yale oncologists also need educating. Too many patients never hear about trials. Patients who don't speak English may be rejected as too time-consuming. Some trials disqualify swaths of inner city minorities because their blood pressure, cholesterol, or glucose levels tend to be higher than those of people in wealthier suburbs.

However, Dr. Silber sees signs of change. The NIH, the National Cancer Institute, and the American Society of Clinical Oncology all have started paying attention to health disparities and funding research. Things are changing at Yale as well. In May, Dr. Silber was appointed to the Cancer Center's Executive Committee as Assistant Director for Diversity and Health Equity.

“We've never been at the table before,” said Dr. Silber, “but because of the leadership at Smilow, there's a new awareness of how this needs to be part of the thinking. Everything is aligning to make OWN IT a way to really change clinical trials for inner city New Haven.”

ACCELERATING development of **NEW DRUGS**



Craig Crews, PhD; Peter G. Schulam, MD, PhD; Mark Lemmon, PhD

The Valley of Death: that's what the co-directors of the new Yale Cancer Therapeutic Accelerator Program (Yale CTAP) call the place where promising lab compounds perish on the rigorous journey towards becoming a new cancer drug. In fact, most patents of discoveries expire before they even reach the valley's outskirts, according to Craig Crews, PhD, Lewis B. Cullman Professor of

Molecular, Cellular and Developmental Biology, and Director of the Yale Center for Molecular Discovery, and his CTAP co-director Mark Lemmon, PhD, David A. Sackler Professor of Pharmacology and co-director of the Cancer Biology Institute.

"Despite all the efforts at translational medicine," said Dr. Crews, "the harsh reality is that it takes a lot to develop

a tool compound into a drug candidate. There's still a gap, the proverbial Valley of Death. An academic can take his or her research only so far towards translation, because there aren't funding mechanisms for it, there isn't the training for it, there isn't the personnel to do it."

"Basic scientists in the Cancer Center are doing amazing work," added Dr. Lemmon, "but there are

huge barriers to taking their discoveries beyond the lab. Expense and lack of access to the right experience stall most potential cancer care discoveries. CTAP would provide stepping stones across the Valley of Death."

The idea for CTAP came from Peter G. Schulam, MD, PhD, Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital at Yale-New Haven (Interim). The program is modeled on a similar one started by Dr. Crews called PITCH (Program in Innovative Therapeutics for Connecticut's Health), which is also aimed at developing new drugs. PITCH received a \$10 million, three-year grant from the state of Connecticut to select and fund projects from Yale and the University of Connecticut, with the goal of developing promising discoveries to the point where they can be pitched to venture capital firms.

CTAP will adopt this concept, but with a focus on generating new cancer drugs and accelerating their development in much the same way as biotech startups. "By coalescing ideas, capital, and talent," said Dr. Crews, "one can drive the whole drug discovery process in a much faster way than the pharmaceutical industry has." CTAP will bring together programs across multiple schools

and faculties at Yale to leverage their unique strengths in this process, allowing Cancer Center members to work alongside faculty who can complement their research goals from throughout the University.

It would work like this: let's say a Cancer Center member makes an intriguing discovery and wants to develop it into a drug that could be tested in Phase I trials at Yale, but doesn't know how to go about it. CTAP and the Yale Center for Molecular Discovery would engage a team of professional drug developers to screen drug candidates for useful compounds. If any of these appeared promising, medicinal chemists and others would design, synthesize, and tweak the compounds to make them more drug-like. CTAP would then help marshal the efforts of labs in the Cancer Biology Institute and elsewhere to generate data packages evaluating the potential of the compounds – facilitating the pipeline from idea to therapeutic approach. At that point, the compounds would be evaluated by an external advisory board, comprised of representatives from biotech and big pharma, to determine which have therapeutic potential and should advance to the next level: pitching to philanthropists, venture capitalists, and others.

