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28 Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven
Research in cancer has never been more important or timely as it is now. In just one year, our ability to sequence the genome quickly and cost effectively has transformed the focus of our research projects at Yale Cancer Center. Each of our seven research programs is seeing the positive impact with exciting new projects that are helping to translate research from our labs to benefit patients at Smilow Cancer Hospital at Yale-New Haven.

Yale Cancer Center and Smilow Cancer Hospital continue to focus on recruiting the very best clinicians and scientists to our team. In 2011, we welcomed Roy S. Herbst, MD, PhD, as Professor of Medicine, Chief of Medical Oncology, and Associate Director for Translational Medicine. Roy joined us from MD Anderson Cancer Center where he was chief of medical oncology in the section of thoracic oncology. Howard Hochster, MD was recruited from New York University Cancer Institute to lead our Gastrointestinal Cancer Program and our clinical research efforts. In addition, Anees Chagpar, MD joined us from the University of Louisville to direct the Breast Center at Smilow Cancer Hospital. Bolstering our research efforts, Lieping Chen, PhD moved his lab from Johns Hopkins University in September to lead our Cancer Immunology efforts.

Over the last two years, 41 clinicians and scientists have joined Smilow Cancer Hospital and Yale Cancer Center. We continue to recruit some of the nation’s best oncologists and scientists to support our patient care and research goals.

This year, we signed two important collaborative agreements with industry leaders to help push our translational research efforts forward. In March, Yale University and Gilead Sciences, Inc. signed a 10-year, $100 million, funding agreement to support new cancer research initiatives in Yale’s Cancer Biology Institute. We are also under a shared agreement with the Sarah Cannon Research Institute, a national leader in cancer clinical research. Our partnership with Sarah Cannon will provide great synergy between Yale’s deep science and translational research efforts and their clinical research expertise.

As we move into the New Year, we will continue to build on these efforts and I look forward to sharing new research advances and outcomes from our laboratories and clinics in 2012.

Sincerely,

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

“Over the last two years, 41 clinicians and scientists have joined Smilow Cancer Hospital and Yale Cancer Center. We continue to recruit some of the nation’s best oncologists and scientists to support our patient care and research goals.”
When Bonnie Lurie was diagnosed with breast cancer, she was already learning the ropes of surgery she could teach her own sons. “It’s a career,” she explained. “I used to do it for fun.” This surgeon explained to her that she could choose between several options to reconstruct what had been lost to the tumor. “I wasn’t even planning on having something there,” Bonnie said. “The choice to have to decide we’re going to reconstruct a breast, even if it’s one breast, is toxic.”

Bonnie explained that the choose because she wanted to avoid radiation therapy and to look younger and healthier. She was aware of the risks and complications associated with radiation therapy, including increased risk of cancer recurrence. Despite these risks, she chose to undergo reconstructive surgery to avoid radiation therapy and to reduce her risk of getting cancer in the other breast. Her plans for a double mastectomy and reconstructive surgery were in place. “I wanted to be in control of the situation,” she explained. “I wanted to be able to make decisions about my own body.”

Bonnie decided on reconstructive surgery and was able to choose from several options to personalize what might be best for her. She was able to choose between a tissue expander and a DIEP flap, which creates a result that looks and feels more natural. She chose the DIEP flap because it offered a better cosmetic outcome and a quicker recovery period. And they get the benefit of “waking up” from anesthesia once instead of twice. They also face a single safety procedure, which is improved because a woman is put under anesthesia once instead of twice. The entire care team plans in close consultation with each other and the patient.

Dr. Chagpar and Alexander Au, MD, a reconstructive surgeon and frequent collaborator. The entire care team plans in close consultation with each other and the patient. The model of collaboration, patient-centered care is one of the reasons that Yale was recently designated a NCI-designated Comprehensive Cancer Center. This surgical teamwork is indicative of a larger philosophy at the Breast Center, says its Director, surgical oncologist Anees Chagpar, MD. “Breast cancer is like a big jigsaw puzzle. We all have pieces,” he explained. “Patients do best when we all work together.”

For Bonnie, speed was key. She was diagnosed with breast cancer in November 23, 2010 and had her surgeries December 3, 2010. “I didn’t want to go into a corner to change,” she explained. “I didn’t want to go into a corner to change.”

Better circulation means more rapid healing and a decrease in complications. Together with reconstructive surgeon Stephanie Kwei, MD, he is also investigating the use of three-dimensional photography to improve shape and assess volume in reconstructed breasts.

For Dr. Au, the drive to provide extraordinary care is personal. He was a high school student when his parents came to the dinner table and explained that his mother had breast cancer. Though his mother remained “very calm” during the news, the experience was obviously stressful and made more so by the traveling required to have her surgery performed at a high volume center specializing in breast reconstruction that was two hours from their home. The simple convenience of having cancer and reconstructive surgery together is no small thing, said Dr. Au. “When immediate reconstruction at the time of mastectomy can be performed, it relieves some of the stress by minimizing the number of operations a woman undergoes,” he explained.

The Breast Center is committed to taking care of the whole patient — mind, body, and spirit — and this patient-centered philosophy percolates every aspect of the organization. A patient’s first appointment includes a thorough discussion with their surgeon, as well as an introduction with other members of the Breast Center team. “Our goal is to ensure that women who often come to see us in a state of high anxiety and confusion, leave fully understanding their condition, their options, and often with a plan of action,” says Dr. Au. “We have the expertise of the fundamental pillars of patient care at Smilow in personalizing therapies to suit individual patients.

Dr. Au, like other plastic surgeons at the Breast Center, is committed to improving reconstructive techniques through research and clinical trials. This is especially true for Dr. Au, who recently joined the Breast Center, is reflective of the elite skill level of surgeons here. He completed a fellowship incutaneous oncology and reconstructive surgery after completing residency in plastic surgery at New York Presbyterian Hospital. He achieved amazing results. He was one of the first patients.

“Women get the gym,” he said. “I don’t go into a corner to change.”

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Yale Cancer Center

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Two Surgeons
are better than one.
The first sign Maureen O’Grady had that something might be wrong was a cough that lingered long after the fall allergy season had come and gone. After having an x-ray, she was told that she needed to visit a pulmonary specialist, who after additional testing gave her the news that she had lung cancer. She was then referred to an oncologist who confirmed the diagnosis as stage IV and told her that she had 12-18 months to live, at most.

At the age of 55 Maureen was not ready to accept this as the truth. She knew there had to be other options out there, and sought the advice of a friend who gave her Dr. Scott Gettinger’s name at Smilow Cancer Hospital at Yale-New Haven. Dr. Gettinger is an Associate Professor of Medicine (Medical Oncology) and an expert in the treatment of lung cancers.

Maureen commented that from the moment she contacted Dr. Gettinger’s office she knew she wasn’t alone, “I was told that a whole team would be taking care of me including nurses, social workers, and physicians. This was wonderful news to hear and gave me the hope I needed to fight this disease. When I met with Dr. Gettinger he told me I was not curable, but treatable. I was relatively young and in good shape. This was not exactly a happy moment for me, but it gave me reassurance that there was something I could do to prolong my life.”

After hearing all of her options, Maureen decided on an aggressive course of chemotherapy. She showed progress, but could no longer tolerate the treatment. She received subsequent standard chemotherapy infusions, including an oral chemotherapy, and when these treatments failed, she entered her first clinical trial. While on this trial, she showed decrease in tumor growth in some areas, but also increases in others. Due to these increases, she was offered the choice between two new clinical trials. After weighing her options carefully and reviewing all the information with her doctor, she chose a trial testing the efficacy of a drug known as an anti-PD1 therapy.

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Beating Cancer
by Trial and Error
Ronald Salem, M.D., came to Yale Cancer Center 21 years ago to operate on patients with a wide range of cancers. But the longer he practiced, the more he found himself concentrating on patients with pancreatic cancer.

“I’ve really been fascinated by how poor the outcome in pancreatic cancer is and how we as surgeons can improve that outcome,” he explained. “Pancreatic surgery was often considered too risky for patients. It has become much safer over the last 10 years, with low mortality rates of about 1%.”

Pancreatic cancer remains one of the most difficult cancers to cure. But at Yale, an interdisciplinary team specializing in pancreatic cancer is creating hope for patients through innovative strategies: catching dangerous lesions before they become cancerous; making “inoperable” tumors operable through other therapies; and developing new drugs to improve outcomes.

“Perhaps what’s most exciting is the fact that we’re now able to identify patients with abnormalities of the pancreas that are going to become cancer,” Dr. Salem explained.

...I will always be grateful.”

For Maura, this discovery was a miracle. A trial of anti-PD-1 therapy was initiated at Yale in five cancers: melanoma, kidney, prostate, colon, and lung. Maura has been on the trial since June of 2010 and has shown a dramatic response to the therapy. At the time she entered the trial her prognosis was poor and her quality of life low. She had full-blown signs of metastatic disease involving her liver, kidneys, lungs, and heart. Over a year later, all signs of disease have shown a substantial reduction in size.

“The ability to identify and treat patients like Maura,” Dr. Getinger said, “is just absolutely incredible.” Maura’s story is a testament to the power of precision medicine, a philosophy that has been embraced at Yale and around the world. Maura’s response has been remarkable, her disease-free interval of 18 months has given her and her family hope that she may be able to live a normal life.

“Many patients with advanced pancreatic cancer have historically been considered ‘untreatable’,” Dr. Getinger said. “But with the development of new drugs and therapies, we are able to offer hope to patients like Maura.”