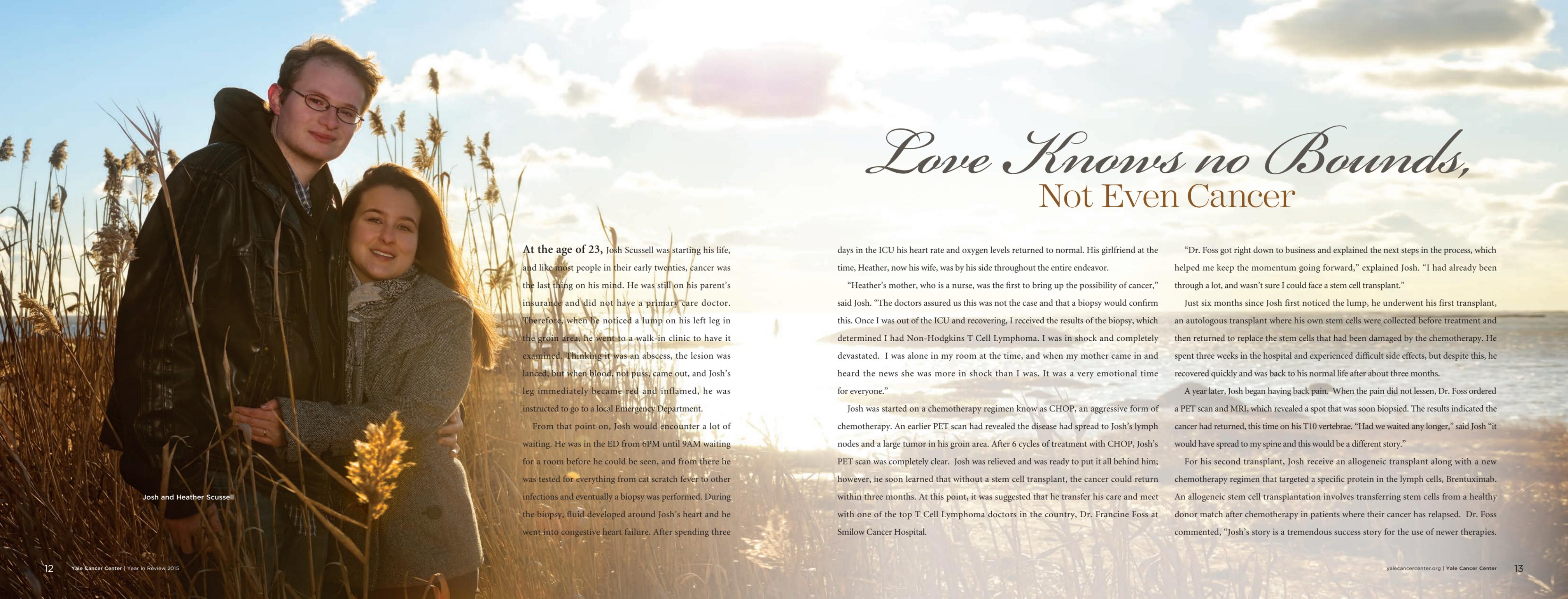
"We want to work with the venture capitalists and

others to ask what it would take to make something attractive enough to put \$5 million or \$15 million into a new startup located here," said Dr. Crews. "So we really aren't doing drug discovery or drug development, but would generate the companies to do that."

Another part of the program's mission is to teach YCC members how to be more entrepreneurial. Once the external advisory committee approves a project, CTAP will work with the initiating faculty member to put together a business plan and coach him/her on how to pitch the discovery to venture capitalists.

Because the program is so new, the search for funding has just begun. Dr. Crews and Dr. Lemmon intend to tap philanthropic and commercial sources that prefer to invest in projects that have moved beyond basic science toward practical application. A strong selling point, said the co-directors, is that CTAP can draw on new state-of-the-art research facilities and Institutes on Yale's West Campus as well as several departments.

"Investors in these new drugs will be getting a lot of added value here," said Dr. Lemmon. "It takes a village to move from a germ of an idea to the exploitation of the idea."



Love Knows no Bounds, Not Even Cancer

Josh and Heather Scussell

At the age of 23, Josh Scussell was starting his life, and like most people in their early twenties, cancer was the last thing on his mind. He was still on his parent’s insurance and did not have a primary care doctor. Therefore, when he noticed a lump on his left leg in the groin area, he went to a walk-in clinic to have it examined. Thinking it was an abscess, the lesion was lanced, but when blood, not puss, came out, and Josh’s leg immediately became red and inflamed, he was instructed to go to a local Emergency Department.

From that point on, Josh would encounter a lot of waiting. He was in the ED from 6PM until 9AM waiting for a room before he could be seen, and from there he was tested for everything from cat scratch fever to other infections and eventually a biopsy was performed. During the biopsy, fluid developed around Josh’s heart and he went into congestive heart failure. After spending three

days in the ICU his heart rate and oxygen levels returned to normal. His girlfriend at the time, Heather, now his wife, was by his side throughout the entire endeavor.

“Heather’s mother, who is a nurse, was the first to bring up the possibility of cancer,” said Josh. “The doctors assured us this was not the case and that a biopsy would confirm this. Once I was out of the ICU and recovering, I received the results of the biopsy, which determined I had Non-Hodgkins T Cell Lymphoma. I was in shock and completely devastated. I was alone in my room at the time, and when my mother came in and heard the news she was more in shock than I was. It was a very emotional time for everyone.”