Now the goal is to determine why this drug is working in patients like Maura, and in others. The Yale clinics and labs have joined forces and are collecting blood samples and tumor tissue from patients; they hope to be able to discern which patients should be treated with this anti-tumor drug, and develop new therapies for those it’s not working for.

“Perhaps what’s most exciting is the fact that we’re now able to identify patients with abnormalities of the pancreas that are going to become cancer,” Dr. Salem explained.
Typically, these abnormalities first show themselves by chance, perhaps during a CT scan to find a kidney stone or to look into a lung infection. “The doctors in our Interventional Endoscopy Program are world-class at identifying these lesions,” Dr. Salem said. By carefully evaluating the risk of a lesion becoming cancerous, they can recommend potentially lifesaving surgery while avoiding unnecessary operations.

Early imaging studies have tremendous benefits, but there is a hitch. “No one is sure who to screen,” said Howard Hochster, MD. He is an oncologist who recently came to Yale to increase clinical trial opportunities for patients with advanced cancers, including pancreatic. A clear set of risk factors has not been identified for pancreatic cancer. That’s one of many examples of how knowledge about the disease is lacking. Dr. Hochster collaborates with doctors from many disciplines, as well as laboratory scientists, to develop more information, and therefore better weapons, against the disease.

One of the newer, and most effective, weapons used against pancreatic cancer is neoadjuvant therapy. “We cannot cure a patient if we can’t operate,” said Dr. Salem, who is the Lampman Professor of Surgery, but some tumors are inoperable. Traditionally cancers are treated first with surgery to remove the tumor, then with adjuvant therapies—the chemotherapy and radiation—to deal with any cancer cells that may be left behind. Neoadjuvant therapy reverses the order. When a patient comes in with a tumor too extensive to remove, chemotherapy and/or radiation can be used to shrink the tumor to the point where a surgeon can excise it. Patients have the choice of standard chemotherapy or radiation therapies and increasingly of new therapies being offered through a growing number of clinical trials at Yale Cancer Center. Many of those trials are being spearheaded by Dr. Hochster, who became fascinated with clinical research as a student at the Yale School of Medicine, under the late Sterling Professor of Medicine and Epidemiology, Alvan Feinstein. “He was trying to inject a degree of scientific rigor into clinical therapies,” remembered Dr. Hochster. Back in the 1970s, studies might consist of only 20 patients, with no control groups and little in the way of statistical analysis. Today, many volunteers participate in a single study, often at multiple sites, and controls and analysis are meticulous. It is painstaking work that ultimately worthwhile. “It makes it possible to offer our own patients the newest therapies,” said Dr. Hochster.

He is currently investigating agents that may block the division of pancreatic cancer cells, which are notorious for their rapid growth. Dr. Hochster is also evaluating ways to deliver effective chemotherapy while reducing the side effects that patients experience. Together with radiation oncologist Peter Glazer, MD, PhD, he is looking into an antibody that can destroy pancreatic cancer’s DNA and increase the effectiveness of radiation therapy. Finally, Yale’s extensive technical resources and expertise in genetics hold the possibility of developing “personalized” treatments that would target the exact molecular structure of an individual’s tumor. Patients are already enrolled in some clinical trials for new pancreatic therapies. Other therapies are still being fine-tuned in laboratories.

Dr. Salem was initially drawn to specialize in pancreatic cancer because of its often daunting prognosis. Physicians are still far from satisfied with the tools at their disposal, but the pancreatic team is able to offer patients new options that are leading to better outcome. “Today there is more hope for our patients because of the extraordinary efforts of our teams.”

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“Clinical trials developed at Yale make it possible to offer our own patients the newest therapies.”

Howard Hochster, MD
In 2007, Francis Corr was facing bad news. He had already begun through chemotherapy and a surgery to remove several melanomas on his lungs. Now a new spot had shown up, close to the heart. The retired teacher’s cardiac health was already poor. Operating to remove the melanoma was problematic at best. Fortunately, Mr. Corr was still not out of options.

He became the first patient at Yale to receive stereotactic body radiotherapy (SBRT), a highly precise and extremely powerful radiation treatment. Four years later, Mr. Corr, 77, is in “the prime of life,” he says. Years of follow-up scanning have revealed no signs of cancer.

Mr. Corr’s radiation oncologist, Roy Decker, MD, PhD, brought the therapy to Yale Cancer Center. When Mr. Corr first came to Yale, he was treating lung cancer patients with conventional radiation therapy. He started an SBRT program for people like Mr. Corr, who were poor candidates for surgery. Patients who are frail or have already lost sections of their lungs to conventional surgery may fall into that category.

“The results were so much better than any of the alternatives,” explained Dr. Decker.