Josh was started on a chemotherapy regimen known as CHOP, an aggressive form of chemotherapy. An earlier PET scan had revealed the disease had spread to Josh’s lymph nodes and a large tumor in his groin area. After 6 cycles of treatment with CHOP, Josh’s PET scan was completely clear. Josh was relieved and was ready to put it all behind him; however, he soon learned that without a stem cell transplant, the cancer could return within three months. At this point, it was suggested that he transfer his care and meet with one of the top T Cell Lymphoma doctors in the country, Dr. Francine Foss at Smilow Cancer Hospital.

“Dr. Foss got right down to business and explained the next steps in the process, which helped me keep the momentum going forward,” explained Josh. “I had already been through a lot, and wasn’t sure I could face a stem cell transplant.”

Just six months since Josh first noticed the lump, he underwent his first transplant, an autologous transplant where his own stem cells were collected before treatment and then returned to replace the stem cells that had been damaged by the chemotherapy. He spent three weeks in the hospital and experienced difficult side effects, but despite this, he recovered quickly and was back to his normal life after about three months.

A year later, Josh began having back pain. When the pain did not lessen, Dr. Foss ordered a PET scan and MRI, which revealed a spot that was soon biopsied. The results indicated the cancer had returned, this time on his T10 vertebrae. “Had we waited any longer,” said Josh “it would have spread to my spine and this would be a different story.”

For his second transplant, Josh received an allogeneic transplant along with a new chemotherapy regimen that targeted a specific protein in the lymph cells, Brentuximab. An allogeneic stem cell transplantation involves transferring stem cells from a healthy donor match after chemotherapy in patients where their cancer has relapsed. Dr. Foss commented, “Josh’s story is a tremendous success story for the use of newer therapies.

“I was really excited to hear that Josh and Heather got married. He has been a tremendous success story and I am so happy for them.” - Dr. Francine Foss

When patients relapse after autologous therapies, it's often difficult to go on with an allogeneic transplant because using conventional chemotherapy, the cancer often does not go into remission. Because Josh did so well with the new drug, Brentuximab, he was the perfect candidate to go ahead with an allogeneic transplant.”

Six months passed before a donor match was found, but unfortunately the donor decided at the last minute not to go through with stem cell donation for Josh. The search continued using Be the Match® and Josh received word that a 25-year-old female in Canada had been located as a near perfect match for him. His transplant was scheduled two years after his first. Due to insurance issues, the transplant was done in Boston at Dana Farber. Dr. Foss was kept informed every step of the way. Josh was in the hospital for three weeks undergoing chemotherapy before the transplant and during this time, Heather spent every night by his side.

“I couldn't imagine having to see her go through something like this. She has been with me from that first night in the ED up until now,” said Josh. “She was commuting from Boston to Guilford, CT every day for almost a month. She had to wear a full gown and mask, and never once complained. We have been together for seven years, and over half of that has been dealing with this cancer. I knew after that, she would always be by my side, and so I asked her if I could spend the rest of my life by hers. She said yes.”

Following the transplant, due to the high risk of infection, Josh had to undergo one year of isolation where he couldn't leave the house. He lost 50 pounds and recovery was

slower this time around. A year post transplant, Josh was eager to contact his donor, the 25-year-old woman from Canada. As it turns out, they had more in common than just bone marrow. Their birthdays are a month apart, and both got married last year. Additionally, from Saskatchewan, her husband, a professional hockey player, is a family friend of Mandi Schwartz, a former Yale University ice hockey player that passed away from acute myeloid leukemia in 2011. For five years, Yale University has been helping save lives through marrow donor registration drives in honor of Mandi, including one that was held in Mandi's hometown, Saskatchewan, Canada, where Josh's donor volunteered and decided to join the registry.

“Her husband's best friend had leukemia and did not survive his transplant, so when they did not hear from me after six months, they thought I had not survived either,” said Josh. “I was able to receive her contact information after one year, and they were very happy to hear from me. My first email to her was titled ‘You saved my life’ and from there we began exchanging photos and information about each other. One of the photos she sent was of her on donation day with the bag of stem cells. It was flown in that day and I remember seeing the bag and touching it. And there she was in a gown, holding the bag of cells and smiling. It was very emotional for me to see that.”

This past October, one year and three months after his second transplant, Josh and Heather were married and honeymooned in Disney World. “I was really excited to hear that Josh and Heather got married. He has been a tremendous success story and I am

so happy for them. It was so exciting to see the picture of Josh and his bride at their wedding – I felt like it was my son getting married,” Dr. Foss said.

“It truly meant a lot to see how genuinely happy Dr. Foss was for me when I got married,” said Josh. “She helped me through this difficult time, by more than just treating me, but by supporting me.”

Josh and Heather are looking forward to a long life together. They will never forget the woman that saved his life and plan to meet her and her husband this spring. Her small gesture in joining the bone marrow registry created a big connection spanning thousands of miles, and allowed for Josh and Heather's happy ending to be possible.