Yale’s program is the oldest in New England. In just four years, Dr. Decker has treated about 300 patients. Establishing the program was no small feat, as it requires advanced technology and collaboration between various medical specialists and physicists.

The procedure, generally repeated for three to five sessions, is completely non-invasive. About half of patients experience no side effects. The most common side effect is mild-to-moderate fatigue.

Stereotactic radiosurgery was introduced in the 1950s, when surgeons used Gamma Knife technology to treat brain tumors, explained Dr. Decker. Because the radiation must be precisely targeted, a frame is screwed into the patient’s skull. But for the patients Dr. Decker treats, targeting is not at all invasive. They are stabilized in a cushion that reminded Mr. Corr of a beanbag chair. A simulator even captures and compensates for the motion of the patient’s breathing.

The radiation is delivered overhead from “what looks like a spaceship,” Mr. Corr remembers. Actually, the machine is complex in part because it includes a cone beam CT scanning, explained Dr. Decker. That allows for extreme precision.

The largest U.S. trial of SBRT showed it to be 91 percent effective. With these outcomes and the low incidence of side effects, the procedure appeals even to patients who may have other options. “People are starting to ask for this as an alternative to surgery,” said Dr. Decker.

But Dr. Decker cautions that the procedure is so new that it is impossible to compare its long-term results with those of surgery. “[We’re] not certain that this is as good as surgery or that it will be as good as surgery 10 to 15 years down the line,” he explained. So his approach remains cautious; SBRT is only used for those patients who are poor candidates for surgery.

As evidence about the procedure grows, in part through Dr. Decker’s own research program, SBRT’s use may increase, according to Frank Detterbeck, MD, surgical director of the Thoracic Oncology Program. “The reality is that we use a different spectrum in lung cancer today,” he explained. SBRT has proven especially effective against less aggressive lung cancers. These cases are on the rise, Dr. Detterbeck said, but identifying cancers that are likely to stay localized is still difficult.

As keenly aware about the chances and potential therapies increases, it becomes more critical that doctors from various disciplines work together to offer a patient optimal treatment. “It is like a crew with some depth and some focus on oncology,” said Dr. Decker.

Typically, a patient’s first visit will show cancers disappearing in nine to 18 months after SBRT. Conventional radiation therapy causes changes over time as well. It is effective because it damages the DNA of cancer cells, causing them to die when they attempt to divide. SBRT may or may not cause the same reaction, said Dr. Decker.

For Mr. Corr, precisely how SBRT eliminated his melanoma is not the point. “It’s worked. They call me The Miracle Man,” he says with a laugh.
The National Cancer Institute estimates that 157,000 people in the U.S. will die from lung cancer in 2011. About 80 percent of all lung cancers are non-small cell (NSCLC), the most deadly type, because it often metastasizes before it is diagnosed.

Roy S. Herbst, MD, PhD, Professor of Medicine (Medical Oncology), Chief of Medical Oncology, and Associate Director for Translational Research, has devoted his career to NSCLC research. He is the co-lead investigator for the groundbreaking clinical trial called BATTLE (Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination).

In the first trial, BATTLE-1, the tumors of NSCLC patients were biopsied for molecular analysis. Based on this molecular profile, each patient was treated with one of four possible drug combinations. Dr. Herbst and his colleagues found that patients treated on the basis of their individual profiles showed more improvement than patients who got the standard drug regimen while identifying predictive markers and signatures.

A second trial, BATTLE-2, will begin at Yale in early 2012, with funding from the National Cancer Institute as well as the Diane and David B. Heller Foundation, which recently pledged $1 million over three years to the project. Dr. Herbst expects the trial to enroll about 400 people. Between 50 and 100 of these will be at Yale, the rest at the University of Texas MD Anderson Cancer Center, where he worked before bringing the BATTLE program with him to Yale in spring of 2011. The trial will run for about three years.

In BATTLE-2, Dr. Herbst will be looking for combinations of drugs that are effective against oncogenes that are currently drug resistant. His primary target is \( \text{RAS} \). "That’s an activated oncogene found in about 30 percent of non-small cell lung cancers," he said. "Tumors that are \( \text{RAS} \) mutated rarely respond to chemotherapy, so to find a drug combination that works against it would be a big deal."

The findings of BATTLE-1 have motivated other cancer centers to begin using biopsy and molecular profiling on patients with lung cancer. But Dr. Herbst said that BATTLE remains unique in one crucial way. "Other cancer centers often use a biopsy done at the initial cancer diagnosis, which can sometimes be long before the patient is treated, or a biopsy done before the patient had different chemotherapies or radiation therapy. We get a new biopsy exactly at the time we’re treating that patient, because that more accurately reflects the state of the tumor in real time," said Dr. Herbst. "We have shown that a new biopsy makes a difference, because the tumor may have become drug resistant, and then you can figure out the best way to target that mechanism."

"There is tremendous potential here for scientific discovery in multiple cancer types."

In the future, he expects all cancers to be biopsied, analyzed, and treated with drugs that match their specific molecular profile. He believes that in the future this personalized approach will reduce or even eliminate the need for chemotherapy.

Identifying new cancer therapies is part of Dr. Herbst’s role as Associate Director for Translational Research. Working closely with his colleague, Dr. Julie Boyer, in the newly-formed Translational Research Program, he launched a funding program for promising collaborative projects between basic scientists and clinicians. Nearly a dozen cooperative projects are underway. "There is tremendous potential here for scientific discovery in multiple cancer types," he said. "I’m trying to bring laboratory work and patient care together, to translate the findings of basic research to the clinic, where we can further understand the mechanisms of drug action and modify their use to achieve the greatest benefit for patients."
In the last 18 months,” said Richard P. Lifton, MD, PhD, Bridgman Professor of Genetics and Professor of Medicine (Neurology), “science related to cancer has changed drastically.” The reason is a revolutionary breakthrough pioneered at Yale by Dr. Lifton: the ability to rapidly, inexpensively, and accurately identify mutations in susceptibility genes across whole-exome sequencing.

“Science related to cancer has changed drastically,” said Richard P. Lifton, MD, PhD, Sterling Professor of Genetics and Professor of Medicine (Nephrology), “science related to cancer has changed drastically.” The reason is a revolutionary breakthrough pioneered at Yale by Dr. Lifton: the ability to rapidly, inexpensively, and accurately identify mutations in susceptibility genes across whole-exome sequencing.

“It’s well known that most cancers are driven by so-called somatic mutations—alterations in DNA that occur after conception. But until now, science has only been able to guess which mutations contribute to cancer. Dr. Lifton’s recent research ends the guessing.

“We can sequence all the genes in the tumor and see what the actual mutations are,” he explained. “And we can identify which ones are the drivers that cause cancer by finding that the same gene is mutated in different tumors more frequently than would be expected by chance.”

Dr. Lifton demonstrated the power of this new technology during the past year by using it on adrenal tumors associated with hypertension. Using gene sequencing, he discovered that either of two mutations in a single gene account for half of these tumors. A diagnostic blood test to detect these mutations in DNA would identify patients with an adrenal tumor, and they could then be prioritized for surgery and cured.

“This is an illustrative example of how this sequencing technology can take a heretofore very mysterious tumor, about which almost nothing was known about its causation,” said Dr. Lifton, “and identify mutations that explain the tumor’s biology lock, stock, and barrel.”

The same technology and approach is being applied to cancers. “In the next several years,” said Dr. Lifton, “thousands of patients will have their tumors sequenced, and this will define the genetic landscape of every cancer in the human body.”

Dr. Lifton is particularly interested in exploring why some primary tumors turn metastatic while others do not. That information would make an immense difference in treatment regimens. If a doctor knows that a patient’s tumor is unlikely to metastasize, surgery might be enough, with no need for chemotherapy and other painful, expensive treatments. On the other hand, if the tumor has a high likelihood of metastasizing, aggressive treatment could begin right away. “These are specific questions that we can tackle just by sequencing patients who did or did not have metastatic disease,” said Dr. Lifton.

His team is also looking for “the fundamental genetic architecture that underlies these cancers.” He expects to learn if systemic changes in the primary tumor initiate metastasis, and if the mutations that drive tumors to metastasize to the lung, the brain, or the liver differ from one another or are shared among all metastatic tumors.

Once the genes are identified, a patient’s treatment can be tailored to the underlying mutation.

This extraordinary breakthrough was made possible by Dr. Lifton’s discovery of a way to sequence the exome rather than the entire genome. The exome represents only one percent of the genome, but it is crucial for protein coding and is the region where most disease-causing mutations occur. “You’re only sequencing one percent of the genome,” said Dr. Lifton, “which makes it faster, and you’re doing it at much less expense.” In two years, the cost of exome sequencing has dropped from $2,500 to under $1,000.

The time and cost will fall drastically as researchers learn more about the mutations responsible for certain cancers, which will allow them to sequence even smaller sets of genes. “When we get down to that level,” said Dr. Lifton, “the cost is going to be a rounding error in the overall cost of care of a cancer patient, so we’re going to do this routinely on everybody. These are very exciting times.”
Testing a New Approach to Make Stem Cell Transplantation Safer for Patients

Chemotherapy and radiation therapy followed by the infusion of blood stem cells from another person (called allogeneic hematopoietic stem cell transplantation or alloSCT) can be a curative therapy for patients with leukemia. However, more than half of patients will develop graft-versus-host disease (GVHD). GVHD occurs when T lymphocytes contained in the donor stem cell graft recognize cells in the patient as “foreign” and attack them.