“I knew after that, she would always be by my side, and so I asked her if I could spend the rest of my life by hers. She said yes.”



Yale scientists have pioneered a new form of positron emission tomography (PET). This new approach to imaging may allow cancer-care specialists to detect the epidermal growth factor receptor (EGFR), a target for cancer therapy that is expressed on the surface of tumor cells. This new type of PET scan will also monitor drugs that target the EGFR in tumors and could provide a new way to image their effectiveness in patients.

The most common form of PET scan is called fluorodeoxyglucose (FDG)-PET, in which a cancer patient is given a radioactive sugar that accumulates in the tumor, allowing doctors to view it. The Yale group is using PET technology in a way that hasn't been done before. Their new technique uses a radiolabeled drug that specifically binds to the EGFR. The goal is to provide a method for doctors to see the tumor, watch the uptake of the drug, and monitor its effectiveness.

"That's what we're really excited about," said Joseph Contessa, MD, PhD, Associate Professor of Therapeutic Radiology and Pharmacology whose laboratory studies the biology of EGFR. "We have not previously been able to non-invasively monitor the interaction of a cancer drug with its target in patients. With this work we hope to translate our knowledge about the biology of EGFR to a simple and clinically useful PET scan."

PET imaging of the EGFR is accomplished by using a radiotracer called [11C]-erlotinib. Erlotinib is a drug that blocks activation of the EGFR, and potently blocks the growth of tumor cells with mutation of the EGFR. EGFR mutations are found in multiple cancers and come in many forms. Those with tyrosine kinase mutations, which activate the receptor's activity, are the Yale team's current focus. The radiolabeled form of erlotinib was planned and synthesized by a member of the team, radiochemist Yiyun Henry Huang, PhD, Professor of Radiology and Biomedical Imaging, and Co-Director of The Yale PET Center. Dr. Huang replaced one of the drug's carbons with a radioactive carbon, which allows the compound to be traced by PET.

The team tested the technique by injecting [11C]-erlotinib into mice with lung cancer tumors harboring EGFR mutations. Evan Morris, PhD, Associate Professor of Radiology and Biomedical Imaging, Psychiatry, and Biomedical Engineering, and Co-Director of the PET Imaging Section, modeled the radiotracer's distribution and the team was able to watch the drug bind to the tumor. This revealed the presence of the mutation and the effectiveness of the drug in blocking EGFR activity.

Their revelation could be a big step in the treatment of NSCLC, explained Dr. Contessa, because a physician

can see whether the drug is hitting the target at every site in the body. If tumors are not imaged by [11C]-erlotinib PET, doctors can consider using another tyrosine kinase inhibitor or irradiating the sites missed by the drug. The technique can also reveal when patients are developing resistance to a drug, either generally or at certain sites, and hence could benefit from changing or supplementing their therapies. "We hope this technique will help physicians make these decisions earlier, by giving them more information more quickly," said Dr. Contessa.

The next step, beginning now, is a Phase I trial with about two dozen patients at Smilow Cancer Hospital. That's where the fourth member of the team comes in, medical oncologist Sarah Goldberg, MD, MPH, Assistant Professor of Medicine. "Dr. Goldberg is very interested in using this new technique to improve therapeutic decision-making for patients with EGFR mutations," said Dr. Contessa.

The team believes this technique can be used for other types of cancer. "There are other tumor sites with specific mutations, and we might be able to develop radiotracers that specifically interact with those mutant proteins to give us a way to image different types of tumors," said Dr. Contessa. "We think we can start to personalize imaging to find mutations, and use imaging as a way to gauge responses to therapy."



Evan Morris, PhD and Joseph Contessa, MD, PhD

Imaging the Epidermal Growth Factor Receptor



Sarah Mougalian, MD

Texting to Check in on Patients

Sarah Mougalian, MD, Assistant Professor of Medicine, specializes in treating patients with breast cancer. She found herself frustrated by one aspect of their care. Most breast cancers – about 75 percent – are fueled by the hormone’s estrogen and/or progesterone. After patients with this type of breast cancer finish their primary treatments, typically surgery and perhaps followed by radiation and/or chemotherapy, they are prescribed a medication to regulate their hormones, with the goal of preventing a recurrence of cancer. The regimen sounds simple – one pill every day for five to ten years.

Yet many of these patients do not follow this regimen. At Smilow Cancer Hospital, said Dr. Mougalian, it’s about 25 percent, and some studies have found non-adherence rates up to 50 percent. The reasons range from forgetfulness to unfilled prescriptions to intolerance of the medication’s side effects. Failure to take the medication or to complete the long-term therapy may put these patients at higher risk of recurrence. Hence Dr. Mougalian’s frustration, which has led to an innovative solution.

Many of Dr. Mougalian’s patients are young women, and she noticed that when she entered an examining room, they often were texting on their smart phones. “So we thought about creating a text messaging system to help

people remember to take their medication and to identify any problems early,” explained Dr. Mougalian. “It can be three to six months between appointments, a long time to wait if you have questions. In some cases, people stop taking their medication and we don’t even know it.”

Dr. Mougalian collaborated with the technology company CircleLink Health to design a new idea in cancer treatment – a pilot study built around automated text messages. She enrolled 100 patients for three months. All of them received a daily text asking if they had taken their medication. They type “Y” for yes or “N” for no. Anyone who didn’t reply or who texted N for three straight days or six times within 30 days received a phone call from a triage nurse to find out what was going on. “This is an effort to identify people who are at risk of discontinuing their medication, and to try to address it in real time,” said Dr. Mougalian.

Every patient also got a weekly text asking whether they were experiencing any of the listed side effects, and if so, to rate them on a scale of severity from one to nine. Anyone who reported severe side effects received a phone call to discuss behavioral modifications or were offered a sooner appointment with their physician. Patients could also free-text non-listed side effects.

Finally, patients got one text per month asking if

“The ultimate goal is to see whether better adherence correlates to better survival in the long run.”

anything was preventing them from continuing their medication, such as side effects or finances.

Dr. Mougalian wanted to know whether patients would be irritated by the daily texts, or if they would develop “alert fatigue” and delete the reminder without replying. Only one patient complained. “Lots of patients say they like it, because they feel like somebody is looking out for them,” said Dr. Mougalian, “and it’s also an accountability tool, because they know someone is checking up on them.”

The text system also seemed to improve adherence: only five of the 100 patients stopped taking their medication (four due to side effects), a much higher rate of adherence than is typical. Dr. Mougalian cautions that this finding is preliminary. She hopes to test it in a long-term randomized study and has applied for funding to do a five-year investigation with 400 patients, half of them using the text system and the other half not, as a control group.

“The ultimate goal,” she said, “is to see whether better adherence correlates to better survival in the long run.”

Not every lab discovery leads directly to a clinical application, but progress in cancer care depends on insights from basic science into the fundamental mechanisms of biology.

A recent paper in the journal *Cell* offers a good example. Scientists from Yale Cancer Center and elsewhere have been studying links between lymphoma and a biological mechanism called V(D)J recombination. This mechanism recombines broken pieces of DNA, and is essential for the development of T cells and B cells, lymphocytes that form the adaptive immune system. Yet this process of genetic recombination is also risky. The paper's lead author, Grace Teng, PhD, a postdoctoral fellow and Associate Research Scientist in Immunobiology, wrote that these developing T and B cells "perch on the edge of genomic instability."

"When broken DNA ends are flopping around in the cell, they can become joined in a haphazard fashion," explained Dr. Teng. "A lot of cancers are associated with these erroneous repair processes. The fact that lymphocytes have to go through programmed DNA damage during development makes them particularly susceptible to errors. That's why lots of lymphomas stem from B and T cells."

In short, the mechanism that creates our adaptive

immune system also exposes us to the risk of lymphoma. "New lymphocytes are being generated in our bodies at a tremendous rate every day," said another of the paper's authors, David Schatz, PhD, Professor of Immunobiology and of Molecular Biophysics and Biochemistry, "and the V(D)J recombination process happens hundreds of millions, if not billions of times per day. So the risk is ongoing and chronic, and even an extremely low error rate gives you a significant risk."

Dr. Teng's research also uncovered an unexpected wrinkle in V(D)J recombination: breaks of DNA in the "wrong" places. In V(D)J recombination, DNA is cut by two proteins called recombination activating genes 1 and 2 (RAG1 and RAG2), which Dr. Schatz discovered 25 years ago. They were thought to cut DNA in a small, limited part of the genome, as a way of protecting the rest of the genome from flawed cuts. But Dr. Teng and her colleagues found RAG1 and RAG2 in thousands of off-target sites. "That seemed to constitute a much broader, more significant threat than previously suspected," said Dr. Schatz.

Dr. Teng and colleagues knew that the RAG complex prefers to sever DNA at specific spots called Recombination Signal Sequences (RSSs), which are abundant in the normal cutting sites. Researchers found that in the off-target sites, RSSs are significantly depleted.

That means fewer places for RAG to cut, which lessens the risk of incorrectly refitted strands of DNA.

"You end up with two different compartments of the genome," said Dr. Teng, "one enriched with RSSs, and another where there's not much of the DNA sequence for RAG to cut." This compartmentalization seems to protect the genome from inappropriate cuts in the off-target sites.

That begs another question: why didn't evolution remove this bug from the system? Dr. Schatz points out that RAG1 and RAG2, with the threat of lymphoma they carry, have been present during vertebrate evolution for hundreds of millions of years. The depletion of RSSs at off-target sites might be evolution's way of putting the threat on the back-burner.