“Nearly half of the deaths from alloSCT can be attributed to graft-versus-host disease or infections that largely occur as a consequence of immunosuppression used to prevent and treat GVHD,” said Warren D. Shlomchik, MD, Associate Professor of Medicine (Hematology) and Co-Director of the Yale Cancer Center Cancer Immunology Research Program.

Because of the dangers of GVHD, all alloSCT patients receive immunosuppressants, but these same drugs inhibit the reconstitution of the patient’s immune system and decrease the power of the graft-versus-leukemia effect (GVL)—that is, the ability of the transplanted T cells to fight the patient’s cancer cells.

Dr. Shlomchik studies immunology related to alloSCT. The goals of his work are to find ways to decrease the incidence of GVHD and to increase the effectiveness of GVL. When T cells attack and clear infections, some of the cells turn into what are called memory T cells, which remain in the body and can respond rapidly to reinfection. “That is why you don’t generally get infected with the same pathogens over and over,” said Dr. Shlomchik. “It’s immunologic memory.”

He wondered whether these memory T cells played any role in GVHD. Working with his brother, Mark Jay Shlomchik, MD, PhD, Professor of Laboratory Medicine and Immunobiology, their group discovered that memory T cells, overall, cause less GVHD than T cells that had never responded to infections. That finding has led to a clinical trial now being conducted at Yale Cancer Center and the Fred Hutchinson Cancer Research Center in Seattle, Washington. The trial is testing the hypothesis that selectively transferring memory T cells, which include those that recognize infections that commonly plague transplant recipients, at the time of alloSCT will protect leukemia patients from infection with a lower risk of GVHD than when all types of donor T cells are transferred.

First the memory T cells in the donor’s blood stem cell product must be separated from the naïve T cells, which are T cells that have never responded to an infection or antigen. Dr. Shlomchik and colleagues devised a new way to do this. Naïve T cells but not memory T cells express on their surface a protein called CD45RA. Donor cells are mixed with small magnetic beads conjugated to an antibody that recognizes CD45RA. The antibody binds to the market, and then the cells are passed through a strong magnet that pulls out the magnetized naïve T cells, leaving memory cells that can be transplanted into the patient.

“We’re hopeful that depletion of naïve T cells will result in less GVHD and better immune reconstitution.”

“One of our ideas for the future is to vaccinate the transplant donors against a target antigen expressed by the patient’s cancer cells but not expressed by the donor,” said Dr. Shlomchik. “That would cause memory T cells in the donor, which are reactive against the cancer cells. Transferring these memory cells to the patient as part of the stem cell transplant should augment the anti-tumor effect.” Dr. Shlomchik’s group recently published proof-of-principle for this approach in a mouse model (Blood, 2011. 118(22): p. 5965-76).
Chronic viral disease often leads to cancer. People with chronic hepatitis B virus (HBV) infection, for instance, are at high risk for liver cancer, a disease that’s usually fatal. Of the 300 to 400 million people worldwide with chronic HBV—ten times the number infected with HIV—500,000 die each year from HBV-related cancer of the liver.

Those staggering figures are behind the collaboration of John K. Rose, PhD, Professor of Pathology, and Michael Robek, PhD, Associate Professor of Pathology. Their research may point the way to a vaccine that could prevent liver cancer in HBV patients.

Their research begins with the unique vaccine vectors developed by Dr. Rose from vesicular stomatitis virus (VSV), which is typically found in livestock. Dr. Rose discovered that VSV vectors induce unusually strong immune responses. He devised the VSV vaccine vectors with another chronic viral disease in mind—HIV. The immunosuppression caused by that disease can open the door to Kaposi’s sarcoma or lymphoma. Dr. Rose’s subsequent research revealed VSV vaccine vectors generated an immune response in monkeys, which controlled the spread of an HIV-like virus following challenge.

Dr. Robek wondered whether VSV could be adapted as a vaccine vector against HBV. The two scientists, whose labs are next door to each other, began collaborating on the idea seven years ago. The results look very promising.

The current vaccine for hepatitis B prevents infection but is useless to people already chronically infected. And though there are drugs to control chronic HBV, noted Dr. Robek, “they don’t cure the infection, and if you stop using them, the virus comes back.” A possible solution to both of these flaws in current treatment is what’s known as therapeutic immunization—a vaccine that not only protects but also heals. “If we could cure people with chronic HBV,” said Dr. Robek, “that would prevent them from getting liver cancer. That’s potentially a very large public health impact.”

Many scientists are working on possible therapeutic immunizations via poxviruses, adenoviruses, and lentiviruses, but only Yale Cancer Center is testing VSV as an HBV vaccine vector. Based on preliminary findings, Rose and Robek believe that VSV has several crucial advantages.