"Cancer is generally a disease of old age," said Dr. Schatz, "and hence lymphomas that would kill people at 50 or 60 would have been a very weak evolutionary force for most of human evolution. I suspect that's why this hasn't been completely selected against."

These discoveries might someday help physicians predict which parts of the genome are at greatest risk of lymphoma. "As basic scientists," said Dr. Schatz, "we're not looking at how the immune system is interacting with tumors, but at what gave rise to the tumors in the first place."

Grace Teng, PhD and David Schatz, PhD

The Immune System and the Risk of Lymphoma



Jorge Galan, PhD, DVM

The Links Between Typhoid, Bacteria, and Cancer

A discovery by a Yale Cancer Center

researcher promises to beget a vaccine against one of the world's most deadly diseases, typhoid fever. This breakthrough is also likely to cause two important side effects: a decline in the incidence of gallbladder cancer, and more research on the links between bacterial pathogens and cancer.

Typhoid fever is one of the scourges of public health, sickening more than 20 million people every year and killing 200,000, almost all of them in undeveloped countries, where it is spread by contaminated food or water, usually via the feces of infected people. The infectious cause of typhoid has been known for more than a century, a bacterium named *Salmonella Typhi*. But the bacteria's mechanism to cause disease has been a mystery, preventing the development of a knock-out vaccine, one of the holy grails of public health.

That may soon change. A team led by Jorge Galan, PhD, DVM, Lucille P. Markey Professor of Microbial Pathogenesis and Cell Biology, and Chair of Microbial Pathogenesis, has identified the basis for *Salmonella Typhi*'s unique virulence properties. Dr. Galan's team identified "typhoid toxin," which is produced by *Salmonella Typhi* and in experimental animals, can reproduce most of the symptoms of typhoid fever.

Virus and Other Infection-associated Cancers RESEARCH PROGRAM

Dr. Galan's team has also solved the atomic structure of "typhoid toxin," which should make possible the development of small molecule inhibitors to block the infection, as well as a vaccine that could potentially eradicate typhoid fever.

"This discovery turned the disease upside down," said Dr. Galan. "Now we know why *S. Typhi* causes typhoid fever, and we can create a vaccine against it. That's the main impact." The Bill & Melinda Gates Foundation has put Dr. Galan's breakthrough onto a fast track towards a vaccine.

The discovery also provides a molecular explanation for the epidemiological link between typhoid and gallbladder cancer. Many survivors of typhoid become asymptomatic carriers of *S. Typhi*, and hold the bacteria in the gallbladder. "We discovered that *S. Typhi* encodes what is essentially a genotoxin – a toxin that damages the genome's DNA," said Dr. Galan. "So the tumorigenesis is likely to be related to the toxin's ability to damage the DNA. When the DNA is mis-repaired, mutations are created, providing the basis for the development of cancer. So a vaccine against typhoid fever should also prevent gallbladder cancer."

That would be significant in the developed world as well. About 10,000 new cases of gallbladder cancer are diagnosed in the United States each year, and 4,000 people die from it.

Dr. Galan believes that the connections between cancer and infections, especially bacterial infections, deserve more attention. "This story of ours is one more example. Cancer researchers sometimes forget that 20 percent of known cancers are caused by an infectious organism," he said, "and that's probably a gross underestimate, because it only captures instances where the microorganism is the direct cause – for example, in the case of human papillomavirus (HPV) and cervical cancer, or the bacterium *Helicobacter pylori* and stomach cancer."

In far more instances, he added, bacteria and viruses are most likely predisposing factors that essentially tilt the scale leading to cancer. "There are many cases of bacteria that produce genotoxic agents, particularly bacteria that hang around in the gut, and the thought is that some of these bacteria could be predisposing factors, for example, for colon cancer. It is also widely believed that the resident microbiota in our body most likely plays an important role in predisposing to certain types of cancer. This is a frontier that we're just beginning to explore."

It is also the impetus behind the name change of the Research Program from Molecular Virology to Virus and Other Infection-associated Cancers. "The idea is to broaden the focus, to think about other microorganisms as cancer causing agents and not just viruses," said Dr. Galan.

Cells constantly produce new proteins, which wear themselves out doing cellular labor. Spent proteins are tagged for removal by a maintenance protein called ubiquitin, and then sent to the proteasome, the body's equivalent of the glue factory. There, the old proteins are broken down and discarded. This process is called protein degradation.

Craig M. Crews, PhD, Lewis B. Cullman Professor of Molecular, Cellular and Developmental Biology, has been studying this process for years, looking for ways to control it with drug-like molecules that target cancer-causing proteins. His lab's first foray into this field led to the drug Kyprolis® (carfilzomib), approved in 2012 for use against multiple myeloma. Kyprolis® is a proteasome inhibitor that prevents the degradation of protein in cancer cells, causing a toxic build-up that kills them.