“We have found that our VSV-based HBV vaccine induces superior immune responses in mice compared to other vaccination approaches,” said Dr. Robek. “It induces much stronger CD8 T cell responses.” That factor also sets the vaccine apart from the current HBV vaccine, which induces an antibody response to prevent infection, but can’t cure an infection that’s already present. By contrast, CD8 T cells not only help infected infected with the virus, they also release cytokines, proteins that bind to other cells and help prevent the infected cells from replicating. Essentially, the VSV vaccine holds the potential of inducing a strong immune response that erases HBV in chronically infected people and prevents the high risk of liver cancer.

Meanwhile a company called Profectus Biosciences recently started a phase I clinical trial of an HBV vaccine based on Dr. Rose’s VSV vaccine vector. The first patient was injected on October 26. “If it’s found to be safe and immunogenic,” said Dr. Rose, “then using the vaccine vectors for other things, such as HBV, will become easier and faster.”

Most recently Dr. Rose’s lab had another breakthrough. Using a VSV vaccine vector, they were able to protect monkeys from becoming infected with an HIV-like virus. That’s been very difficult to do,” said Dr. Rose. “This is definitely where things are in terms of the last year.”

Molecular Virology RESEARCH PROGRAM

Vaccine Vectors to Cure Chronic Disease
A diagnosis of cancer is often the first step in a long, convoluted journey through the healthcare system. A patient and family can easily get lost in the maze. The role of the advanced practice registered nurse (APRN) in oncology has emerged as key in meeting the goals of patient-centered care. The APRN directs the coordination of patient care, lowers the chance of medical errors, functions as the patient’s confidante, provides support during decision making, improves the patient’s outlook, and facilitates recovery. The care the APRN provides translates into fewer readmissions, better symptom control, and fewer urgent care provider visits, reducing stress on the patient, the family, and the healthcare system. These are the conclusions of Ruth McCorkle, PhD, Director of the Psycho-Oncology Program at Yale Cancer Center, and also Florence S. Wald Professor of Nursing and Professor of Epidemiology. Her findings of the impact of the APRN role are being translated into better care at Smilow Cancer Hospital at Yale-New Haven. Several factors are driving the need to re-think cancer care, said Dr. McCorkle. Cancer has largely become a chronic illness. Patients with advanced disease are living longer, which presents challenges for the patients, their families, and providers. Their cancer may be complicated by co-existing chronic illness, such as high blood pressure or diabetes. Similarly, cancer survivors may be faced with long-term treatment-related problems and may be at risk for other chronic illness related to cancer therapy. The number of patient(s) they communicate with also complicates their care, adding further psychological stress. Fragmentation of care places onus on patients and family for poor outcomes. The majority of patients are seen for provider visits and treatment in the outpatient setting. Patients and families must be knowledgeable and skilled to manage their own care outside of these episodic visits. The interactions between drugs must be vigilantly monitored and all providers must be kept apprised of the patient’s care and any changing conditions. If you don’t have someone who’s on top of all this,” said Dr. McCorkle, “the patient comes in and is asked, ‘What’s going on today?’ And they do something to take care of their problem that day and then say, ‘Come back in one or two weeks or a month.’ A person can really get into a lot of trouble even over the course of one week if they are not adequately prepared to manage their symptoms, know what to expect, and recognize when to call for help. The APRN on the disease management team is in the constant contact with the patient and family, the glue that holds everything together. For example, someone with diabetes who has cancer surgery might be worried about the incision healing and managing their blood glucose. The APRN has the knowledge and skill to monitor the physiologic parameters (blood glucose, incision healing, proper diet), assess the level of psychological stress, and provide timely intervention to decrease the risk of complications, which may delay treatment.” Dr. McCorkle’s convictions about the contribution of APRNs in cancer care are strongly based on 35 years of research and are being put into practice with the system of multidisciplinary disease management teams at Smilow Cancer Hospital. The teams see patients together in order to facilitate treatment options and ensure compliance with the best treatment plan. “The whole team is in the same place,” said Dr. McCorkle, “and the teams APRN manages patients throughout all of their treatment. The APRN’s communication and collaboration with the teams on behalf of every patient ensures coordinated care.” “Patients like having a relationship with an APRN,” said Dr. McCorkle. “They say, ‘Hey, I’ve got somebody who’s going to take care of me, and can help. That means makes me feel like I matter.’”
DNA is so unstable that scientists estimate there are more than 20,000 DNA lesions per cell each day. The body’s base excision repair system (BER) stays busy removing these lesions and mending DNA. But sometimes, if the repair system is imperfect or damaged in some way, DNA lesions go unfixed. This defective DNA can cause cellular mutations that result in cancer.

Joann Balazs Sweasy, PhD, Professor of Therapeutic Radiology and of Genetics, studies DNA repair processes. She has recently reported two exciting findings. She and her colleagues searched databases from the National Institutes of Health, looking for DNA repair genes that might be mutated in the germline. They typed 2,700 individuals and found two coding variants that might result in abnormal proteins that could cause cancer.

Dr. Sweasy began the first-ever study of one of those polymorphisms, polymerase beta (Pol ß). When BER is functioning correctly, it excises the DNA lesion and then fills in the gap with a DNA polymerase. Dr. Sweasy discovered that Pol ß works more slowly than a normal polymerase and doesn’t fill in all the gaps, which accumulate. “That leads to double-strand breaks, chromosomal aberrations, and massive genomic instability,” said Dr. Sweasy.

The discovery is important, she added, because it suggests that people who carry this Pol ß variant—about three percent of the world’s population, mostly Eastern Europeans—could be at increased risk for cancer. If the Pol ß population were identified, doctors could do early monitoring for cancer. These people also might be candidates for studying the role of anti-oxidants, since reactive oxygen is linked to DNA base damage.

At the moment, it’s unknown what types of cancer Pol ß might be related to. One small experiment reported that tumors with the variant who were treated for lung cancer did much worse than everybody else. Dr. Sweasy has found a possible link to increased risk for breast cancer. She and her colleagues screened breast cancer patients for the variant and found that about 10 percent of the population—a significant number—carry the variant.

The second exciting finding, also drawn from the databases, relates to an enzyme called glycosylase, which cuts out the base of damaged DNA in this system. Dr. Sweasy discovered that about 10 percent of the population has a glycosylase mutation in the germline, which makes their tumors become extremely sensitive to 5-fluorouracil (5-FU), an inexpensive drug used to treat a variety of cancers, including breast, pancreatic, and colon.

Finding Flaws in the Body’s DNA Repair System

Joann Balazs Sweasy, PhD

The question we’re really asking is which mutations are actually associated with cancer risk and which can possibly cripple the repair system.
Breast cancer spreads when tumor cells grow protrusions called invadopodia. These structures jab and chew holes in the basement membrane surrounding the tumor, allowing cancer cells to escape. But how are invadopodia created within the cell? If that process could be discovered and disrupted, breast cancer might lose the ability to spread.

Anthony J. Koleske, PhD, Professor of Molecular Biophysics and Biochemistry and Neurobiology, is well on the way to understanding and perhaps disabling invadopodia. “The secret is that all the building materials for invadopodia are in the cell, ready to go,” said Dr. Koleske, “but there needs to be a chemical cue or signal to assemble these materials into one of these structures. One of the cues is a growth factor called epidermal growth factor (EGF). We’ve elucidated a series of steps that involves passing signals from one protein to the next, which eventually triggers the assembling of these building blocks into a protrusion.”

Dr. Koleske and his lab traced the path of all these signals to their ultimate destination: a protein called cortactin. “You can think of cortactin as the joists that help assemble the scaffolding for the structure,” said Dr. Koleske. “From our earlier work showing that cortactin could promote cellular protrusions, we started getting really interested in cancer, because invadopodia has been associated with invasiveness and cancer invasion. That’s when we turned to Dr. John Gendolotti.”

Gendolotti, Professor of Neurosciences and Medical Imaging at Albert Einstein College of Medicine of Yeshiva University, specializes in tracking the migration of cancer cells. “One expert is in biochemistry and bioengineering; the other, tracking the formation of these structures, called invadopodia,” said Dr. Koleske. “It’s a joint effort at reaching how this happens in cells in real time. The combination of approaches makes for a very potent attack.”

The biggest breakthrough, published in a paper in 2011, was Koleske’s discovery that cortactin can’t send out the signals that trigger other proteins to assemble into invadopodia until it has been phosphorylated by a tyrosine kinase called Arg. Koleske’s team is currently testing whether disrupting communication between Arg and cortactin could prevent invadopodia from forming or functioning, thereby preventing the tumor cells from escaping the tumor. To test this idea, they knocked down Arg in invasive human breast cancer cells, then transplanted them into the mammary fat pads of mice to see if the cells could invade and metastasize to the lung—which is what this particular type of breast cancer metastasizes to about 80 percent of the time. That’s very promising and we’re very excited by the right track.”

Dr. Koleske has received pilot funding from Yale Cancer Center to begin looking for compounds that stop Arg and cortactin from interacting. “We’re already making significant progress here,” said Dr. Koleske. “The strategy would be a drug that targets this interaction and the simplest way to begin would be to find a target in collaboration with Forte Biosciences and the National Cancer Institute.”

“It’s an idea that the drugs would be used in the adjuvant setting for people who had early-stage breast cancer and had a residual tumor,” said Dr. Koleske. “It would be a way to reduce the long-term risk of recurrence or progression by invasive cells that had been missed.” Koleske added that this is a perfect illustration of the “translational science” that the Cancer Center encourages—translating basic science into practical applications that solve problems in cancer medicine.
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