Now Dr. Crews and his colleagues have developed a different line of attack. "Instead of blocking protein degradation," said Dr. Crews, "we're inducing it. We've developed a drug strategy whereby the drug enters the cell, seeks out and binds to rogue cancer-causing proteins, and drags them to the proteasome for degradation. It's a seek and destroy approach." These drug-like molecules, called PROTACs (Proteolysis-Targeting Chimeras), were first reported by Dr. Crews in 2001.

Most targeted cancer drugs are inhibitors that bind to receptors and block the mutant proteins that cause cancer. "But when the drug leaves the system, the protein can start working again," Dr. Crews explained. "So, to get the clinical benefit, you need to maintain a high level of the drug in the body. What we're doing is different. It's not binding and gumming up the process, it's tricking the cell's own quality control machinery to destroy rogue proteins. It's also permanent. And the drug survives to eat its way through a protein population, so in theory, one needs less of our drug. This approach should greatly reduce the side effects that accompany high dosing in the inhibitor paradigm."

Another strength is the strategy's broad reach. Dr. Crews points out that each cell contains an estimated 20,000 different proteins, but only about 25 percent are potentially vulnerable to inhibitors, which work by binding receptors or blocking enzymatic functions. That leaves the great majority of proteins untouched, such as scaffolding proteins and transcription factors. Since Dr. Crews' approach doesn't depend on inhibition, it should work against this so-called 'undruggable' majority.

The science of tagging and eliminating oncogenic proteins is new, and so is the technology that makes it possible: a new class of small-molecule PROTACs

designed by Dr. Crews and his lab, a collection of cell biologists, biochemists, medical chemists, and pharmacologists. Dr. Crews believes that small-molecule PROTACs open up wide new possibilities for cancer therapies. He has started a company called Arvinas to explore them and to develop the technology further.

For now, Dr. Crews and his partners are interested in developing PROTACs for leukemias, lymphomas, prostate cancer, breast cancer, and lung cancer. "But this approach doesn't really have any limitations with respect to cancer type," said Dr. Crews. "It's a platform technology, so the learning around developing one drug could be applied to address the oncogenic proteins that cause different cancers in different tissues." He hopes that clinical trials for prostate cancer will begin sometime next year.

The National Institutes of Health (NIH) noticed this breakthrough and Dr. Crews was recently selected for the inaugural class of a new program at the NIH. He received an Outstanding Investigator Award and funding of \$1 million for each of the next seven years.

"I'm very fortunate that for the last 20 years my lab has worked right at the interface of chemistry and biology. It allows me to recognize the important questions in biology and allows my lab to then go out and tackle those problems using chemical approaches," said Dr. Crews.

Molecules That Seek and Destroy Mutant Proteins

Craig M. Crews, PhD

Bioinformatics Boosts Cancer Research

Michael Krauthammer, MD, PhD

Biomedical informatics is changing our understanding and treatment of cancer. That was recently illustrated when a team of Yale Cancer Center scientists used molecular sequencing and computational biology to reveal startling new information about melanoma.

The team analyzed exome data from 213 melanoma patients, the second largest such screening ever done. “We were looking for a better understanding of all the types of mutations that must happen for melanoma to occur,” said Michael Krauthammer, MD, PhD, Associate Professor of Pathology.

They found several surprises. Scientists already knew that most melanomas stem from mutations in either the BRAF gene (about 50 percent) or the NRAS gene (20 to 30 percent), but the mutations that caused the remaining 20 to 30 percent were unclear. Researchers did know that some melanomas contained mutations in the NF1 gene, but NF1’s role wasn’t well defined.

The Yale screen, conducted as part of the Yale SPORE in Skin Cancer, showed that mutations of NF1 account for 10 to 15 percent of melanomas, making them the third most important driver of the cancer. Further, NF1 mutations help activate the MAPK pathway, the same one activated by oncogenic mutations in BRAF and NRAS.

“This moves patients with an NF1 mutant melanoma

into a much better understood category,” explained Dr. Krauthammer, “particularly because it’s acting on a pathway for which we already have multiple drugs available. We didn’t have this knowledge before.”

There were other surprises. First, the genome of NF1 patients was much more mutated than those of other melanoma patients. Second, patients in the NF1 subgroup were also much older.

“That puzzled us,” said Dr. Krauthammer. “Why would they have so many more mutations – thousands of them – and be older?” The researchers noticed that NF1 mutations didn’t seem to be strong activators of MAPK. “That led to the interesting hypothesis that maybe these NF1 melanomas have to reside in the body longer and acquire more mutations to become as active and malignant as a BRAF or NRAS melanoma.”

The research team discovered that NF1 melanomas were acquiring additional mutations from a parallel disease, RASopathies. RASopathies are developmental disorders, such as Noonan syndrome and Neurofibromatosis, caused by germline (inherited) genetic mutations, as distinct from somatic mutations in cancer, which happen after conception and can’t be inherited. RASopathies were not known to be related to melanoma, but they do activate the MAPK pathway – the same one used by NF1. Dr.

Krauthammer and his team found that the mutations in RASopathies were identical to those in mutated NF1. Further analysis suggested that NF1 mutations by themselves are too weak to cause melanoma, but when joined with RASopathy mutations, the combination may activate the MAPK pathway for melanoma.

These findings began with the analysis of 20,000 genes for the mutations most important to melanoma. They have narrowed the list to about 100 genes – still a sizable number. “Melanoma has so many more mutations than other cancers,” said Dr. Krauthammer, “but we were able to identify a key subset of genes that we are going to sequence across a large cohort of melanoma patients that are treated at Yale. That will give us a big hint about what his or her response will be to the targeted therapies already in use against melanoma, or possibly to the new immunotherapies.”

The fact that so many mutated genes are implicated in melanoma is altering our understanding of cancer. “Suddenly it’s less about whether a disease is a developmental delay, or a skin cancer, or a blood cancer,” he added, “and more about the underlying molecular mechanism. That’s why bioinformatics is so useful in modern cancer research – to analyze a lot of data, recognize patterns, and establish links to mutations in other diseases.”

“There is a bit of a misplaced emphasis in the clinic and in clinical science as to how we think about targeting cancer,” said Andre Levchenko, PhD, John C. Malone Professor of Biomedical Engineering and Director of the Yale Systems Biology Institute. “There has been a strong focus on controlling primary tumor growth, even though we know that more than 90 percent of cancer deaths occur because of invasive cell behavior, or metastasis. The main problem isn’t the growth of the primary tumor, it’s the ability of cancer cells to change their behavior to invasive migration and travel to secondary sites.”

The emphasis on tumor growth, he added, stems partly from the difficulty of studying the causes and engines of cancer cell migration. That’s changing, thanks to new tools and technologies, some of them unique to Dr. Levchenko’s lab, where custom-built devices and new methods of analysis are allowing researchers to trace the movement of cancer cells, the cues that incite their invasion, and the signals that guide them to new locations during metastasis.

“Their circuits get rewired,” said Dr. Levchenko, “so instead of staying put, they start moving toward this big highway system, the bloodstream.” Eventually they navigate toward tissues very different from their native environments, constantly adjusting to different

circumstances, and colonize. “The process is very complex and not well understood,” said Dr. Levchenko, “but it’s a systems problem, so we need to use systems approaches.”

His lab and other groups at the Systems Biology Institute, which he has been leading for the past two years on Yale’s West Campus, are trying to understand what transforms site-specific tumor cells into a far-ranging invasive army. What networks of molecules mediate this switch? How do invasive cells communicate and coordinate? Which neighboring cells resist? Which collaborate with the invaders? How do cancer cells develop new behaviors and change the behaviors of neighboring cells?

Many of the answers lie within the complex system of signaling networks, the fundamental interest of Dr. Levchenko’s lab and the Institute. In cancer, normal communication between cells gets misinterpreted, disrupted, or corrupted. “If we can understand the signaling mechanisms,” he said, “we can develop new therapies that prevent invasive spread – for instance, by rewiring these networks. There’s already a lot of activity to generate novel therapeutics to do that, and we are working with others to determine the fastest translational path for clinical applications. That’s the ultimate goal.”

They are concentrating on what Dr. Levchenko calls

“the champions of invasive behavior” – glioblastoma and melanoma, two of the most deadly and fast-moving cancers, and also breast cancer, another aggressive malignancy. A recent paper described how individual metastasizing breast cancer cells become generally exploratory, searching for the bloodstream, and then, in response to a cue, suddenly band together in one direction, as if they have received their orders of invasion. “As soon as there is a clear indication of where they want to go,” explained Dr. Levchenko, “they begin moving almost in goose step with each other.”

He and his colleagues were able to collect this extraordinary information by building devices that can track the path of a single cell and its changing behaviors in response to cues and signaling networks. These tools give the scientists novel ways to investigate and analyze a single cell, looking at every gene, at the metabolizing proteins, and other factors.

He believes that understanding the complexity of signaling networks and the process of metastasis demands a multidisciplinary approach. The teams he has put together at his lab and institute include researchers of diverse disciplines: evolutionary biologists, synthetic biologists, and systems biologists, but also physicists, mathematical modelers, and biomedical engineers.



Andre Levchenko, PhD

Decoding the Signals of Metastasis

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